CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020675

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

NDA 20-675

Axcan Pharma U.S., Incorporated
Attention: Leon Gosselin
25 - 27 Margaret Street
Plattsburgh, New York 12901

MAR 24 1997

Dear Mr. Gosselin:

Please refer to your new drug application dated March 22, 1996, received March 26, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Urso (ursodiol) Tablets.

We acknowledge receipt of your submissions dated April 18, May 5, 8, 14 and 23, June 27, July 11 and 18, August 2, 12 and 23, September 18, October 8 and 28, and November 6, 1996 and February 17 1997. The User Fee goal date for this application is March 26, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit a satisfactory response to the following items:

Chemistry, Manufacturing, and Controls:

DRUG SUBSTANCE

1. [redacted]

2. [redacted]

3. Specify the retest period for bulk drug substance and the tests performed at that time.

DRUG PRODUCT

1. Either specify the composition of [redacted] or provide a reference to where this information can be found. If a DMF is referenced, then provide a letter of authorization for the file.

2. Regarding the proposed manufacturing procedure:

   A. Specify the acceptable shelf life for the [redacted], for the [redacted] and for the [redacted]

   B. Specify the acceptable [redacted] for [redacted]

   C. Specify the acceptable range [redacted] and whether the proposed [redacted] is intended to adhere to the mouth of the bottle.

   D. Either specify that tablets which fail to meet all product release specifications will not be [redacted] or provide a detailed description of the [redacted]

3. Either provide data which demonstrates that changes in [redacted] over time do not have a significant effect on the dissolution profile and the purity of the finished drug product, or establish a product release and stability specification for [redacted]

4. Regarding the proposed regulatory methods:

   A. Revise each of the [redacted] methods [redacted] to include system suitability.

   B. Specify the acceptable range for column temperature in Biopharm method [redacted]

   C. Specify the [redacted] of the [redacted] on the [redacted] in Biopharm methods [redacted]

5. Regarding the proposed container-closure system:

   A. Revise the bottle specifications to identify the actual [redacted] to be used; [redacted] is no longer available.

   B. Specify whether the proposed container-closure system is intended to be a tight and/or light resistant package and provide the results of USP [redacted] testing which supports this claim. Provide the results of light stress testing on the proposed drug product which provide the basis for determining the need for protection from light.

6. Regarding the submitted stability information:

   A. Provide a detailed description of the protocol to be used to monitor the stability of drug product after approval of this application.

   B. Specify the ranges for temperature and relative humidity in the submitted stability studies.

   C. Provide the results of USP [redacted] testing which demonstrates that the package used in the submitted stability studies provides the same level of moisture permeation and light transmission protection as the package proposed for marketing.

7. Regarding the environmental assessment (EA) statements:

   A. Revise the EA statement for the [redacted] site to include the signature of the preparer and the date of signature. Alternately, provide a statement that [redacted] will not manufacture this product for distribution.

   B. Provide an EA statement for the production of bulk drug substance at the [redacted] sites. Note that certification of compliance with all applicable laws and regulations will be acceptable.

Final Printed Labeling

It will be necessary for you to submit final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-675

DEC - 5 1997

Name of Drug: Urso (ursodiol) Tablets

Sponsor: Axcan Pharma U.S., Incorporated

Material Reviewed:

Submission Date	Receipt Date	Type of Labeling
June 27, 1997	June 30, 1997	Revised Draft
July 30, 1997	July 31, 1997	Revised Draft
November 14, 1997	November 14, 1997	Revised Draft
December 3, 1997	December 4, 1997	FPL (November, 1997)

Background and Summary Description

NDA 20-675, submitted March 22, 1996, provides for the treatment of all stages of primary biliary cirrhosis (PBC). An approvable action, pending final printed labeling and a complete response to CMC questions, was taken March 24, 1997. The firm submitted a complete response, including revised draft labeling, June 27, 1997. Since the June 27, 1997 labeling was not readable in WordPerfect 6.1 for Windows, the firm submitted identical labeling in WordPerfect 6.1 for Windows July 30, 1997. They further revised the labeling to include revisions recommended by the CMC and Biopharm reviewers on November 14, 1997. The FPL dated December 3, 1997 includes all previous revisions. It will be compared to the marked-up draft attached to the March 24, 1997 AE letter with the differences listed below.

