March 22, 1996.

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

ORIGINAL NEW DRUG APPLICATION

FOOD AND DRUG ADMINISTRATION
Central Document Control Room HFN-46
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852
USA

RE: **Original NDA 20-675, URSO™ (ursodiol) Tablets 250mg**

Dear Sir, Madam:

We are submitting herewith an original New Drug Application (Archival copy and Review copy) for URSO™ tablets in the treatment of patients with Primary Biliary Cirrhosis (PBC).

URSO™ was granted the Orphan Drug status on June 20, 1991 for this indication.

By this letter, Axcan Pharma US Inc. certifies that we have not and will not use, in any capacity, the services of any person debarred under Section 306(a) or (b) of the Food, Drug and Cosmetic Act in connection with this NDA. We further certify that a field copy of this NDA has been provided to the FDA North East Regional Office, 599 Delaware Avenue, Buffalo, NY 14202, attention: Mr. John Podsadowski.

A cheque of [redacted] for User fee was sent to [redacted] on February 6, 1996 together with FDA 3397.

For additional information regarding this submission, please contact the undersigned at (514) 467-5138, fax (514) 464-9979.

Sincerely,

APPEARS THIS WAY ON ORIGINAL

Léon F. Gosselin
President

LFG:lg
Encls.

cc: Dr. Stephen B. Fredd (FDA - Rockville)
Dr. H. Gallo Torres (FDA - Rockville)
Mr. Brian Strongin (FDA - Rockville)
Mr. John Podsadowski (FDA - Buffalo)

MEMORANDUM OF TELECON

DATE: October 27, 1997

APPLICATION NUMBER: NDA 20-675; Urso (ursodiol) Tablets

BETWEEN:

Name: Quyen Vinh
Phone: (612) 417-0684
Representing: Axcan Pharma U.S. Inc.

AND

Name: Eric Duffy, Ph.D. — Team Leader, CMC
Mike Adams — Review Chemist
Brian Strongin — Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: CMC Information Request/Comments

Background

NDA 20-675 was submitted March 22, 1996 for the treatment of all stages of primary biliary cirrhosis. The application was approvable March 24, 1997 pending an acceptable response to CMC questions and final printed labeling identical in content to that attached to the action letter. The firm submitted a complete response June 27, 1997 and the user fee due date is December 31, 1997. Review chemist, Mike Adams, and CMC team leader, Eric Duffy, Ph.D., requested a response to several questions/comments prior to completion of the review. The questions were faxed to the firm prior to the teleconference and are attached.

Today's Call

Dr. Duffy opened by explaining that the CMC questions/comments should be addressed prior to the next action. He asked the firm to submit a response, including an acknowledgment of the comments, as soon as possible. The firm stated that they intend to respond to the questions/comments, as well as submit final printed labeling, within 1½ to 2 weeks. The call was then concluded.

/S/

Brian Strongin
Regulatory Health Project Manager

APPEARS THIS WAY ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Brian Strongin	**Phone:** (301) 443-0483
Date: April 10, 1996	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Urso	**NDA/ANDA#** 20-675
Established name, including dosage form: ursodiol tablets	
Other trademarks by the same firm for companion products: N/A	
Indications for Use (may be a summary if proposed statement is lengthy): The treatment of all stages of primary biliary cirrhosis.	
Initial Comments from the submitter (concerns, observations, etc.): No concerns at this time.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-675; HFD-180/division file; HFD-180/B.Strongin; HFD-180/M.Adams

Rev. December 95

Consult #595 (HFD-180)

URSO ursodiol tablets

The LNC is concerned that the trademark is using too much of the USAN syllables, however, the LNC found no look alike/sound alike conflicts nor misleading aspects in the the proprietary name.

Overall, the LNC has no reason to find the proposed proprietary name unacceptable.

/S/ [redacted] 5/23/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 12, 1997

Axcan Pharma U.S., Inc.
Attention: Leon Gosselin
25 - 27 Margaret Street
Plattsburgh, NY 12901

Dear Mr. Gosselin:

Reference is made to your orphan product ursodiol (Urso®), which was designated an orphan drug pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 360bb) on June 20, 1991 [redacted] for the treatment of patients with primary biliary cirrhosis.

