

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21252

ADMINISTRATIVE DOCUMENTS



Axcán Scandipharm Inc.

FIV-ASA (mesalamine) Suppositories, 500 mg
Original New Drug Application
June 28, 2000

NDA 21-252

SECTION 11: PATENT CERTIFICATION

Under 21 CFR 314.50 (i)(1)(ii), in the opinion and to the best knowledge of Axcán Scandipharm Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Francois Martin, M. D.
Vice President, Scientific Affairs

20.06.2000

Date

YES /___/ NO /_X_/

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

e) Has pediatric exclusivity been granted for this Active
Moiety?

YES /___/ NO /_X_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO
DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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? (Rx to OTC)
Switches should be answered No - Please indicate as such).

YES /___/ NO /___/

If yes, NDA # 19-919 Drug Name Rowasa mesalamine)Suppositories

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE
SIGNATURE BLOCKS ON Page 9.**

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

YES /___/ NO /___/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE
SIGNATURE BLOCKS ON Page 9 (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 /___/ NO /___/

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

NDA # _____
NDA # _____
NDA # _____

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 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /___/ 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 9:**

- (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 /___/ 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 /___/

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 / /

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, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 / /

Investigation #2 YES / / NO / /

Investigation #3 YES / / NO / /

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 /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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 # __, Study # _____

Investigation # __, Study # _____

Investigation # __, Study # _____

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 # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(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 _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (-) 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 /___/

If yes, explain: _____

Signature of Preparer
Title: _____

Date

Signature of Office of Division Director

Date

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00



AXCAN SCANDIPHARM INC

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On behalf of Axcan Scandipharm Inc., I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA FIV-ASA.

Jean Spénard

Dr. Jean Spénard
Associate-Director, Clinical Research

June 14, 2000

Date

MEMORANDUM OF TELECON

DATE: January 4, 2001

APPLICATION NUMBER: NDA 21-252, Canasa (mesalamine) Suppositories

BETWEEN: —

Name: Anne Tomalin, Regulatory Affairs Consultant
Phone: (905) 689-3980 x 221
Representing: Axcan Scandipharm Inc.

AND

Name: Melodi McNeil, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Marked Up Draft Labeling

BACKGROUND: NDA 21-252 was submitted June 29, 2000 by Axcan Scandipharm Inc. and seeks marketing approval for Canasa (mesalamine) Suppositories in the treatment of active ulcerative proctitis. The user fee goal date is February 28, 2001.

The firm's proposed labeling was revised by the Division, based on the various discipline review recommendations, and faxed to the applicant's representative on December 22, 2000. The firm responded to this fax with a December 29, 2000 submission containing revised draft labeling. Following a January 3, 2001 labeling teleconference with representatives of Axcan, the labeling was further revised and faxed to the firm on January 4, 2001. Note: The marked up draft labeling (package insert and patient package insert) that was faxed to the firm on January 4, 2001 is provided as an attachment. The background text is the firm's proposed labeling; FDA deletions are represented by a strikethrough, and FDA additions are represented by an underline.

(Note: The immediate container and carton labeling was also discussed during the January 3, 2001 labeling teleconference with Axcan. In addition to the revisions requested in the December 22, 2000 fax, the firm also agreed to add "Do not refrigerate" to the suppository labeling.)

TODAY'S PHONE CALL: I informed Ms. Tomalin that the FDA revised labeling had just been faxed. The call was then concluded.

Melodi McNeil
Regulatory Health Project Manager

MEMORANDUM OF TELECON

DATE: December 22, 2000

APPLICATION NUMBER: NDA 21-252, Canasa (mesalamine) Suppositories

BETWEEN:

Name: Anne Tomalin, Regulatory Affairs Consultant
Phone: (905) 689-3980 x 221
Representing: Axcan Scandipharm Inc.

AND

Name: Melodi McNeil, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Marked Up Draft Labeling

BACKGROUND: NDA 21-252 was submitted June 29, 2000 by Axcan Scandipharm Inc. and seeks marketing approval for Canasa (mesalamine) Suppositories in the treatment of active ulcerative proctitis. The Division plans to take an action on January 3, 2001.

The firm's proposed labeling was revised by the Division, based on the various discipline review recommendations, and faxed to the applicant's representative. Note: The marked up draft labeling that was faxed to the firm is provided as an attachment. The background text is the firm's proposed labeling; FDA deletions are represented by a strikethrough, and FDA additions are represented by an underline.

TODAY'S PHONE CALL: I informed Ms. Tomalin that the FDA revised labeling had just been faxed. I asked her to provide a response as quickly as possible (in the form of revised draft labeling), given the Division's rapidly approaching action goal date. The call was then concluded.