Review

1. DESCRIPTION section

   In his review dated November 3, 1997, CMC reviewer Mike Adams recommended adding cetyl alcohol, sodium lauryl sulfate and hydrogen peroxide to the list of inactive ingredients.

   These ingredients were included in the December 3, 1997 FPL.

2. CLINICAL PHARMACOLOGY section

   This section was extensively revised in the June 27, 1997 revised draft labeling. The text from the labeling attached to the March 24, 1997 AE letter is reprinted below in the left column and the firm's proposed revision is printed in the right column.

AGENCY'S PROPOSED LABELING 3/24/97	AXCAN'S REVISED DRAFT LABELING 6/27/97
[redacted]	

[redacted]

In her review dated August 6, 1997, Biopharm Team Leader Lydia Kaus, Ph.D., accepted the sponsor's revisions with the following changes:

1. [redacted]

2. [redacted]

On August 12, 1997 Dr. Talarico accepted the firm's changes as well as Dr. Kaus' revisions. The December 3, 1997 FPL includes Dr. Kaus' recommended changes.

3. CLINICAL STUDIES section

In the June 27, 1997 revised draft labeling the firm included several changes to the second paragraph and the first sentence in the fourth paragraph in this section. The relevant text from the labeling attached to the March 24, 1997 AE letter is reprinted below in the left column and the firm's proposed revision is printed in the right column.

[redacted]

[redacted]

Hugo Gallo-Torres, M.D., Ph.D. accepted these revisions with the following change: the first sentence in the second paragraph should be changed from,

[redacted]

On August 12, 1997 Dr. Talarico accepted these changes as well. The FPL submitted December 3, 1997 included the revision recommended by Dr. Gallo-Torres.

4. HOW SUPPLIED section

In his review dated November 3, 1997, Mike Adams recommended revising the storage statement from, [redacted]

The firm included this change in the FPL dated December 3, 1997 labeling.

Conclusions

The FPL dated December 3, 1997 includes all of the changes described above. I recommend finding the FPL acceptable.

/S/ [redacted]

Consumer Safety Officer

cc: T. 12-5-97

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-675

Name of Drug: Urso (ursodiol) Tablets

MAY - 2 1996

Sponsor: Axcan Pharma U.S. Inc.

Material Reviewed

Submission Date(s): March 22, 1996

Receipt Date(s): March 26, 1996

Background and Summary Description: This NDA was submitted for the treatment of all stages of primary biliary cirrhosis (PBC).

Ciba-Geigy's Actigall brand of 300 mg ursodiol capsules (NDA 19-594, approved December 31, 1987) is approved for gallstone dissolution in selected patients, and the prevention of gallstone formation in obese patients experiencing rapid weight loss. [redacted]

NDA 20-675 contains one pivotal study, the Mayo Study, entitled, "A randomized trial of ursodeoxycholic acid in the treatment of Primary Biliary Cirrhosis", and one supportive study, the Heathcote Study, entitled, "A double-blind, randomized, placebo-controlled multicenter trial of ursodeoxycholic acid in primary biliary cirrhosis".