This letter is to inform you that as the first sponsor of ursodiol to obtain marketing approval for this indication, you are entitled to seven years of exclusive marketing approval pursuant to Section 527 of the FFDCA (21 U.S.C. § 360cc) for the use of ursodiol in the treatment of primary biliary cirrhosis. The exclusive seven year approval period began on December 10, 1997, the date of approval of your new drug application (NDA 20-675).

Please note that holders of exclusivity for approved orphan products are required to assure the availability of sufficient quantities of an orphan drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug product's exclusive approval [21 CFR 316.36(b)].

Thank you for your efforts in developing ursodiol for the treatment of primary biliary cirrhosis. The whole premise of the Orphan Drug Act and program is based on the realization that the resources and commitment devoted to the development of drugs for "orphan" populations may not provide financial returns to their sponsors. It is with genuine gratitude that we recognize your efforts.

Sincerely yours,

/S/ [redacted]

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

APPEARS THIS WAY ON ORIGINAL

Strongin

NDA 20-675

FEB 25 1997

Axcan Pharma U.S., Inc.
Attention: Leon Gosselin
25 - 27 Margaret Street
Plattsburgh, N.Y. 12901

Dear Mr. Gosselin:

Please refer to your new drug application for Urso (ursodiol) Tablets.

We also refer to the December 10, 1997 teleconference between Mr. Leon Gosselin, Ms. France Guay, Dr. Claude Sauriol, and Ms. Quyen Vinh of Axcan Pharma, Incorporated and Dr. Eric Duffy, Mr. Mike Adams, Dr. Lydia Kaus, and Mr. Brian Strongin of this Agency where qualifying [redacted] as a new drug product manufacturing site was discussed. We agreed to provide a suggested bioequivalence protocol for comparing drug product manufactured by [redacted] and a guidance document entitled, "Guidance, Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design". These documents are enclosed for your consideration.

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

Sincerely yours,

/S/ [redacted]

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

enclosed documents:
Clinical Pharmacology and Biopharmaceutics Review dated 2/14/97

APPEARS THIS WAY ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 9, 1996

FROM: Brian Strongin, Project Manager

SUBJECT: NDA 20-675, Urso (ursodiol) Tablets

TO: Dr. Stephen Fredd
Dr. Hugo Gallo-Torres
Dr. Eric Duffy
Mr. Mike Adams
Dr. Lydia Kaus
Ms. Kati Johnson

I have just be notified that as of December 31, 1996 [redacted] the drug product supplier for this pending NDA, will not extend their manufacturing agreement for Axcan Pharma. Axcan has a new supplier lined up, [redacted] is in the process of manufacturing the first pilot batch of Urso Tablets. The firm has requested a teleconference to discuss this situation. Before scheduling the teleconference, I've scheduled an internal meeting on Tuesday, December 10, 1996 at 11AM in 6B-45 to discuss the situation.

[redacted] has not been inspected, but they were scheduled for inspection the week of January 13, 1997. Although [redacted] has not stated in writing that they will not allow an FDA inspection, from information given by the firm it appears that they are not ready and may not allow an inspection.

The user fee due date is March 27, 1997. Since this application is a 5,6 P, it will require Office level sign-off. The following reviews are outstanding: CMC, biopharm, pharmacology, and expiration stats

APPEARS THIS WAY ON ORIGINAL

[redacted] [redacted] [redacted]

DRAFT
PROJET

AXCAN PHARMA

Axcan Pharma Inc.
597, boul. Laurier
Mont-Saint-Hilaire (Québec)
Canada J3H 4X8
Tél.: (514) 467-5138 - Fax: (514) 464-9979
1-800-565-3255

December 9, 1996

Mr. Brian Strongin
Project Manager
Food and Drug Administration
Division of Gastrointestinal and Coagulation Drug Products
Document Control - Room 6B-24
5600 Fishers Lane
ROCKVILLE, MD 20856
U.S.A.

FAX: (301) 443-9285

Dear Mr. Strongin:

RE: **NDA 20-675 - URSO in PBC**

The present letter will confirm that Axcan Pharma Inc. has been informed by [redacted] that they will not extend the manufacturing agreement for ursodiol tablets beyond December 31, 1996, despite the fact that we have completed the validation of the manufacturing process contained in the above-named submission.

It is our intention to use [redacted] as our alternate site.

We hereby urgently request a meeting with Dr. Steven Fredd and Mr. Eric Duffy to discuss the situation and to present our plans relating to the qualification of Global Pharm Inc.

We are distressed by this turn of events and thank you for your kind cooperation.