Melodi McNeil
Regulatory Health Project Manager

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE: July 24, 2000
TIME: 3:30-4:30 PM
LOCATION: Room 6B-45 (PKLN)
APPLICATION: NDA 21-252; FIV-ASA (mesalamine) Suppositories
TYPE OF MEETING: Filing/Planning

MEETING CHAIR: Dr. L. Talarico, Division Director

MEETING RECORDER: Ms. M. McNeil, Regulatory Health Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

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

Dr. L. Talarico, Division Director
Dr. S. Aurecchia, Deputy Division Director
Dr. H. Gallo-Torres, Medical Team Leader
Dr. R. Joseph, Medical Officer
Dr. L. Zhou, Chemistry Team Leader
Ms. M. Ysem, Chemistry Reviewer
Dr. J. Choudary, Supervisory Pharmacologist
Dr. S. Chakder, Pharmacology Reviewer

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. S. Doddapaneni, Biopharmaceutics Team Leader
Dr. D. Udo, Biopharmaceutics Reviewer

Division of Biometrics (HFD-715)

Dr. T. Permutt, Acting Statistical Team Leader

Division of Scientific Investigations (HFD-46)

Dr. K. Malek, Investigator

BACKGROUND: NDA 21-252 was submitted June 29, 2000 by Axcan Scandipharm Inc. and seeks marketing approval for FIV-ASA (mesalamine) Suppositories in the treatment of active ulcerative proctitis. (Note: The applicant submitted a chemistry presubmission on April 28, 2000.) This is a 505(b)(2) application; the applicant is relying upon the Agency's previous finding of safety and efficacy following the review of NDA 19-919; Rowasa (mesalamine) Suppositories. Specifically, the applicant appears to neither own nor have right of reference to all of the data which will be required for approval.

(Note: In mid 1999 Solvay Pharmaceuticals Inc. voluntarily withdrew Rowasa Suppositories from the US market because some drug product lots failed dissolution testing. There are no other

approved mesalamine suppositories in the US. Given 1) the prospect of no mesalamine suppositories for an indefinite time period and 2) that the Division considers this product medically necessary, the Agency allowed Canada's Axcan Pharma [the parent company to Axcan Scandipharm Inc.], to export and distribute its non US-approved formulation of mesalamine 500 mg suppositories to the US Market. As part of the agreement, Axcan was encouraged to submit an NDA for its formulation of mesalamine suppositories. A pre-NDA meeting and follow up teleconference [minutes available] were held with the applicant on December 16, 1999 and February 24, 2000, respectively.)

The filing date for the application is September 1, 2000.

MEETING OBJECTIVES:

1. To determine whether the application is fileable
2. To identify the Division management lead for the application
3. To determine the review priority classification for the application
4. To establish review timelines
5. To identify any information requests

DISCUSSION POINTS:

1. Clinical:
 - a. Filing Issues: None
 - b. Information Requests: None
 - c. Misc: The clinical database in this NDA consists of the following:
 - i. Two double-blind, placebo-controlled multicenter trials (Protocols 300 and 330) in patients with ulcerative proctitis from the Rowasa NDA-Axcan does not own or have right of reference to these data, with the exception of the 27 patients described below.
 - ii. Twenty-seven patients from Protocol 300 (i.e., from the original Rowasa database), for which Axcan has access to source documents and raw data.
2. Chemistry, Manufacturing, and Controls:
 - a. Filing Issues: None

- b. **Information Requests:** At the reviewer's request, the firm will be asked to provide drug product stability data under stress conditions.
- c. **Misc:** The Division's chemistry representatives said the NDA should be designated chemical type 5 ("New Manufacturer").

3. **Preclinical Pharmacology:**

- a. **Filing Issues:** None
- b. **Information Requests:** None

4. **Biopharmaceutics:**

- a. **Filing Issues:** According to the Division's biopharmaceutics representatives, the applicant has not provided comparative bioavailability data between FIV-ASA and a reference (i.e. approved) mesalamine rectal product, as requested at the pre-NDA meeting. They said the lack of this information would constrain the ability to compare the relative safety profiles of FIV-ASA and Rowasa Suppositories. Further (in the absence of comparative bioavailability data), they questioned whether the firm had established a true 505(b)(2) linkage between their product and Rowasa Suppositories. The Biopharmaceutics representatives recommended against filing of the application for these reasons.

In response, the Division's clinical representatives, including Dr. Talarico, said that while no comparative bioavailability data were provided, the firm provided clinical data that may bridge FIV-ASA and Rowasa Suppositories. Specifically, the applicant states in the application that the required bridge is provided on the basis of clinical data. The adequacy of this approach is a review, not a filing issue. Ultimately, the clinical representatives did not agree with the recommendation against filing the application.

- b. **Information Request:** At the reviewer's request, the firm will be asked to provide the supportive data obtained in determining the final parameters used to select the dissolution method. In addition, the firm plans a four month safety update which will include (among other things) pharmacokinetic results of a bioavailability study of FIV-ASA suppositories in healthy volunteers. At the reviewer's request, we will request that the applicant provide the pharmacokinetic data as soon as they are available.

5. **Statistics:** A statistical reviewer has not yet been assigned to this project. The statistical representative present for today's meeting did not identify any filing issues or information requests.

