

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21252

CORRESPONDENCE



NDA 21-252

INFORMATION REQUEST LETTER

Axcan Scandipharm Inc.
Attention: Anne M. Tomalin
U.S. Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

Dear Ms. Tomalin:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Canasa (mesalamine) Suppositories.

Please provide a written commitment to conduct the following study, post-approval: a clinical efficacy trial in pediatric patients with ulcerative proctitis, aged 12 to 18 years. This study should be of similar design and execution (e.g., randomized, double-blind, placebo-controlled) as the pivotal studies submitted in support of the adult efficacy claim.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



AXCAN SCANDIPHARM INC

22 Inverness Center Parkway
Birmingham Alabama 35242
USA

Tel (205) 991-8085
Fax (205) 991-9547

www.axcanscandipharm.com

December 28, 2000

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

Dear Ms. DuBeau:

Further to your letter of December 28, 2000, regarding our new drug application NDA 21-252, we commit to conduct the following study post-approval:

A clinical efficacy trial in pediatric patients with ulcerative proctitis, aged 12 to 18 years. This study will be of similar design and execution (e.g., randomized, double-blind, placebo-controlled) as the pivotal studies submitted in support of the adult efficacy claim.

We further commit to conduct this study within a 2-year time from the date of approval of CANASA.

Should you have any questions regarding this request, please contact me at (450) 467-5138.

Yours sincerely,

Leon Gosselin
Chief Executive Officer

NDA 21-252

DISCIPLINE REVIEW LETTER

Axcan Scandipharm Inc.
Attention: Anne M. Tomalin
U.S. Regulatory Affairs
22 Inverness parkway
Birmingham, AL 35242

OCT 13

Dear Ms. Tomalin:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FIV-ASA (mesalamine) Suppositories.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Drug Master Files (DMFs):

The following DMFs, submitted in support of your application, have been reviewed and found deficient:

- a. DMF
- b. DMF
- c. DMF

The deficiencies have been conveyed to each DMF holder in writing.

2. Drug Product:

- a. Please include the Certificates of Analysis for the reference standards obtained from
- b. The regulatory specification provided for the dissolution test seems too broad. Please tighten dissolution specifications based on your submitted data.
- c. Include the particle size specification in the mesalamine USP raw material acceptance specifications.
- d. Please add an IR identity test in addition to the identity test.
- e. Establish microbial limits as part of the drug product specifications. Alternatively,

provide scientific justification that the drug product is incapable of supporting microbial growth.

3. Container Closure:

Please provide to the NDA or to the DMF the characteristics of the Red Pantone 186C ink used to print the name Salofalk® 500mg on the side of the Rotoplast. Please include any test done to ensure that there is no migration of the ink to the drug product.

4. Stability:

The storage statement should follow the recommendations of USP 24.

Labeling comments will be provided at a later date.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

10/13/00

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug
Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

INFORMATION REQUEST LETTER

Axcan Scandipharm Inc.
Attention: Anne M. Tomalin
U.S. Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

SEP 12 2000

Dear Ms. Tomalin:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FIV-ASA® (mesalamine) Suppositories.

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please submit the following information related to the analysis of 5-ASA and N-acetyl-5-ASA in biological samples:
 - a. The validation data demonstrating long term stability of 5-ASA and N-acetyl-5-ASA in urine samples (i.e., stability of these moieties in urine samples for the period of storage prior to analysis); and
 - b. A description of and the validation data for the method of analysis of 5-ASA and N-acetyl-5-ASA in rectal tissue samples.
2. Please conduct dissolution testing of FIV-ASA® 500 mg suppositories using the USP Apparatus 2 (paddle) operated at speeds of 50 rpm and 75 rpm in a phosphate buffer (pH = 7.5, volume = 900 mL) maintained at 37°C. For each dose unit tested at each paddle speed, please provide tabulated dissolution data and a plot of the dissolution profile. Based on the results of the dissolution tests conducted, please propose the Drug Product Dissolution Method and Specification for our consideration.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

IS/ 9/12/00
J

IS/ 9/11/00

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Mencil

NDA 21-252

Axcan Scandipharm Inc.
Attention: Anne M. Tomalin
U.S. Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

SEP 8

Dear Ms. Tomalin:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for FIV-ASA (mesalamine) Suppositories.