Sincerely yours,

Léon F. Gosselin, B.Sc., M.B.A.
President

LFG/fg

NDA 20-675

APR - 9 1996

Leon Gosselin
Attention: Axcan Pharma, U.S. Inc
25-27 Margaret Street
Plattsburgh, N.Y. 12901

Dear Mr. Gosselin:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Urso (ursodiol) Tablets 250 mg

Therapeutic Classification: Priority

Date of Application: March 22, 1996

Date of Receipt: March 26, 1996

Our Reference Number: 20-675

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 25, 1996 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0483.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Brian Strongin
Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-675

Axcan Pharma U.S. Inc.
Attention: Leon Gosselin
25 - 27 Margaret Street
Plattsburgh, N.Y. 12901

JAN 16 1997

Dear Mr. Gosselin:

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

We also refer to your amendments dated May 23, August 12, August 23, September 18, and October 8, 1996.

We have completed our review of the clinical pharmacology and biopharmaceutics section of your submission and have the following comments and suggestions:

1. We suggest performing a pharmacokinetic and pharmacodynamic study in patients with stable liver disease to characterize the distribution and elimination of ursodiol and its conjugates (measured separately) using different dosing regimens. Collection of serum, bile, urine and fecal data would enhance the knowledge of ursodiol's pharmacokinetics and enable the determination of a suitable dosage regimen. The Agency may be consulted concerning study design.

2. We suggest performing in vitro binding studies using blood collected from patients in different stages of liver disease. These studies would characterize the comparative binding of ursodiol to serum lipoproteins and albumin in the presence of its' glycine and taurine conjugates and in the presence of other bile acids. Detailed information on the binding kinetics of ursodiol would determine the role of albumin and lipoproteins as carriers of ursodiol and the degree of competition of other bile acids and bilirubin on its' binding.

3. We suggest performing a dose proportionality study in patients with stable liver disease to further characterize the pharmacokinetics of ursodiol and its' conjugates.

4. The proposed dissolution specification is acceptable.

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

MEMORANDUM OF TELECON

DATE: December 10, 1996

APPLICATION NUMBER: 20-675; Urso (ursodiol) Tablets

BETWEEN:

Name:	Mr. Leon Gosselin	President
	Ms. France Guay	Vice President, Operations
	Dr. Claude Sauriol	Vice President, Research and Development
	Ms. Quyen Vinh	Director, Regulatory Affairs

Phone: (514) 856-7849

Representing: Axcan Pharma, Incorporated

AND

Name:	Dr. Eric Duffy	Team Leader, CMC
	Mike Adams	Review Chemist
	Dr. Lydia Kaus	Team Leader, Biopharmaceutics
	Brian Strongin	Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Imprinting the Drug Product Produced by [redacted] and Qualifying [redacted] as the New Drug Product Manufacturer

Background

NDA 20-675 was submitted March 22, 1996 for Urso (ursodiol) Tablets for the treatment of all stages of primary biliary cirrhosis and is pending. On December 9, 1996 the Agency was informed via a fax from the firm that [redacted], the drug product manufacturer for most of the clinical trials and validation batches, would not extend their manufacturing agreement with Axcan beyond December 31, 1996. The fax also identified [redacted] of [redacted] as the proposed new drug product supplier. The firm requested this teleconference to discuss the steps necessary to qualify the [redacted] validation batches for marketing and [redacted] as a new drug product supplier.

Today's Call

1. Dr. Duffy explained that [redacted] must receive an acceptable pre-approval inspection if the validation batches are to be marketed. Mr. Gosselin explained that an inspection is arranged for January 13 - 17, 1997 and although [redacted] has indicated that preparing for the Urso inspection is not a priority, they will not turn away the inspector.

2. Mr. Gosselin stated that the validation batches were not marked with an identifying [redacted] Citing 21 CFR 206.10, Dr. Duffy explained that unless exempted, a solid oral dosage form is misbranded if not marked with an [redacted] Adding that Urso would not qualify for an exemption, he asked if the tablets could be [redacted] The firm responded that they would explore the possibility of having [redacted] the tablets.

3. In response to Dr. Duffy's question, Mr. Gosselin stated that Axcan had approximately [redacted] tablets or an estimated six-month supply of Urso from the [redacted] validation batches.

4. In response to the firm's question, Dr. Duffy explained that the identifying marking on the tablet must correspond to the information in the HOW SUPPLIED section of the labeling.

