

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21252

MEDICAL REVIEW

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER REVIEW**

NDA: 21-252

Sponsor: Axcan Scandipharm Inc.
Birmingham, Alabama

Date Submitted: June 28, 2000

Drug: Mesalamine FIV-ASA Suppositories
(CANASA®)

Pharmacologic Category: Anti-inflammatory; anti-colitis

Formulation/Route of Administration: Rectal Suppositories (500 mg)

Proposed Indication: Treatment of Active Ulcerative Proctitis

Material Submitted/Reviewed: Pediatric waiver letter and five
Literature articles

Reviewer: Raymond E. Joseph M.D.

In accordance with 21 CFR 314.55 (c)(2), Axcan Scandipharm Inc. requested a full waiver of the pediatric assessment requirement for FIV-ASA.

NDA 21-252 was filed under the provisions of Section 505 (b)(2) of the Federal Food, Drug and Cosmetics Act. The sponsor referenced FDA's prior approval of mesalamine 500 mg suppositories in NDA 19-919, which also did not contain pediatric studies.

The sponsor requests this waiver for the following reasons:

1. Pediatric ulcerative proctitis is an uncommon disease.
2. Historically, 5-ASA has been associated with rare, idiosyncratic adverse events which would be deleterious in pediatric populations.
3. The mechanism of action in ulcerative proctitis is local and does not require systemic metabolism. This local action would be the same in a pediatric population as in adults.

- This reviewer agrees with the waiver for the age group (newborn to age 11 years).
- Because there is an increased incidence of ulcerative proctitis in the adolescent age group, I recommend clinical studies for the age group (12 to 18 years) in the form of a phase IV commitment.

The details of the (one) clinical trial in patients ages 12 to 18 years will be decided with the sponsor at a later date. A design similar to that used in the pivotal clinical trials in adult patients is suggested. An approximate time period for the study would be two years following approval.

Raymond E. Joseph M.D.

cc:

NDA 21-252

HFD-180

HFD-180/LTalarico

HFD-180/HGallo-Torres

HFD-180/RJoseph

HFD-181/MMcNeil

HFD-180/JChoudary

HFD-180/LZhou

f/t 1/5/01 jgw

N/21252101.0RJ

/s/

Hugo Gallo Torres
1/8/01 09:34:05 AM
MEDICAL OFFICER

Lilia Talarico
1/8/01 10:30:32 AM
MEDICAL OFFICER

Finalized hard copy review signed on 1-5-01. Lilia Talarico, M.D.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 21-252

Sponsor: Axcan Scandipharm Inc.
Birmingham, Alabama

Date Submitted: July 3, 2000

Drug: Mesalamine FIV-ASA Suppositories (Canasa[®])

Pharmacological Category: Anti-inflammatory; anti-colitis

Formulation/Route of Administration: Rectal Suppositories (500 mg)

Proposed Indication: Treatment of Active Ulcerative Proctitis

Material Submitted/Reviewed: Volumes 2.01, 2.14, 2.15, 2.16, 2.17, 2.18, 2.20
and other pertinent information and literature
references

Reviewer: Raymond E. Joseph, M.D., F.A.C.P.

Abstract. This NDA includes historical data from two sources. (1) NDA 19-919 (Rowasa[®], Solvay), the suppository formulation of mesalamine which was discontinued because of dissolution problems. (2) Published literature on a new proposed suppository formulation FIV-ASA for the treatment of active ulcerative proctitis. The data in the historical trials from Solvay mesalamine suppositories included two adequate and well controlled trials (Protocols 300 and 330, respectively). These two trials included 173 patients diagnosed with active ulcerative proctitis and treated for 6 weeks with the Solvay mesalamine suppositories (Rowasa[®]). The therapeutic gain over placebo (total n=84) was manifested by improvement in the disease activity index (DAI). This therapeutic gain ranged from 43 to 78. From the historical published clinical data, this reviewer selected two randomized clinical trials; one had placebo as control, the other hydrocortisone as active comparator. These two trials included a total of 141 ulcerative proctitis patients. Similar to the results achieved by the Solvay suppository trials, patients treated with FIV-ASA revealed significant superiority in DAI over placebo or were comparable to hydrocortisone after four weeks of treatment. Safety submitted with either Solvay suppository or new proposed FIV-ASA suppository did not reveal any appreciable risks. Approval of NDA 21-252 is recommended.