6. **Administrative:**

- a. **Filing Issues:** None

b. Information Requests:

- i. The firm has already been asked to provide an English translation of any foreign labeling.
- ii. The firm has already been asked to provide color computer mock-ups of the immediate container and carton labeling.

c. Misc:

- i. Given the current lack of an approved, commercially available mesalamine suppository, Dr. Talarico said this application would be designated for priority review. Accordingly, the user fee goal date is January 3, 2001.
- ii. To meet the user fee goal date, the review team agreed that all reviews should be finalized by December 4, 2000.
- iii. The draft labeling (which includes a patient package insert) was consulted to DDMAC on July 20, 2000.
- iv. The proposed tradename ("FIV-ASA") was consulted to OPDRA on July 20, 2000.
- v. Dr. Talarico will be the Division's management lead for this application.

CONCLUSIONS: The application will be filed, and all identified information requests will be conveyed to the applicant.

Minutes Preparer: JS/ 8/2/00

Chair Concurrence: JS/ ME 8-7-00

cc: Original

HFD-180/Div. Files

HFD-180/Meeting Minutes files

HFD-180/McNeil

HFD-180/Talarico

HFD-180/Aurecchia

HFD-180/Gallo-Torres

HFD-180/R. Joseph

HFD-180/Zhou

MEMORANDUM OF MEETING MINUTES

Meeting Date: February 24, 2000

Time: 1:15-2 PM

Location: Room 6B-45 (PKLN)

Application: N/A; Mesalamine Suppositories

Type of Meeting: Follow-Up to December 16, 1999 pre-NDA meeting (Today's meeting was conducted via teleconference)

Meeting Chair: Dr. Lilia Talarico, Division Director

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

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

Dr. Lilia Talarico, Division Director

Dr. Steven Aurecchia, Deputy Division Director

Dr. Hugo Gallo-Torres, Medical Team Leader

Dr. Jasti Choudary, Pharmacology Team Leader

Dr. Liang Zhou, Chemistry Team Leader

Ms. Maria Ysern, Chemistry Reviewer

Ms. Melodi McNeil, Regulatory Health Project Manager

Office of Clinical Pharmacology and Biopharmaceutics (HFD-870)

Dr. Suliman Al-Fayoumi, Biopharmaceutics Reviewer

Mr. John Hunt, Deputy Director

External Constituent Attendees and titles:

Axcan Pharma Inc.

Dr. Francois Martin, Vice President, Scientific Affairs

Dr. Jean Spenard, Associate Director of Clinical Research

Dr. France Guay, Vice President, Operations

Ms. Anne Tomalin, CanReg Inc. (Regulatory Consultant to Axcan)

Dr. Diane Turkin, DTAssociates (Regulatory Consultant to Axcan)

Background: On December 16, 1999 a pre-NDA meeting was held between FDA and representatives of Axcan Pharma U.S. Inc. (minutes available). Axcan has notified the Agency of its intention to obtain a marketing application for mesalamine suppositories in the treatment of ulcerative proctitis.

In a February 2, 2000 submission, the firm requested a teleconference to clarify several outstanding issues from the December 1999 pre-NDA meeting.

Meeting Objectives: To clarify the firm's understanding of several outstanding items from the December 1999 pre-NDA meeting.

Discussion Points: The firm's February 17, 2000 pre-meeting submission contained a summary of their proposed NDA strategy. Specifically, they plan to submit a chemistry presubmission on (approximately) March 31, 2000, followed by the remainder of the NDA in approximately 60 days. The pre-meeting

document also contained several specific questions for the Agency to answer. These questions are reproduced below in regular type, followed by the Agency's answers in bold type.

1. Regarding our biopharmaceutic question 3 [See the December 16, 1999 meeting minutes], we are unsure if under a "505(b)(2) application-Referencing your finding of safety/efficacy for Rowasa Suppositories" we would be required to submit pharmacokinetic information with our suppository NDA, i.e., whether a pharmacokinetic study would be necessary. Would a therapeutic comparison using historical controls be sufficient to bridge from our suppository to Rowasa?

Agency Response: A therapeutic comparison using historical controls will not be sufficient.

For safety reasons, we need pharmacokinetic exposure data on the product proposed for marketing. Please conduct a pharmacokinetic study in the relevant patient population (patients with ulcerative proctitis, preferably those with active disease). The study should employ the dose and regimen proposed for marketing and assess drug levels in relevant biological fluids (blood, urine, and feces). Alternatively, you may choose to collect this information from a subset of patients in the clinical study (if it still ongoing). In response to a question, the firm said they would measure mesalamine metabolites levels as part of their pharmacokinetic assessment as well.

2. For the two animal rectal studies, is it sufficient to monitor rectal irritation only, or is a complete histopathology necessary?

Agency Response: Complete histopathology of all tissues is needed. In addition, we reiterate our recommendation from the December 1999 pre-NDA meeting that you also assess toxicokinetics.

(The firm also described an ongoing rabbit rectal toxicity study and said they were having difficulty getting the rabbits to retain the mesalamine suppositories. In response to a question from the firm, the Division's pharmacology representative said that if the rabbits expel the suppositories, the time of expulsion should be recorded, but the suppositories should not be reinserted.)