5. Axcan stated that [redacted] had manufactured a pilot batch using different manufacturing equipment than that used by [redacted] Dr. Kaus responded that if the manufacturing process or equipment or the drug product formulation is changed, a bioequivalence study comparing [redacted] product will be necessary. She promised to provide guidance concerning study design.

6. Dr. Duffy explained that it may be possible to develop a validation schedule in conjunction with the Agency.

7. Dr. Duffy explained that the application must be amended or supplemented for CMC information including a complete description of [redacted] manufacturing process and a comparison with the [redacted] process. He promised to provide guidance regarding the appropriate amount of stability data to include in the submission at a later point.

The call was then concluded.

/S/ [redacted]

Brian Strongin
Regulatory Health Project Manager

cc: Original 20-675
HFD-180/Div. File
HFD-180/Brian Strongin/2-7 /S/ [redacted] 6/23/97
HFD-180/E.Duffy/6-16-97
HFD-180/M.Adams/2-7-97
HFD-870/L.Kaus
BS/dob F/T 6-19-97/WP: c:\wpfiles\chem\N\20675702.0BS
TELECON

Strongin

NDA 20-675

OCT 25 1996

Axcan Pharma U.S., Inc.
Attention: Leon Gosselin
25 - 27 Margaret Street
Plattsburgh, N.Y. 12901

Dear Mr. Gosselin:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, Cosmetic Act for Urso (ursodiol) Tablets.

We also refer to the meeting between representatives of your firm and FDA on September 25, 1996. The following represents our summary of the meeting.

MEMORANDUM OF MEETING

Meeting Date:	September 25, 1996
Time:	9AM - 10AM
Location:	Conference Room, 6B-45
Application:	NDA 20-675, Urso (ursodiol) Tablets
External Meeting Requestor:	Axcan Pharma U.S., Inc.
Type of Meeting:	Discussion of Axcan's presentation and background package for the November 5, 1996 meeting of the Gastrointestinal Drugs Advisory Committee
Meeting Chair:	Stephen Fredd, M.D.
Meeting Recorder:	Brian Strongin, CSO

FDA Attendees, Titles and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Stephen Fredd, M.D.	Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical Officer
Brian Strongin	Consumer Safety Officer

External Constituent Attendees and Titles:

Axcan Pharma U.S., Inc.

Patrick Colin	Director of Clinical Research
Quyen Vinh	Director, Regulatory Affairs

Background:

NDA 20-675 was submitted March 26, 1996 for Urso (ursodiol) Tablets for the treatment of all stages of primary biliary cirrhosis (PBC) and is pending. This application will be discussed at the November 5, 1996 meeting of the Gastrointestinal Drugs Advisory Committee.

Objectives:

1. review the proposed agenda for Axcan's presentation at the Advisory Committee meeting

2. review the list of medical questions from the Division to the Committee

3. define a timeline for the submission of the background package

Discussion Points:

1. Discussion of the proposed agenda (attached) for the firm's presentation at the Advisory Committee meeting

   In response to the firm's proposed agenda, Drs. Fredd and Gallo-Torres provided the following comments:

   A. If desired, include an overview of PBC and a discussion of current therapy in the background package and limit the presentation of these issues at the meeting.

   B. Dr. Hofmann's discussion should focus on the human pharmacology of ursodiol and rather than the mechanism of action of ursodiol in PBC since that has not been clearly defined.

   C. Dr. Lindor should be given adequate time for a complete discussion of the Mayo Study including study design, endpoints, statistical analysis methods, and

results from both the blinded and open-label phases.

D. Dr. Heathcote may need at least 15 minutes for a complete discussion of her study.

F. Allow at least 15 - 20 minutes for a discussion of the overall safety of ursodiol including a discussion of the risk of breast cancer. Safety data from the pivotal and supportive studies, including the Poupon Study, should be discussed.

G. Concentrate on presenting the efficacy and safety data as submitted in the NDA.

H. If desired, a discussion of the meta-analysis of the Mayo, Heathcote, and Poupon Studies may be included in the background package, but need not be discussed at the meeting.

I. The Mayo Study is the sole pivotal study, with support provided by the Heathcote and Poupon Studies. If the proposed market image is identical to the formulation used in the Mayo Study, demonstrating bioequivalence between the Mayo Study formulation and the formulations used in the Heathcote and Poupon Studies will be unnecessary. Dr. Fredd recommended not addressing bioequivalence of the clinical trial formulations in the background package since the Committee members will probably not focus on it

J. Slides used during the firm's presentation should be numbered to facilitate referring to them. A list of slides used in the presentation may be submitted to the NDA, and copies added to the background package.