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I. INTRODUCTION AND BACKGROUND

A. Brief Review of History

Sulphasalazine was developed in the 1930s, originally for use in patients with rheumatic polyarthritis. Its mild effects in arthritis were soon overshadowed by the striking benefits seen when the drug was given to patients with active colitis¹. Multiple controlled clinical trials confirmed the efficacy and established a role for sulphasalazine in the treatment of active ulcerative colitis and in the maintenance of disease remission. Although sulphasalazine had benefits for many patients with ulcerative colitis it had two major limitations. Firstly, little more than half the patients treated achieved symptomatic remission with an annual relapse rate of 30% or more. Secondly, side effects and allergic reactions were common, occurring in up to one-third to one-half of those treated with therapeutic doses.²

Drs. Peppercorn and Goldman demonstrated the role of intestinal bacteria in the metabolism of salicylazosulfapyridine in 1972.³

In another important article in 1977, Azad Khan et al. reviewed the therapeutic activity of the component parts of sulphasalazine and discovered that 5-aminosalicylic acid (5-ASA; mesalamine) was the active ingredient and that sulphapyridine was therapeutically inert.⁴

Most of the adverse reactions to sulphasalazine were thought to be caused by sulphapyridine. This led to the development of new formulations to deliver 5-ASA to the colon without the toxic effects of sulphapyridine. Oral forms include Pentasa[®], Dipentum[®] and Asacol[®]. The suppository form of mesalamine (Rowasa Solvay) was taken off the market. A similar formulation FIV-ASA sponsored by Axcan lead to the submission of this NDA (21-252).

B. Chronology

- 12/18/90 NDA 19-919; Rowasa[®] suppositories approved
- Mid 1999 Rowasa[®] suppositories no longer commercially available. Withdrawn by the manufacturer because of abnormal dissolution profile found in some lots
- 7/22/00 FDA meets re: what to do about drug shortage. As a result of the Rowasa

¹ Suartz N. Salazopyrin, a new sulfanilamide preparation. Acta Med. Scand. 1942; 110:577-598.

² Taffet SL, Das KM, Sulphasalazine-adverse effects and desensitization. Dig. Dis. Sci. 1983; 28:833-842

³ Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. J Pharmacol Exp Ther 181(3):555-561.

⁴ Azad Khan et al. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977, 77:892-895

removal, all non-US firms were encouraged to submit an NDA for their mesalamine suppositories.

- 7/29/00 Axcán suppository was selected as the most appropriate substitute for Rowasa®. The firm was advised that they should submit an NDA as soon as possible.
- 12/16/99 Pre-NDA meeting with Axcán
- 6/29/00 Axcán submits FIV-ASA NDA
- 1/04/01 NDA 21-252 due date

The sponsor submits this NDA as a 505(b)(2) application. To be supported by 505(B)(2) the application would be based upon the following:

- a) One or more of the investigations by the applicant for approval were not conducted by or for the applicant
- b) Can rely either on published literature or their own generated clinical data.

II. NDA 21-252 CONTENTS

- Single and repeat dose bioavailability studies.
- One adequate and well controlled clinical trial consisting of 27 ulcerative proctitis patients providing a clinical bridge to Rowasa® suppositories (NDA 19-919).
- A review of the medical literature since the time of approval of NDA 19-919 (1990).
- Axcán's post-marketing experience with mesalamine suppositories.

III. PROPOSED LABELING

IV. CHEMISTRY

The details of the chemistry of the new Axcan FIV-ASA suppository will be reviewed by the chemistry reviewer.