3. For the in vitro chromosomal aberration test in human lymphocytes, we are using 5-ASA, with and without metabolic activation. Can you confirm that this is appropriate?

Agency Response: These plans are appropriate.

4. We will be filing the CMC portion of our submission on March 31, 2000 (possibly March 29th), Will it suffice to state in the cover letter that the rest of the submission will follow within 60 days?

Agency Response: Your plans for a chemistry pre-submission are acceptable, provided that the entire chemistry, manufacturing, and controls (CMC) section (as defined in 21 CFR 314.50) is complete (including all manufacturing facilities being ready for inspection) at the time of submission.

5. If we file the rest of our submission in 60 days, i.e., by May 31, 2000, a 120 day safety period then follows. If all of the histopathology from the rectal toxicity study is not available on May 31, could we file the complete toxicology reports with the safety update?

Agency Response: This proposal is not acceptable. All histopathology from the rectal toxicity study should be submitted with the remainder of the NDA (i.e., the part of the NDA that is submitted 60 days after the chemistry presubmission).

6. Our review of the fee cover form leads us to believe that there is no fee for our FIV-ASA NDA because it is filed under Section 505(b)(2). A copy of the Fee Cover Form is attached. Also attached is an overview of what we intend to file. Can you confirm that no fee is required?

Agency Response: Based on the proposed NDA strategy provided in the February 17, 2000 pre-meeting package, no application fee will be required.

7. For the biopharmaceutics section of the NDA we are not intending to submit the dissolution data in March. We are submitting it in May. Please confirm that this is acceptable.

Agency Response: This proposal is not acceptable, given your plans to make a chemistry presubmission in March. Our expectation is that both the CMC and biopharmaceutics sections of the NDA will contain dissolution data. As indicated in our response to question four (above), a chemistry presubmission is acceptable only if it contains the complete chemistry, manufacturing, and controls section of the NDA. Please refer to ICH guidance Q1A for additional information.

8. We would like to review some of the specifics of the NDA submission, i.e.,
- a. Would we submit Section 3 (summary) for CMC?

Agency Response: This section should be included in the remainder of the NDA submission.

- b. How would we handle the other summaries, i.e., pharmacology, marketing, nonclinical, clinical and conclusion?

Agency Response: These summaries should be included in the remainder of the NDA submission. It is acceptable for you to reference individual studies reports as available.

- c. For the pharmacology and nonclinical summaries should we simply refer to your previous decision or should we provide a summary of the data?

Agency Response: Please provide a summary of available absorption, distribution, metabolism, and excretion data. In addition, please reference the individual study reports contained elsewhere in the NDA.

- d. Would a reference in the cover letter to the rest of the submission be sufficient?

Agency Response: The cover letter of the presubmission should provide the approximate date on which the remainder of the NDA will be submitted. The cover letter of the remainder of the NDA should reference the date of the chemistry presubmission.

e. Number of copies to be submitted? _____

Agency Response: Please refer to 21 CFR 314.50 as well as available administrative guidelines for this information.

Should we submit a package insert in March?

Agency Response: Labeling need not be included in the chemistry presubmission. Instead, please include it with the submission containing the remainder of the NDA.

Minutes Preparer: JS 3/15/00
Chair Concurrence: JS 3-16-00

cc: Original
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/McNeil
HFD-180/Talarico
HFD-180/Aurecchia
HFD-180/Gallo-Torres
HFD-180/Zhou
HFD-180/Ysern
HFD-180/Choudary
HFD-870/Hunt
HFD-870/Doddapaneni
HFD-870/Al-Fayoumi
HFD-604/Hare

Drafted by: mm/March 2, 2000/c:\mydocuments\cso\minutes\axcan-2-24-00-t-con.doc

Initialed by: HGallo-Torres 3/7/00

LTalarico 3/7/00

MYsern 3/7/00

JHunt 3/14/00

final: March 15, 2000

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 16, 1999
Time: 12:00-1:30 P.M.
Location: Chesapeake Conference Room (PKLN)
Application: N/A; Mesalamine Suppositories
Type of Meeting: Pre-NDA
Meeting Chair: Dr. Lilia Talarico, Division Director
Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

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

Dr. Lilia Talarico, Division Director
Dr. Steven Aurecchia, Deputy Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Robert Prizont, Medical Officer
Dr. Jasti Choudary, Pharmacology Team Leader
Dr. Liang Zhou, Acting Chemistry Team Leader
Dr. Marie Kowblansky, Chemistry Reviewer
Ms. Maria Ysem, Chemistry Reviewer
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of Biometrics (HFD-715)

Dr. Paul Flyer, Statistical Team Leader

Office of Clinical Pharmacology and Biopharmaceutics (HFD-870)

Dr. David Lee, Biopharmaceutics Team Leader
Dr. Suliman Al-Fayoumi, Biopharmaceutics Reviewer
Mr. John Hunt, Deputy Director

Office of Drug Evaluation III (HFD-103)

Dr. Victor Raczkowski, Deputy Director
Ms. Bronwyn Collier, Associate Director for Regulatory Affairs

Office of Generic Drugs (HFD-604)

Dr. Rabi Patnaik, Deputy Division Director (HFD-651)
Dr. Barbara Davit, Team Leader (HFD-658)
Mr. Don Hare, Special Assistant to the Director

External Constituent Attendees and titles:

Axcan Pharma Inc.