The Mayo Study is a double-blind, randomized, placebo-controlled study to demonstrate the safety and efficacy of ursodiol for the treatment of biopsy confirmed PBC. The principal investigator is Keith Lindor, M.D. of the Mayo Clinic in Rochester, Minnesota. Patients were stratified according to histological stage, the presence or absence of esophageal varices, and bilirubin level. Ursodiol formulations manufactured by [redacted] were used. Patients randomized to ursodiol were dosed at 13 - 15 mg/kg/day in four divided doses. The primary efficacy endpoint was incidence of and time to treatment failure. Treatment failure was defined as; death; liver transplantation; histologic progression by two stages or to cirrhosis; development of varices, ascites, or encephalopathy; doubling of bilirubin; marked worsening of fatigue or pruritus; inability to tolerate the drug; or voluntary withdrawal. The secondary efficacy endpoints were defined as: the change in serum lab measurements (alkaline phosphatase, AST, bilirubin, albumin, IgM and PT); change in symptoms such as fatigue or pruritus; development or clinical progression of esophageal varices, ascites or edema and encephalopathy; and histologic changes

The Heathcote Study is a double-blind, randomized, placebo-controlled study to demonstrate the safety and efficacy of ursodiol for the treatment of biopsy confirmed PBC. Patients were stratified according to the presence or absence of symptoms at baseline. Ursodiol capsule formulations manufactured by [redacted] were used. Patients randomized to ursodiol were dosed at 14 mg/kg/day given as a single daily dose with the evening meal. The primary efficacy endpoint was the percent change in bilirubin after two years of treatment. The secondary efficacy endpoints were defined as; change in symptoms; change in serum lab measurements (alkaline phosphatase, total-C, ALT, AST, serum albumin, and immunoglobulins levels); liver biopsy results; and time to death or liver transplantation. A post-hoc analysis of time to treatment failure stratified by baseline bilirubin and histological stage was performed. Treatment failure was defined as: discontinuation for any reason; bilirubin doubling from the baseline level; and the development of ascites or encephalopathy.

The sponsor presented results from the Mayo and Heathcote studies at an end-of-Phase 2 meeting with the Division on April 18, 1995. At the meeting, Dr. Fredd suggested that the sponsor reanalyze one of the primary endpoints in the Mayo Study, time to treatment failure, after redefining the endpoint to exclude patients that voluntarily withdrew from the study and those experiencing a doubling of bilirubin. He also suggested the sponsor provide a life-table analysis of the long-term follow-up data from both studies, and an analysis of the relationship between a change in bilirubin and efficacy. The results of these analyses, submitted on July 17, 1995, demonstrated a prolonged time to death or transplantation in the combined studies.

At a pre-NDA meeting on October 25, 1995, the Division recommended using the Mayo Study as the main support for efficacy, but delaying the submission of the NDA until the data is compelling. It was Dr. Fredd's contention that the long-term data for time to death or transplantation were trending toward significance and an analysis of additional long-term data may strengthen the effect. The firm was advised that a single study NDA must be compelling to receive approval, and that they must make the case that the Mayo Study alone is sufficient to warrant approval.

Review

1. Type I DMF [redacted] for [redacted]

2. The letters of authorization for DMF [redacted] and Type II DMF [redacted] do not specify the volume and page numbers where the referenced information can be found.

3. The annotations in the annotated labeling reference the technical sections only, not the summary volume.

4. On December 18, 1995 the firm sent the Division samples of case report tabulations for the Mayo Study in a format proposed for the NDA. Dr. Hugo Gallo-Torres, a medical officer, reviewed the format of these tabulations and his comments were conveyed to the firm. A review of the case report tabulations in this NDA revealed that several of Dr. Gallo-Torres' recommendations were not followed. They are listed below:

   A. Appendix 2A, Etiological Factors, lists several potentially hepatotoxic drugs and indicates whether or not (yes or no) the patient was taking them prior to study entry. Dr. Gallo-Torres asked the firm to provide the dosage and duration of treatment for positive responses. The firm indicated that this information was not available.

   B. Appendix 7A, Toxicity, lists several adverse reactions to drug therapy and indicates whether or not (yes or no) the patient experienced them. Dr. Gallo-Torres asked the firm to provide clear definitions of the adverse events. The firm indicated that the events were recorded only if the investigator considered them clinically significant and that criteria were not developed.