2. The Division will send the firm the list of questions to the Committee approximately one week prior to the meeting.

3. A draft background package should be sent to the Division for comment by October 7, 1996. The package must be finalized and sent to Committee members by October 21, 1996. The Division will send copies of the medical and statistical reviews to the firm in early October.

MEMORANDUM OF TELECON

DATE: December 17, 1996

APPLICATION NUMBER: 20-675; Urso (ursodiol) Tablets

BETWEEN:

Name: Ms. Quyen Vinh — Director, Regulatory Affairs
Phone: (514) 856-7849
Representing: Axcan Pharma, Incorporated

AND

Name: Eric Duffy, Ph.D. — Team Leader, Chemistry
Mike Adams — Review Chemist
Brian Strongin — Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Suggested Content of the Planned CMC Amendment Describing [redacted] by [redacted]

Background

NDA 20-675 was submitted March 22, 1996 for Urso (ursodiol) Tablets for the treatment of all stages of primary biliary cirrhosis. On December 9, 1996 the Agency was informed via a fax from the firm that [redacted] (the drug product manufacturer for most of the clinical trials and validation batches) would not extend their manufacturing agreement with Axcan beyond December 31, 1996. The fax also identified [redacted] as the proposed new drug product manufacturer. In a December 10, 1996 teleconference the Agency told the firm that the validation batches manufactured by [redacted] must be [redacted] if they are to be marketed. The firm stated that they intended to explore the possibility of [redacted]. The firm requested this teleconference to receive Agency guidance regarding the content of the planned CMC amendment describing the [redacted]

Today's Call

The Agency recommended including the following information in the CMC amendment describing the imprinting process:

1. the name of a contact person and the address of the imprinting facility at [redacted]
2. an assurance that the [redacted] will not rub off
3. a description of the composition of the [redacted]

4. amended labeling with the HOW SUPPLIED section of the package insert corresponding to the text of the [redacted]

5. a specification and release test from [redacted] requiring a physical inspection of the tablets for correctness of the [redacted]

The firm agreed to include these in the planned amendment. The call was then concluded.

[redacted]

Brian Strongin
Regulatory Health Project Manager

cc: Original 20-675
HFD-180/Div. File
HFD-180/Brian Strongi[redacted]APPEARS THIS WAY ON ORIGINAL
HFD-180/E.Duffy
HFD-180/M.Adams
drafted: BS/February 7, 1997
r/d init: MA/February 7, 1997
EPD/November 3, 1997
final: BS/November 4, 1997

TELECON

MEMORANDUM OF TELECON

DATE: October 27, 1997

APPLICATION NUMBER: NDA 20-675; Urso (ursodiol) Tablets

BETWEEN:

Name: Quyen Vinh
Phone: (612) 417-0684
Representing: Axcan Pharma U.S. Inc.

AND

Name:	Eric Duffy, Ph.D.	Team Leader, CMC
	Mike Adams	Review Chemist
	Brian Strongin	Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: CMC Information Request/Comments

Background

NDA 20-675 was submitted March 22, 1996 for the treatment of all stages of primary biliary cirrhosis. The application was approvable March 24, 1997 pending an acceptable response to CMC questions and final printed labeling identical in content to that attached to the action letter. The firm submitted a complete response June 27, 1997 and the user fee due date is December 31, 1997. Review chemist, Mike Adams, and CMC team leader, Eric Duffy, Ph.D., requested a response to several questions/comments prior to completion of the review. The questions were faxed to the firm prior to the teleconference and are attached.

Today's Call

Dr. Duffy opened by explaining that the CMC questions/comments should be addressed prior to the next action. He asked the firm to submit a response, including an acknowledgment of the comments, as soon as possible. The firm stated that they intend to respond to the questions/comments, as well as submit final printed labeling, within 1½ to 2 weeks. The call was then concluded.

/S/ [redacted]

Brian Strongin
Regulatory Health Project Manager

Strongin

MEMORANDUM OF TELECON

DATE: August 21, 1997

APPLICATION NUMBER: NDA 20-675; Urso (ursodiol) 250 mg Tablets

BETWEEN:

Name: Ms. Quyen H. Vinh
Phone: (514) 856-7849
Representing: Axcan Pharma Inc.