Dr. Francois Martin, Vice President, Scientific Affairs

Dr. Patrick Colin, Director of Clinical Research
Dr. Jean Spenard, Associate Director of Clinical Research
Dr. France Guay, Vice President, Operations
Ms. Anne Tomalin, CanReg Inc. (Regulatory Consultant to Axcan)
Dr. Diane Turkin, DTAssociates (Regulatory Consultant to Axcan)

Background: Rowasa (mesalamine) 500 mg Suppositories are currently approved under an NDA (sponsored by Solvay Pharmaceuticals, Inc.) for the treatment of active ulcerative proctitis. Rowasa Suppositories are the only mesalamine suppositories approved for marketing in the United States.

In mid 1999, Solvay voluntarily withdrew Rowasa suppositories from the US market because some drug product lots failed dissolution testing. (Note: The information in the previous sentence is publicly available on the Crohn's and Colitis Foundation of America's web page: <http://www.ccfa.org/news/previous/rowasa.htm>.) Given 1) the prospect of no mesalamine suppositories for an indefinite time period and 2) that the Division considers this product medically necessary, the Agency made an arrangement with Canada's Axcan Pharma, whereby that firm agreed to supply its non US-approved formulation of mesalamine 500 mg suppositories to the US Market. This arrangement is intended to be a temporary way of meeting the demand for mesalamine suppositories during the time the Solvay product is unavailable. As part of the agreement, Axcan was encouraged to submit an NDA for its formulation of mesalamine suppositories.

In an October 14, 1999 submission, Axcan Pharma U.S. Inc. requested a pre-NDA meeting with the Agency to discuss whether they have sufficient data to submit an NDA, and if not, what additional data are required.

Meeting Objectives: 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.

Discussion Points: The firm's December 1, 1999 pre-meeting submission contained several specific questions for the Agency to answer. These questions are reproduced below in regular type. The Division's responses follow in bold type.

Note: Based on information provided in the December 1, 1999 pre-meeting submission, Axcan Pharma U.S., Inc. has three options for submitting a marketing application for mesalamine 500 mg suppositories. These options are,

1. Submit an ANDA along with a copy of a Citizen's Petition requesting affirmation that the

innovator (Rowasa Suppositories) has not been discontinued from marketing for safety or efficacy reasons,

2. Submit an NDA in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act which references the Agency's finding of safety and effectiveness for Rowasa Suppositories (this option is available as long as there is no reference product on the market). This submission will be in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, if Axcan has not performed and/or does not have right of reference to all of the data contained in the application and required for approval, or

3. Submit a full NDA

This submission will be in accordance with section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, if Axcan has performed and/or does have right of reference to all of the data contained in the application and required for approval.

(Where applicable, the firm's questions were answered in the context of each of the three options described above.)

1. Does the FDA agree that Axcan has proven that the formulation that we would like to register and the formulation that is currently approved in the United States are the same?

Agency Response: Although both products appear to have very similar formulations, we cannot consider these formulations "the same" because (among other things) they are manufactured at different sites, with different personnel, different equipment, etc. Additional information is needed to demonstrate an acceptable link between the mesalamine suppositories manufactured by Axcan Pharma and those manufactured by Solvay, if any part of the data required for approval is derived from the Solvay product.

2. Does the FDA agree that the preclinical data that Axcan intends to submit will be sufficient to meet the requirements of an NDA?

Agency Response:

- a. 505(b)(1) or 505(b)(2) referencing Agency's finding of safety/effectiveness:
 - i) ICH S2B, July 1997 Guidance for Industry entitled "Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals" calls for a standard test battery of (i) a test for gene mutation, (ii) an in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in vitro mouse

lymphoma tk assay, and (iii) an in vivo test for chromosomal damage using rodent hematopoietic cells. Your listing of toxicology studies on page 62 of the pre-meeting submission does not contain item ii of the battery. We recommend conducting an in vitro chromosomal aberration test in human lymphocytes or an in vitro mouse lymphoma tk assay.

- ii) There are insufficient toxicity studies of the FIV-ASA suppositories by rectal administration. We recommend conducting 2-week rectal toxicity studies in dogs and rabbits with FIV-ASA suppositories. The studies should include at least three doses, and all standard toxicological parameters including toxicokinetics should be evaluated.
- iii) If you wish to apply for a maintenance indication for FIV-ASA suppositories at a future date, consider conducting a two-year mouse carcinogenicity study of 5-ASA.

b. ANDA/Citizen's Petition: No additional preclinical data are required.

3. Does the FDA agree that the kinetic information available to Axcan from the literature is sufficient to describe the release characteristics of the product?