   C. Case report tabulations are reported both "by panel", i.e. patient data is reported in several subject-specific tables, and "by patient", i.e. complete patient data is reported in one table. Dr. Gallo-Torres commented that the "by patient" tabulations were crowded and not user friendly. The firm did not modify them.

   After reviewing the case report tabulations in the NDA on April 26, 1996, Dr. Gallo-Torres indicated that they were acceptable as is.

5. Concerning the Summary volume:

   A. The Foreign Marketing History did not list the countries marketed and the dates introduced.

   B. The Chemistry, Manufacturing, and Controls section did not contain a narrative summary of the drug substance stability information.

6. Concerning the study report for the Mayo Study:

   A. Investigator CVs could not be located.

   B. A statement that the Study was conducted in compliance with the institutional review board regulations in 21 CFR part 56, and that it was conducted in compliance with the informed consent regulations in 21 CFR part 50 could not

be located.

7. Concerning the study report for the Heathcote Study:

   A. Investigator CVs could not be located.

   B. A statement that the Study was conducted in compliance with the institutional review board regulations in 21 CFR part 56, and that it was conducted in compliance with the informed consent regulations in 21 CFR part 50 could not be located.

In an April 26, 1996 telephone conversation, the firm stated that the items in number 6A, 6B, 7A, and 7B were not included in the submission, but would be submitted in an amendment.

8. Concerning the Integrated Summary of Safety:

   A. A summary and analysis of dose-response and blood-level response information from animal, pharmacokinetic, pharmacodynamic, and other clinical pharmacology studies, and from controlled and uncontrolled clinical studies that supports the dosing recommendations proposed in the labeling could not be located.

   B. An analysis of the responses of subsets of the overall population (i.e. age, sex, race) could not be located.

9. SAS datasets and programs on diskette for stability studies and human pharmacokinetic studies could not be located.

10. After a filing review, Supervisory Pharmacologist Dr. Jasti Choudary, listed several deficiencies in a memo to the NDA dated April 21, 1996. A copy of the memo is attached. These deficiencies were communicated to the firm on April 24, 1996, and the firm indicated that they will submit a written response by May 9, 1996.

Conclusions

A 45-Day Planning/Filing meeting is scheduled for May 9, 1996. From an administrative standpoint, this application is acceptable for filing. The review team will discuss the need to submit any information necessary to rectify the listed deficiencies and any others discussed at the meeting.

/S/ [redacted]
Consumer Safety Officer

5/2/96

/S/ [redacted]

ITEM 13:

AXCAN PHARMA US INC.
25-27 Margaret Street
Plattsburgh, NY 12901
USA
Tel. (518) 563-7354
Fax (518) 563-3359
Toll free 1-800-742-6706

PATENT INFORMATION

PATENT AND EXCLUSIVITY INFORMATION ON URSO™
PRODUCT OF: AXCAN PHARMA PLATTSBURGH, NEW YORK
(21 U.S.C. 355 bb)

The following is provided for:

1.	**Active ingredient:**	Ursodeoxycholic acid	
2.	**Strength:**	250 mg	
3.	**Trade Name:**	URSO™	
4.	**Dosage form:**	Film-coated tablets	
5.	**NDA number:**	20-675	
6.	**Approval date:**	Pending - NDA being submitted	
7.	**Applicable Patent number and expiration date:**	US Patent Number:	4,859,600
		Date:	August 22, 1989
		Expires:	August 22, 2006 (17 years)

as an Orphan drug for the treatment of Primary Biliary Cirrhosis (PBC) as per the FDA letter dated June 20, 1991.

Pursuant to Section 316 - Orphan drugs of the Federal Food, Drug and Cosmetic Act, we are requesting a **seven-year period of marketing exclusivity from the date of approval** of this NDA.