AND

Name: Maria R. Walsh, M.S.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Revisions to Approvable Draft Labeling

BACKGROUND: Ms. Vinh sent a facsimile dated August 21, 1997 describing several revisions to the labeling which was approvable on March 24, 1997 (see attached facsimile). She wishes confirmation that the proposed revisions are acceptable before they are incorporated into final printed labeling (FPL) to be submitted to the NDA. Dr. Gallo-Torres reviewed the revisions and they are acceptable.

TODAY'S CALL: I called Ms. Vinh and relayed to her that the proposed revisions are acceptable. I asked that she submit the information contained in the August 21, 1997 facsimile to the NDA. She agreed to do so and the call was then concluded.

/S/ [redacted] 8/21/97

Maria R. Walsh, M.S.
Regulatory Project Manager

Attachment [redacted] APPEARS THIS WAY ON ORIGINAL

cc: Original NDA 20-675
HFD-180/Div. File
HFD-180/B.Strongin
HFD-180/L.Talarico
H.Gallo-Torres

final: M.Walsh 8/21/97
filename: 20675708.tel

TELECON

NDA 20-675

Axcan Pharma U.S., Inc.
Attention: Leon Gosselin
3940 Quebec Avenue North
Minneapolis, MN 55427

JUL 6 1997

Dear Mr. Gosselin:

We acknowledge receipt on June 30, 1997 of your June 27, 1997 amendment to your new drug application (NDA) for Urso (ursodiol) Tablets.

This amendment contains additional chemistry, manufacturing, and controls information and labeling submitted in response to our March 24, 1997 approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is December 30, 1997.

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

Sincerely yours,

/S/ [redacted] 7-15-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMO
To: NDA 20-675
From: Brian Strongin
Date: 6/12/97

June 11, 1997

Mr. Brian Strongin
Project Manager
FOOD AND DRUG ADMINISTRATION
Division of GastroIntestinal and Drug Coagulation products
Document Control room **6B-24**
5600 Fishers Lane
Rockville, MD 20857

AXCAN PHARMA U.S. INC.
3940 Quebec Avenue North
Minneapolis, MN 55427 USA
Tel.: (612) 417-0684
Fax: (612) 417-9039
Toll free: 1-800-742-6706
Fax: (301) 443-9285

RE: URSO® (ursodiol) Tablets 250 mg , NDA # 20-675
Clarification: Additional information, Biopharmaceutics

Dear Mr. Strongin:

As per our conversation we would like to confirm that the document sent to Dr. Gallo-Torres " ***Bioavailability of Ursodeoxycholic acid"*** last month, is the update of the study done by [redacted] in 1991 and submitted as follows:

- the protocol was filed on August 12, 1996, clinical amendment no. 10
- additional information was filed on September 18, clinical amendment no.12;
- and on September 27, 1996.

copies of the covering letters attached (Att .# 1- 3 p)

The May 1997 edition includes *The statistical analysis* with additional sections from page 3 to 12, with Details on the cross-over analysis (par. 5.1);Serum results (par. 6- 6.1-6.2-6.3); Dose proportionality (par. 7); Intra-participant variability (par.8); and tables (par. 10). A copy of [redacted] letter to Axcan Pharma Inc dated May 1, 1997 is attached (Att. # 2-2p) for your information and files.

For further information, please call us at **Phone** (514) 856-7849, **Fax** (514) 669-5161. Thank you.

Truly yours,

Quyen H. Vinh (Mrs.), M.Sc., Phm.
Director, Regulatory Affairs

att.

[redacted]

150

AXCAN PHARMA

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

March 3, 1997

Mr. Brian Strongin
Project Manager
Food and Drug Administration
Division of Gastrointestinal and Drug Coagulation Products
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

FAX: 301-443-9285

Re: URSO® (Ursodiol) Tablets 250 mg, NDA #20-675
Notification: Addition of a Distributor: [redacted]

Dear Mr. Strongin:

As per our recent conversation, we would like to notify the FDA of an addition to the NDA 20-675 filed in March 1996: [redacted], a newly created joint venture, will promote and distribute URSO® tablets once approved, as per Mr. L. F. Gosselin's letter dated March 3, 1997, a copy of which is attached; all labelling material will be amended accordingly.