You were notified in our letter dated August 29, 2000, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of August 31, 2000.

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 October 30, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 28, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies

submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, 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. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

JS/ 9-8-00 JS/ 9/8/00

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

NDA 21-252

AUG 29 2000

Axcan Scandipharm Inc.
Attention: Anne M. Tomalin
U.S. Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

Dear Ms. Tomalin:

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: FIV-ASA (mesalamine) Suppositories

Date of Application: June 29, 2000

Date of Receipt: July 3, 2000

Our Reference Number: NDA 21-252

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

The receipt date for this submission (which begins the review for fileability) will be the date the

review division is notified that payment was received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

IS/ 8-30-00 IS/ 8/29/00

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

cc:

Archival NDA 21-252
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-005/User Fee Staff
DISTRICT OFFICE

Drafted by: mm/August 29, 2000

Final: August 29, 2000

filename: c:\mydocuments\cso\n\21252008.DOC

UNACCEPTABLE FOR FILING (UN)

NDA 21-252

Axon Scandipharm Inc.
Attention: Anne M. Tomalin
U.S. Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

JUL 26 2000

Dear Ms. Tomalin:

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: FIV-ASA (mesalamine) Suppositories

Therapeutic Classification: Priority (P)

Date of Application: June 29, 2000

Date of Receipt: July 3, 2000

Our Reference Number: NDA 21-252

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 September 1, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 3, 2001.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

/S/ 7/26/00

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 21-252
HFD-180/Div. Files
HFD-180/M.McNeil
DISTRICT OFFICE

ACKNOWLEDGEMENT (AC)

NDA 21-252

Axcan Scandipharm Inc.
Attention: Anne M. Tomalin
President, CanReg Inc.
22 Inverness Parkway
Birmingham, AL 35242

Dear Ms. Tomalin:

MAY 11 2000

We have received your pre-submission of chemistry, manufacturing, & controls information for the following:

Name of Drug Product: FIV-ASA (mesalamine) Suppositories

Date of Application: April 28, 2000

Date of Receipt: May 2, 2000

Our Reference Number: NDA 21-252

We will review this early submission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all additional pre-submissions as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: CENTRAL DOCUMENT ROOM
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

If you have any questions, call me at (301) 827-7310.

Sincerely,

/S/ 5/11/00

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



Axcan Pharma-U.S., Inc.
c/o CanReg Inc.
Attention: Anne M. Tomalin
Regulatory Officer
Greater Hamilton Technology Enterprise Centre
7 Innovation Drive
Flamborough, Ontario L9H 7H9

MAR 22 2000

Dear Ms. Tomalin:

Please refer to the meeting between representatives of your firm and FDA on February 24, 2000. The purpose of the meeting was to follow-up the December 16, 1999 pre-NDA meeting.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely yours,

/S/

Helen Wilson
Consumer Safety Technician
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

U

JAN 14 2000

Axcan Pharma U.S. Inc.
c/o CanReg Inc.
Attention: Anne M. Tomalin
Regulatory Officer
Greater Hamilton Technology Enterprise Centre
7 Innovation Drive
Flamborough, Ontario L9H 7H9

Dear Ms. Tomalin:

Please refer to the meeting between representatives of Axcan Pharma U.S. Inc. and FDA on December 16, 1999. The purpose of the meeting was to discuss whether available data held by Axcan are sufficient to submit an NDA for Mesalamine 500 mg Suppositories in the treatment of active ulcerative colitis, and if not, what additional data are required.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/S/ 1/14/00

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:

Original

HFD-180/M.McNeil

Drafted by: mm/January 14, 2000

final: January 14, 2000

filename: c:\mydocuments\cso\axcan-gc.doc

GENERAL CORRESPONDENCE (MINUTES SENT)