Léon Gosselin, President

March 22, 1996
Date

1 020

ITEM 14

AXCAN PHARMA

AXCAN PHARMA US INC.
25-27 Margaret Street
Plattsburgh, N.Y. 12901
USA
Tel.: (518) 563-7354
Fax: (518) 563-3359
Toll free: 1-800-742-6706

PATENT CERTIFICATION

PATENT AND EXCLUSIVITY INFORMATION ON URSO™
PRODUCT OF: AXCAN PHARMA PLATTSBURGH, NEW YORK
(21 U.S.C. 355 bb)

I certify that URSO™ (ursodiol) tablet 250 mg is registered with the United States Department of Commerce, Patent and Trademark Office:

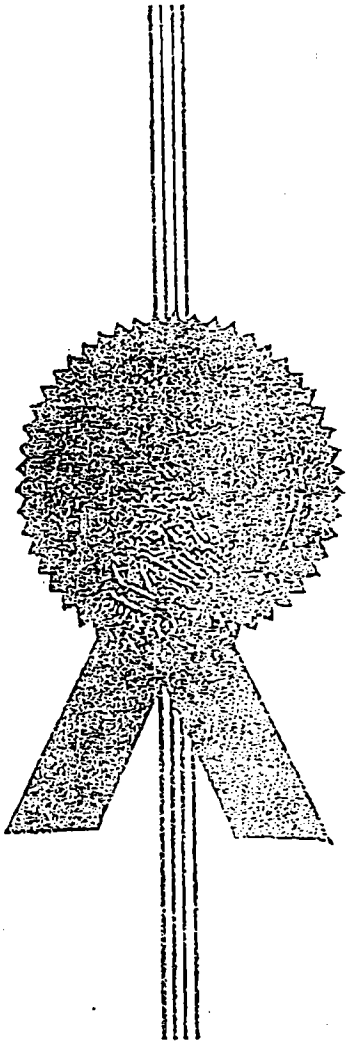
US Patent Number:	4,859,600
Date:	August 22, 1989
Expires:	August 22, 2006 (17 years)

with the Trademark Serial Number: 74/264521 filed 04/10/1992

Léon Gosselin, President

March 22, 1996
Date

The United States of America



The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Commissioner of Patents and Trademarks

Attest

INTERFALK
1 022

United States Patent [19]
Poupon

[11] Patent Number: 4,859,660
[45] Date of Patent: Aug. 22, 1989

[54] METHOD OF TREATING CIRRHOSIS

[75] Inventor: Raoul Poupon, Paris, France
[73] Assignee: Synthelabo, Paris, France

[21] Appl. No.: 122,867
[22] Filed: Nov. 19, 1987
[30] Foreign Application Priority Data
Nov. 20, 1986 [FR] France 86 16159
[51] Int. Cl.[4] A61K 31/56; C07J 1/00
[52] U.S. Cl. 514/182; 260/397.1
[58] Field of Search 260/397.1; 514/182

[56] References Cited
U.S. PATENT DOCUMENTS
4,033,994 4/1978 Noda et al. 514/545

OTHER PUBLICATIONS
Chemical Abstracts, vol. 101 (1984), #104084a; Mukata et al.
French Vidal Dictionary, p. 1659, "Ursolvan".
Merck Index, 9695, 10th Ed., 1983, p. 1413.

Primary Examiner—Leonard Schenkman
Assistant Examiner—Joseph A. Lipovsky
Attorney, Agent, or Firm—Fleit, Jacobson, Cohn, Price, Holman & Stern

[57] ABSTRACT
A method of treating primary biliary cirrhosis comprising administering ursodeoxycholic acid to a patient suffering therefrom.

4 Claims, No Drawings

APPEARS THIS WAY
ON ORIGINAL

METHOD OF TREATING CIRRHOSIS

The present invention relates to the treatment of primary biliary cirrhosis.

Ursodeoxycholic acid is a known compund that has been used for the dissolving treatment of cholesterolic biliary lithiasis. It has now been found that ursodeoxycholic acid also acts effectively in the treatment of primary biliary cirrhosis (PBC).

PBC is a deadly disease. PBC is said to be "primary" because it is not induced by alcohol abuse or drugs or infectious hepatitis.