Agency Response:

a. 505(b)(1):

- i) Additional data describing the bioavailability of the drug product are needed (following both single and multiple doses), as well as data characterizing the drug levels in blood, urine, and feces. This information may be collected in the proposed additional clinical study, if conducted. A renal and hepatic in vitro guidance document is available on CDER's web page.
- ii) Drug exposure information is also needed under multiple dosing conditions.
- iii) Please provide information on the drug's metabolism and protein binding. This information may be supplied from literature.
- iv) Also, please provide in vitro dissolution methodology, proposed specification, and information on the drug's disposition in the target population.

b. 505(b)(2):

It is necessary to show the same therapeutic effect of your product to that of Rowasa Suppositories. This may be done through a comparative bioavailability study with a clinical endpoint or in a single arm study (open label, measuring within-subject change from baseline) which is then compared to a relevant historical control. Note, if you choose to use a historical control, the historical control population should be comparable to the trial population in terms of (among other things) baseline characteristics and concomitant medications. (Some of the data described in point a, above, may also be required.)

c. ANDA/Citizen's Petition:

Since the reference listed drug is not available, an acceptable comparative bioavailability study against another marketed product must be completed. Since the effects of mesalamine are local, the study may need clinical endpoints. However, if the Solvay product returns to the market before your approval, you will be requested to show bioequivalence to the reference listed drug. (Agency representatives commented that mesalamine blood levels do not necessarily correlate with efficacy, but they may provide useful safety information. They also said an in vitro dissolution test is needed.)

4. It is Axcan's intention to file one full placebo-controlled study on 27 patients done with FIV ASA. The rest of the NDA would be a "paper NDA" as described under Section 505 of the Food, Drug and Cosmetics Act which states the following:

"(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted..."

Will the Division accept an NDA with one study conducted by the applicant, supported by the Canadian HPB's approval report of the product, which cites the studies that were conducted for its Canadian approval, and which Axcan cannot use outside of Canada.

Agency Response: This proposal is acceptable. Refer to the draft guideline entitled "Guidelines for the Clinical Evaluation of Drugs for Ulcerative Colitis (Third Draft)" for endpoint definition. This trial could also be supplemented with Canadian Post-Marketing safety data.

Does the FDA agree that the single study supported by a thorough literature review would be sufficient for an NDA?

Agency Response: This proposal is also acceptable for the efficacy portion of the NDA submission, provided the relevant literature are analyzed appropriately. Any regulatory decisions (e.g., filing, approvability) will depend on the strength and consistency of the data.

ANDA/Citizen's Petition: A comparative bioavailability trial with clinical endpoints will need to be included. Please see the response to question 3c for more information and contact the Office of Generic Drugs for additional details.

5. If a further clinical study is necessary, will a 6 week study in proctitis patients (final number to be calculated to achieve statistical significance) be sufficient. Admission would be based on a DAI score of 3 or more involving at least 2 of the 4 categories. The primary measurement of efficacy would be reduction activity from baseline measured by the DAI Score which involves:

Frequency of stools
Frequency of bleeding episodes
Sigmoidoscopic improvement
Physician overall rating

Agency Response:

- a. **505(b)(1):** Much of the proposed clinical database is with mesalamine suppositories administered tid. This study will be useful to support either a tid or a bid regimen. Refer to the draft guideline entitled "Guidelines for the Clinical Evaluation of Drugs for Ulcerative Colitis (Third Draft)" for endpoint definition. This trial could also be supplemented with Canadian Post-Marketing safety data.

- b. **505(b)(2):**

A further clinical study would not be needed in this instance, provided you met the requirements outlined in our response to question 3b.

- c. **ANDA/Citizen's Petition:**

This information would not be needed for an ANDA.

6. Will the Division exempt FTV ASA from needing to provide information on use of this product in a pediatric population?

Agency Response:

- a. **If you propose to market FIV-ASA for a bid dosing regimen, the Pediatric Rule does not apply.**
 - b. **If you propose to market FIV-ASA for a tid dosing regimen, the Pediatric Rule does apply. You may request a deferral or waiver of the requirement for pediatric data in the NDA, if submitted. Refer to 21 CFR 314.55 for additional information.**
7. **Given the current circumstances of no drug being available on the US market under an approved NDA, does the FDA agree that this NDA can have expedited review?**

Agency Response: Priority review status would be warranted in the absence of a marketed 5-ASA suppository. [In response to a question from the firm, Agency representatives commented that if Axcan submits a 505(b)(2) application and the innovator returns to the market while review of that application is pending, review of Axcan's 505(b)(2) application will not be stopped. They also noted that if approved, the Axcan product may be rated "therapeutically inequivalent" in the Orange book, since based on the information presented today, Axcan does not have any head to head data comparing their product with Rowasa Suppositories.]