Axcan Pharma U.S. Inc., Plattsburgh, N.Y., continues to remain the Sponsor of NDA 20-675 and maintain all regulatory liaison with the FDA.

For further information, please contact us by phone at 514-856-7849 or by fax at 514-669-5161.

Sincerely,

Quyen H. Vinh (Mrs.), M. Sc. Phm.
Director, Regulatory Affairs

QHV/sam

attch. (1)

[redacted]

March 3, 1997

AXCAN PHARMA

AXCAN PHARMA U.S. INC.
25-27 Margaret Street
Plattsburgh, N.Y. 12901
USA
Tel.: (518) 563-7354
Fax: (518) 563-3359
Toll free: 1-800-742-6726

Mr. Brian Strongin, Project Manager
Food and Drug Administration
Div. of GI and Coagulation Drug Products
Document Control Room 68-24
5800 Fishers Lane
Rockville MD 20857
USA (**Fax: 301-443-9285**)

RE: URSO™ (Ursodiol) Tablets 250 mg NDA 20-675:
Additional Information: New Distributor, Joint Venture

Dear Mr. Strongin:

We would like to inform you that URSO™ tablets, once approved, will be distributed and promoted in the United States by [redacted] Attached for your file is a copy of the Certificate of Formation of the [redacted] company.

The NDA will continue to remain the property of Axcan Pharma U.S. Inc., Plattsburgh, NY. [redacted] will entrust the physical distribution to [redacted]

All labelling and documentation pertaining to the distribution of URSO™ tablets in the U.S. will contain the following to reflect the above physical distribution arrangement:

[redacted]

We will amend the NDA 20-675 accordingly to reflect such changes. For any further information, please contact Mrs. Quyen Vinh, Director, Regulatory Affairs, by phone at (514) 856-7849 or by fax at (514) 669-5161.

Sincerely,

Léon F. Gosselin, B.Sc., M.B.A.
President

Encl.

[redacted]

let - strongin - 03mar97 gosselin

[redacted]

CERTIFICATE OF FORMATION
OF
[redacted]

This Certificate of Formation is being executed as of January 15, 1997, for the purpose of forming a limited liability company pursuant to the [redacted] Limited Liability Company Act, 6 Del. C. §§18-101, et seq. (the "Act").

The undersigned, being duly authorized to execute and file this Certificate, do hereby certify as follows:

1. Name. The name of the limited liability company is [redacted] (the "Company").

2. Registered Office and Registered Agent. The Company's registered office in the State of [redacted] is located at [redacted]. The registered agent of the Company for service of process is [redacted] and the address of such registered agent is [redacted] County, [redacted].

3. Management. The business and affairs of the Company shall be managed by or under the direction of the Board of Managers.

BEST POSSIBLE COPY

[redacted]

IN WITNESS WHEREOF, the undersigned, being all the Members of the Company, have duly executed this Certificate of Formation as of the day and year first above written.

[redacted] as a Member

By: [signature]
Title: President and CEO

[redacted]

Title:

By: [redacted]
VP Corporate Development

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

[signature]

Strongin

MEMORANDUM OF MEETING

Meeting Date:	September 25, 1996
Time:	9AM - 10AM
Location:	Conference Room, 6B-45
Application:	NDA 20-675, Urso (ursodiol) Tablets
External Meeting Requestor:	Axcan Pharma U.S., Inc.
Type of Meeting:	Discussion of Axcan's presentation and background package for the November 5, 1996 meeting of the Gastrointestinal Drugs Advisory Committee
Meeting Chair:	Stephen Fredd, M.D.
Meeting Recorder:	Brian Strongin, CSO

FDA Attendees, Titles and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Stephen Fredd, M.D.	Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical Officer
Brian Strongin	Consumer Safety Officer

External Constituent Attendees and Titles:

Axcan Pharma U.S., Inc.

Patrick Colin	Director of Clinical Research
Quyen Vinh	Director, Regulatory Affairs

Background:

NDA 20-675 was submitted March 26, 1996 for Urso (ursodiol) Tablets for the treatment of all stages of primary biliary cirrhosis (PBC) and is pending. This application will be discussed at the November 5, 1996 meeting of the Gastrointestinal Drugs Advisory Committee.