PBC afflicts mainly middle aged women. It is a disease in which small biliary intrahepatic vessels are progressively destroyed.

The evolution of the disease varies, usually between 5 and 10 years. The symptomatology starts with fatigue, itching followed by increased liver size and icterus. Hepatic transplantation is the only long term survival means as yet.

Up to now it was thought that the disease was an autoimmune one because mitochondrial antibodies were observed in the patients. This is why all the treatments used so far have been immunosuppressive, such as high doses of corticoids and azathioprine.

The present invention based upon ursodeoxycholic acid hinges on the hypothesis that the symptomatology and the extent of the disease are not immunological, but are due to the toxicity of the biliary acids synthesized by the liver. These acids are involved in the lipids metabolism. The biliary acids are involved in a closed cycle of elimination by the bile and reabsorption by the intestine.

When administered chronically, ursodeoxycholic acid, which is non-toxic, substitutes itself for these biliary acids which allows the elimination from the body.

After administration of 13 to 15 mg/kg/day of ursodeoxycholic acid to patients for 2 years, the total concentration of serum bile acids was unaltered; the percentage of patients having pruritus fell from 53 to 8%; the patients' blood bilirubin concentration became less than 34 μM; the serum alkaline phosphatase, transaminase and γ-glutamyltransferase activities decreased in all the patients; and the levels of prothrombin, albumin, γ-globulins and immunoglobulins M were unaltered.

Results obtained during the last 5 years confirm previous results. With increased numbers of patients, it can be shown that the therapeutic effect increases with time and with no adverse effects.

The ursodeoxycholic acid may be administered to a patient in association with any suitable excipient. Preferably, the ursodeoxycholic acid is administered orally, for example, in capsule form. An example of a suitable formulation in the form of a gelatin capsule is as follows:

ursodeoxycholic acid 200 mg;

excipient: magnesium stearate, talc, Amijel corn starch;

gelatin capsule: gelatin, titanium dioxide, indigotin, sulphur dioxide.

I claim:

1. A method of treating primary biliary cirrhosis which comprises administering an effective amount of ursodeoxycholic acid to a patient suffering from primary biliary cirrhosis.

2. A method according to claim 1 wherein 13 to 15 mg/kg/day of ursodeoxycholic acid is administered to the patient.

3. A method according to claim 1 wherein the ursodeoxycholic acid is administered orally.

4. A method according to claim 3 wherein the ursodeoxycholic acid is administered in the form of gelatin capsules.

* * * * *

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOTICE OF PUBLICATION UNDER 12(a)

1. Serial No.:
74/264,521

2. Mark:
URSO

3. Applicant:
AXCAN SCIENTIFIC CORPORATION

4. Publication Date:
SEP. 29, 1992

The mark of the application identified appears to be entitled to registration. The mark will, in accordance with Section 12(a) of the Trademark Act of 1946, as amended, be published in the Official Gazette on the date indicated above for the purpose of opposition by any person who believes he will be damaged by the registration of the mark. If no opposition is filed within the time specified by Section 13(a) of the Statute or by rules 2.101 or 2.102 of the Trademark Rules, the Commissioner of Patents and Trademarks may issue a notice of allowance pursuant to section 13(b) of the Statute.

Copies of the trademark portion of the Official Gazette containing the publication of the mark may be obtained at $9.50 each for domestic orders, or at $11.88 each for foreign orders from:

The Superintendent of Documents
U.S. Government Printing Office
Washington,D.C. 20402

By direction of the Commissioner.

1 025

FILING RECEIPT FOR TRADEMARK APPLICATION

Receipt on the DATE OF FILING of the application for registration and filing fees is acknowledged for the mark identified below. The DATE OF FILING is contingent upon the collection of any payment made by check or draft. Your application will be considered in the order in which it was received and you will be notified as to the examination thereof. Correspondence should be expected from the Patent and Trademark Office in approximately 6o months. When inquiring about this application, include the SERIAL NUMBER, DATE OF FILING, OWNER NAME, and MARK

A. Yates Dowell, III
Dowell & Dowell
Suite 705
2001 Jefferson Davis Highway
Arlington, VA 22202

ATTORNEY
REFERENCE NUMBER

PLEASE REVIEW THE ACCURACY OF THE FILING RECEIPT DATA.