Minutes Preparer: / S / 1/14/00
Chair Concurrence: / S / 1/14/00

cc: Original
HFD-180/McNeil (3 copies)
HFD-180/Talarico
HFD-180/Aurecchia
HFD-180/Gallo-Torres
HFD-180/ Prizont
HFD-180/Choudary
HFD-180/Zhou
HFD-180/Kowblansky
HFD-180/Ysem
HFD-715/Flyer
HFD-870/Hunt
HFD-870/Lee

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-252

JUL 26 2000

Name of Drug: FIV-ASA (mesalamine) Suppositories

Sponsor: Axcan Scandipharm Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Paper (with review aids)

Submission Date: June 29, 2000

Receipt Date: July 3, 2000

Filing Date: September 1, 2000

User-fee Goal Date(s):

Standard: May 3, 2001 (primary goal date)
July 3, 2001 (secondary goal date)

Priority: January 3, 2001

Proposed Indication: Treatment of active ulcerative proctitis

Other Background Information: In mid 1999 Solvay Pharmaceuticals Inc. voluntarily withdrew its approved mesalamine suppositories (marketed with the tradename "Rowasa") from the US market because some drug product lots failed dissolution testing. There are no other approved mesalamine suppositories in the US. Given 1) the prospect of no mesalamine suppositories for an indefinite time period and 2) that the Division considers this product medically necessary, the Agency made an arrangement with Canada's Axcan Pharma (the parent company to Axcan Scandipharm Inc.), whereby that firm agreed to supply its non US-approved formulation of mesalamine 500 mg suppositories to the US Market. As part of the agreement, Axcan was encouraged to submit an NDA for its formulation of mesalamine suppositories.

A pre-NDA meeting and follow up teleconference (minutes available) were held with the applicant on December 16, 1999 and February 24, 2000, respectively. NDA 21-252 consists of 21 archival volumes, as well as the appropriate technical volumes. The applicant appears to own/have right of reference to some (but not all) of the data in the NDA that will be required

for approval.

Note: The applicant submitted a chemistry presubmission on April 28, 2000.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper with original signature.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 2.01; no page number
2. Form FDA 356h	X		Volume 2.01; no page number
a. Reference to DMF(s) & Other Applications	X		Volume 2.01; no page number
3. Patent information & certification	X		Volume 2.21, page 002
4. Debarment certification (Note: Must have a definitive statement)	X		Volume 2.14, page 004
5. Financial Disclosure	X		Volume 2.21; page 003
6. Comprehensive Index	X		Volume 2.01; page 001
7. Pagination	X		Volume 2.01 contains several unpaginated documents
8. Summary Volume	X		Volume 2.01
9. Review Volumes	X		The applicant provided CMC, Preclinical Biopharmaceutics, Clinical and Statistical review volumes.
10. Labeling (PI, container, & carton			See below

labels)	X	(Tradename consulted to OPDRA 7/20/00)
a. unannotated PI	X	Volume 2.01; page 19-29 (Consulted to DDMAC 7/20/00)
b. annotated PI	X	Volume 2.01; page 45-58
c. immediate container	X	Volume 2.01; page 38
d. carton	X	Volume 2.01; page 34-47
e. foreign labeling (English translation)	X	(Requested from the firm; 7/21/00)
f. PPI	X	Volume 2.01; page 39-44 (Consulted to DDMAC 7/21/00)
11. Foreign Marketing History	X	Volume 2.01; page 65
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X	Volume 2.20; page 1-73
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X	Volume 2.20 ;page 74-123

Y = Yes (Present), N = No (Absent)

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Volume 2.01; page 60-64
2. Summary of Each Technical Section			

	X		See Below
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 2.01; page 66-68
b. Nonclinical Pharmacology/Toxicology	X		Volume 2.01; page 82-141
c. Human Pharmacokinetic & Bioavailability	X		Volume 2.01; page 142-167
d. Microbiology		X	N/A
e. Clinical Data & Results of Statistical Analysis	X		Volume 2.01; p 168-212
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Volume 2.01; page 213-215
4. Summary of Safety	X		Volume 2.01; page 200-212
5. Summary of Efficacy			Volume 2.01; p 168-199

Y = Yes (Present), N = No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		Volume 2.14; page 2
2. Controlled Clinical Studies	X		See Below
a. Table of all studies	X		Volume 2.14; page 1

b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Volume 2.15; page 1-141 (protocols could not be located)
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Volume 2.14; page 66-82
4. Integrated Summary of Safety (ISS)	X		Volume 2.14; page 83-94
5. Drug Abuse & Overdosage Information		X	N/A
6. Integrated Summary of Benefits & Risks of the Drug	X		Volume 2.14; page 97-99
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	X		Volume 2.21; page 045 Full waiver requested
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on	X		See below

paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in MS WORD	X		Desk copy (project manager)
b. Stability data in SAS data set format (only if paper submission)		X	
c. Efficacy data in SAS data set format (only if paper submission)		X	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	
3. User-fee payment receipt		x	N/A

Y = Yes (Present), N = No (Absent)

"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

If the review team agrees, the firm will be requested to address the administrative deficiencies identified above.