Objectives:

1. review the proposed agenda for Axcan's presentation at the Advisory Committee meeting

2. review the list of medical questions from the Division to the Committee

3. define a timeline for the submission of the background package

Discussion Points:

1. Discussion of the proposed agenda (attached) for the firm's presentation at the Advisory Committee meeting

   In response to the firm's proposed agenda, Drs. Fredd and Gallo-Torres provided the following comments:

   A. If desired, include an overview of PBC and a discussion of current therapy in the background package and limit the presentation of these issues at the meeting.

   B. Dr. Hofmann's discussion should focus on the human pharmacology of ursodiol and rather than the mechanism of action of ursodiol in PBC since that has not been clearly defined.

   C. Dr. Lindor should be given adequate time for a complete discussion of the Mayo Study including study design, endpoints, statistical analysis methods, and results from both the blinded and open-label phases.

   D. Dr. Heathcote may need at least 15 minutes for a complete discussion of her study.

   F. Allow at least 15 - 20 minutes for a discussion of the overall safety of ursodiol including a discussion of the risk of breast cancer. Safety data from the pivotal and supportive studies, including the Poupon Study, should be discussed.

   G. Concentrate on presenting the efficacy and safety data as submitted in the NDA.

   H. If desired, a discussion of the meta-analysis of the Mayo, Heathcote, and Poupon Studies may be included in the background package, but need not be discussed at the meeting.

   I. The Mayo Study is the sole pivotal study, with support provided by the Heathcote and Poupon Studies. If the proposed market image is identical to the formulation used in the Mayo Study, demonstrating bioequivalence between the Mayo Study

formulation and the formulations used in the Heathcote and Poupon Studies will be unnecessary. Dr. Fredd recommended not addressing bioequivalence of the clinical trial formulations in the background package since the Committee members will probably not focus on it

J. Slides used during the firm's presentation should be numbered to facilitate referring to them. A list of slides used in the presentation may be submitted to the NDA, and copies added to the background package.

2. The Division will send the firm the list of questions to the Committee approximately one week prior to the meeting.

3. A draft background package should be sent to the Division for comment by October 7, 1996. The package must be finalized and sent to Committee members by October 21, 1996. The Division will send copies of the medical and statistical reviews to the firm in early October.

Minutes Prepar /S/ [redacted]

Chair Concurrence: /S/ [redacted] 10/24/96

ATTACHMENT (the firm's proposed agenda)

APPEARS THIS WAY ON ORIGINAL

cc:
NDA 20-675
HFD-180/Div. File
HFD-180/Minutes File
HFD-180/CSO/B.Strongin
HFD-180/H.Gallo-Torres
drafted: BS/October 18, 1996/c:\wpfiles\minutes\20675610.0
r/d init: M.Walsh/October 22, 1996
S.Fredd/October 24, 1996
final: BS/October 24, 1996

MEETING MINUTES

Urso
Strongin

NDA 20-675

SEP 25 1996

Leon Gosselin
Attention: Axcan Pharma U.S., Inc.
25 - 27 Margaret Street
Plattsburgh, N.Y. 12901

Dear Mr. Gosselin:

Please refer to your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Urso (ursodiol) Tablets.

We have completed the medical review of this application and are enclosing a copy in this letter. This information may assist you in your preparation for the Advisory Committee meeting scheduled for November 5, 1996.

Should you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
Telephone: (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

enclosed documents:
Medical Officer's Review 9/19/96

NDA 20-675

MAY 31 1996

Axcan Pharma, U.S. Inc.
Attention: Leon Gosselin
25-27 Margaret Street
Plattsburgh, N.Y. 12901

Dear Mr. Gosselin:

Please refer to your pending March 22, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Urso (ursodiol) Tablets 250 mg.

To continue our review of the Statistical section of your submission, we request the following:

1. Patients in the Mayo Study were randomized within strata, but only one randomized scheme was included in the submission. Clarify whether one scheme was used for all strata or a separate scheme was used for each. If a separate scheme was used for each strata, submit the schemes.

2. Provide results by center for all efficacy endpoints.

3. Explain the discrepancy between the number of treatment failures in Table 1, volume 1.39, page 39.007 and Table 2, volume 1.39, page 39.008. Clarify how the numbers in Table 2 were derived from Table 1.

4. Clarify if a statistical analysis of the values in Table 1-20, volume 1.35 was performed. If so, provide the analysis.

5. If possible, provide a copy of the SAS programs for the time-to-treatment failure and incidence of death or transplantation analyses as well as the analysis of at least one of the other efficacy endpoints.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Brian Strongin
Consumer Safety Officer
(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

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