A request for correction to the filing receipt should be submitted within 30 days to the following address: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231. The correspondence should be marked to the attention of the OATPA DATA BASE MAINTENANCE STAFF. The Patent and Trademark Office will review the request and make corrections when appropriate.

SERIAL NUMBER: 74/264521
DATE OF FILING: 04/10/1992
MARK: URSO
MARK TYPE(S): TRADEMARK
DRAWING TYPE: WORDS, LETTERS, OR NUMBERS IN TYPED FORM
SECTION 1(A): NO
SECTION 1(B): YES
SECTION 44: NO

ATTORNEY: A. Yates Dowell, III
OWNER NAME: AXCAN SCIENTIFIC CORPORATION
OWNER ADDRESS: 25, Margaret Street
Plattsburg
NEW YORK 12901
ENTITY: CORPORATION
CITIZENSHIP/DOMICILE: NEW YORK

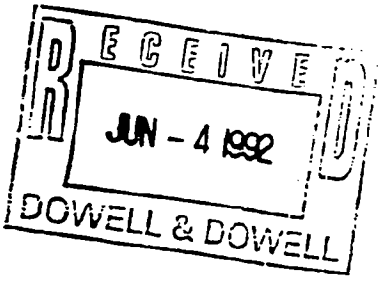
INTERNATIONAL CLASS	DATE OF FIRST USE	DATE OF FIRST USE IN COMMERCE

ONLY THOSE DATES OF USE AND CLASSES FILED UNDER SECTION 1(A) ARE LISTED

GOODS/SERVICES BY INTERNATIONAL CLASS

005—pharmaceutical preparation in the form of a powder, tablet, capsule or granule, for the treatment of liver, gallbladder, gallstone and forming a cholagogic activator of vitamins

ALL OF THE GOODS/SERVICES IN EACH CLASS ARE LISTED



ADDITIONAL INFORMATION MAY BE PRESENT IN THE PTO RECORDS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

MARK: URSO (design)
CLASS:

UNITED STATES TRADEMARK APPLICATION

TO THE ASSISTANT SECRETARY AND
COMMISSIONER OF PATENT AND TRADEMARKS

Applicant:

AXCAN SCIENTIFIC CORPORATION, a New York State corporation, having a business address at 25, Margaret Street, Plattsburg, New York 12901, U.S.A.

1. The applicant has adopted and requests registration of the above-identified trademark shown in the accompanying drawing for the following wares:

Pharmaceutical preparation in the form of a powder, tablet, capsule or granule, for the treatment of liver, gallbladder, gallstone and forming a cholagogic activator of vitamins.

and requests that said trademark be registered in the United States Patent and Trademark Office on the Principal Register established by the Act of July 5, 1946 (15 U.S.C. 1051 et seq; as amended).

.../2

/S/ [redacted]

2. Applicant has a bona fide intention to use the mark in commerce on or in connection with the following wares:

Pharmaceutical preparation in the form of a powder, tablet, capsule or granule, for the treatment of liver, gallbladder, gallstone and forming a cholagogic activator of vitamins.

Section 1(b) of the Act of July 5, 1946 as amended (15 U.S.C. 1051 (b). The intended manner or mode of use of the mark on or in connection with the wares will be by applying said mark on labels and packaging.

APPOINTMENT OF DOMESTIC REPRESENTATIVE

The firm of DOWELL & DOWELL Law Offices, located at 2001 Jefferson Davis Hwy., suite 705, Arlington, Virginia 22202, United States of America, are hereby designated as applicant's representative upon whom notices or process in proceedings affecting the mark may be served.