/S/ 7/26/00
Melodi McNeil
Regulatory Project Manager

cc:

- Original NDA
- HFD-180/Div. Files
- HFD-180/McNeil
- HFD-180/Talarico
- HFD-180/Aurecchia
- HFD-180/Gallo-Torres
- HFD-180/R. Joseph
- HFD-180/Zhou
- HFD-180/Ysern
- HFD-180/Choudary
- HFD-870/Doddapaneni
- HFD-870/Udo
- HFD-715/Permutt

/S/ 7-26-00

draft: mm /July 21, 2000
r/d Initials: L.Talarico 7/21/00
final: July 25, 2000
ADMINISTRATIVE REVIEW

Revised 2/25/00

McNeil

MEMORANDUM

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

DATE: August 17, 2000

TO: Dr. Khairy Malek, Medical Officer, Division of Scientific Investigations (HFD-46)

THROUGH : Dr. Lilia Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180) *LT 8-17-00*

FROM: Ms. Melodi McNeil, Regulatory Health Project Manager, Division of Gastrointestinal and Coagulation Drug Products (HFD-180) *-MM 8/17/00*

SUBJECT: Cancellation of Request For Clinical Site Inspections
NDA 21-252, FIV-ASA (mesalamine) Suppositories

Background: On June 29, 2000 Axcan Scandipharm Inc. submitted NDA 21-252. The application, submitted under 505(b)(2) of the Act, provides for FIV-ASA (mesalamine) Suppositories in the treatment of active ulcerative proctitis.

In a July 19, 2000 memo the Division identified the following protocols/sites for inspection:

Indication	Protocol #	Site (Name and Address)
Treatment of active ulcerative proctitis	Protocol 300/Center 301	C. Noel Williams, MD Victoria General Hospital 1278 Tower Road Halifax, Nova Scotia Canada B3H 2Y9
Treatment of active ulcerative proctitis	Protocol 300/Center 302	Gregory Haber, MD Rosedale Medical Center 600 Sherbourne St., Suite 611 Toronto, Ontario Canada M4X 1W4

In an August 15, 2000 correspondence, the NDA applicant requested a waiver of the clinical site inspections for the following reasons:

NDA 21-252

Page 2

1. The pivotal studies were conducted more than 15 years ago (February through October 1985).
2. The two centers (301 and 302) were part of a pivotal study that was reviewed by the FDA in support of the approval of NDA 19-919 [Rowasa (mesalamine) Suppositories]. Note: The applicant noted that the pivotal study may already have been audited by FDA, yet acknowledged that these particular centers may not have been inspected.
3. ICH Good Clinical Practice Guidelines require that investigators keep case record forms for two years post approval. Given that mesalamine suppositories were approved by FDA in December 1990, the required time for case report form retention has passed.

Dr. Talarico reviewed the applicant's request, along with available supporting data, and she agrees with the applicant's position that inspection of Centers 301 and 302 are not needed at this time.

Conclusion: Please cancel the pending request for inspection of Protocol 300, Centers 301 and 302.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

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

Date: July 19, 2000

To: Khairy Malek, GCPB Reviewer/HFD-46

Through (optional): David A. Lepay, M.D., Ph.D., Director, DSI, HFD-45
Lilia Talarico, M.D., Director, HFD-180 *7-21-00*

From: Melodi McNeil, Regulatory Health Project Manager, HFD-180 *mm 7/21/00*

Subject: **Request for Clinical Inspections**
NDA 21-252
Axcan Scandipharm Inc.
FIV-ASA (mesalamine) Suppositories

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Treatment of active ulcerative proctitis	Protocol 300/Center 301	C. Noel Williams, MD Victoria General Hospital 1278 Tower Road Halifax, Nova Scotia Canada B3H 2Y9
Treatment of active ulcerative proctitis	Protocol 300/Center 302	Gregory Haber, MD Rosedale Medical Center 600 Sherbourne St., Suite 611 Toronto, Ontario Canada M4X 1W4

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

Request for Clinical Inspections

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **December 22, 2000**. We intend to issue an action letter on this application by (action goal date) **January 3, 2001**.

Should you require any additional information, please contact Melodi McNeil.

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number: 021252 **Trade Name:** CANASA (MESALAMINE) 500MG SUPPOSITORY
Supplement Number: 000 **Generic Name:** MESALAMINE
Supplement Type: N **Dosage Form:**
Regulatory Action: UN **COMIS Indication:** TREATMENT OF ACTIVE ULCERATIVE PROCTITIS
Action Date: 7/8/00
Indication # 1 Treatment of active ulcerative proctitis.
Label Adequacy: Other - See Comments
Formulation Needed: NO NEW FORMULATION is needed
Comments (if any): DISREGARD THIS INFORMATION--THIS PORTION IS TO BE DELETED

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
Adult	Adult	Completed	

Indication # 2 treatment of active ulcerative proctitis
Label Adequacy: Adequate for SOME pediatric age groups
Formulation Needed: Other
Comments (if any): Asking for efficacy study; not sure if new formulation is needed.

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
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This page was last edited on 1/3/01

Signature

IS/

Date

1/3/01