POWER OF ATTORNEY

The undersigned hereby appoints DOWELL & DOWELL Law Offices, a firm composed of A. YATES DOWELL, Jr. (Registration No. 16,295) of the Bars of Commonwealth of Virginia and the District of Columbia, A. YATES DOWELL, III (Registration No. 28,070) of the Bar of Commonwealth of Virginia and RALPH A. DOWELL (Registration No. 26,868) of the Bars of the State of Georgia and the Commonwealth of Virginia, having its offices at 2001 Jefferson Davis Highway, Suite 705, Arlington, Virginia 22202, United States of America, telephone: (703) 415-2555, its attorneys to prosecute this application to register, to transact all business in the Patent and Trademarks Office in connection therewith, and to receive the certificate or registration.

Please direct all correspondence and phone inquiries to A. YATES DOWELL, III of DOWELL & DOWELL Law Offices, 2001 Jefferson Davis Highway, Suite 705, Arlington, Virginia 22202, United States of America, Telephone: (703) 415-2555.

.../3

/S/ [redacted]

DECLARATION

The undersigned, being hereby warned that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any resulting registration, declares that: he/she is properly authorized to execute this application on behalf of the Applicant; he/she believes the Applicant to be the owner of the trademark/service mark sought to be registered, or if the application is being filed under 15 U.S.C. 1051(b), he/she believes Applicant to be entitled to use such mark in commerce; to the best of his/her knowledge and belief no other person, firm, corporation, or association has the right to use the above-identified mark in commerce, either in the identical form thereof or in such near resemblance thereto as to be likely, when used on or in connection with the goods/services of such other person, to cause confusion, or to cause mistake, or to deceive; and that all statements made of his/her own knowledge are true and all statements made on information and belief are believed to be true.

AXCAN SCIENTIFIC CORPORATION,
a New York State Corporation

By: _____

Name:
Title:

Plattsburg, New York 12901, U.S.A.

this 25th day of January 1993.

.../4

1 029

DRAWING

Applicant's name and address: AXCAN SCIENTIFIC CORPORATION,
a New York State Corporation
25, Margaret Street
Plattsburg, New York 12901, U.S.A.

Intent to use basis

WARES: Pharmaceutical preparation in the form of a powder, ...

Mark:

URS

1 030

EXCLUSIVITY SUMMARY for NDA # 20-675 SUPPL # _____

Trade Name Urso Tablets Generic Name ursodiol
Applicant Name Axcan Pharma U.S., Inc. HFD-180

Approval Date December 10, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity?

   YES /_X_/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   SEVEN - Orphan Product

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-594 Actigall (ursodiol) Capsules

2. Combination product.

If the product contains more than one active moiety (as defined in **Part II, #1**), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if

known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /X/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, "A randomized trial of ursodeoxycholic acid in the treatment of Primary Biliary Cirrhosis" (Keith Lindor, M.D., Mayo Clinic)

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /__/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, "A randomized trial of ursodeoxycholic acid in the treatment of Primary Biliary Cirrhosis" (Keith Lindor, M.D., Mayo Clinic)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 IND # [redacted] YES /_x_/ NO /___/

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 YES /___/ Explain _____ NO /___/
Explain: _N/A, conducted under an IND.__

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____

/S/ [redacted]
Signature
Title: Project Manager

12/10/97
Date

/S/ [redacted]
Signature of Division Director

12-10-97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-675 Supplement # N/A Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF D-180 Trade and generic names/dosage form: Urso (ursodiol) Tablets Action: AP AE (NA)

Applicant Axcan Pharma U.S. Inc. Therapeutic Class 5,6 P

Indication(s) previously approved None
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Indication in this application Treatment of primary biliary cirrhosis (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
3/18/97 /S/ [redacted] not a pediatric disease.

___ 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ [redacted]
Signature of Preparer and Title

3-18-97
Date

cc: Orig NDA/PLA/PMA # 20-675
HF D-180 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

3/19/97 /S/ [redacted]