The following are the relevant chemistry issues:

- 1) The abnormal dissolution profile found in some Rowasa lots was the cause for the voluntary withdrawal from the US market.
- 2) The agency specifications calls for % dissolution of the drug in 120 minutes.
- 3) According to Axcan's submission the FIV-ASA suppositories fulfill the agency's dissolution profile.

- **Composition and Dosage Form**

The FIV-ASA (mesalamine) suppositories, 500 mg are light tan to grey, smooth torpedo shaped, and contain the following components:

Active Ingredient: Mesalamine USP

Other Ingredients: Hard Fat (Witepsol H-15, Suppository Base) NF

NOTE: 1) There are no additional components used in the manufacturing of the drug product.

TABLE I

COMPOSITION OF FIV-ASA (MESALAMINE) SUPPOSITORIES, 500 mg			
Ingredient	Test Standard	Unit Formula per suppository	As Percent of Suppository
Mesalamine	USP	grams	%
Hard Fat (Witepsol H-15, Suppository Base)	NF	grams	%
Total Suppository Weight		grams	%

⁵ Hanauer, S, Borgen L, Reiss L. Maintenance treatment of ulcerative proctitis with mesalamine suppositories: results of a multicenter two year controlled trial. Gastroenterol 1992; 102:A634.

V. PHARMACOKINETICS AND BIOAVAILABILITY

Since the therapeutic efficacy of mesalamine is thought to result from a predominantly topical effect, standard pharmacokinetic parameters bear little relationship to clinical efficacy. However, pharmacokinetic data may contribute to the characterization of safety.

In this section the sponsor submitted the reviewer's notes from NDA 19-919, an updated literature review from 1991 after Rowasa[®] suppositories were approved, and two human pharmacokinetic and bioavailability studies conducted by Axcan Scandipharm Inc.

(NOTE: Azo-bound, enteric coated oral forms of mesalamine will not be reviewed in this section.)

Axcan submitted results of two PK/PD studies, protocol MSN-PO-083 and MSN-PO-019.

A. Protocol MSN-PO-083

Title: Pharmacokinetic Evaluation of 5-ASA 500 mg Suppository Following A Single and Multiple Dose Administration in Ulcerative Proctitis Patients

The study was an open label trial of single and multiple-dosing of 5-ASA suppositories in 9 adult ulcerative proctitis patients. There were 3 males and 6 females with active ulcerative proctitis ranging in age from 24 to 50 years. The patients were not to have taken ASA, 5-ASA or NSAIDs in the 5 days prior to and during the entire study period.

a) The Single Dose Study

Patients were given a single dose of test medication via suppository (500 mg). Blood samples were obtained hourly for the first 12 hours, then at 18, 24 and 30 hours post dose. Urine was collected pre-dose and over the 30 hour period in five intervals. Feces were collected once over the 30 hour period.

b) The Repeated Dose Study

Two days after the single 500 mg dose, a rectal dose of the suppository (500 mg) was given at 8 hour intervals over six consecutive days. Eight hours after the final drug dose, rectal biopsies (3-4, 5 to 10 cm) were taken. Blood, urine and fecal samples were taken as in the single dose study.

Safety was assessed by physical examination, vital signs, laboratory tests and adverse event recording.

c) Results

PK parameters Following Single Dose (mean and S.D.)

C_{max} = 353 (196) ng/ml seen at 6 (2.9) hours

half-life = 5 (3.6) hours

5-acetylmесalamine C_{max} = 713 (281) μ g/ml seen at 7 (3.5) hours;

half-life = 5.8 (3.7) hours

Urinary recovery over 30 hours = 117 (178) ng as unchanged mesalamine and 143 (80) as 5-acetylmесalamine

Mean mesalamine concentration in rectal tissues was 168 (1.4-541) ng/kg of tissue

Mean 5-acetylmесalamine concentration in rectal tissues was 19 (2.8-28.3) mg of tissue.

d) Safety

Seven of the nine subjects from this trial reported adverse events during the course of the study.

• The reported events:

abdominal pain
constipation
diarrhea
flatulence
headache
melena
nausea
vomiting
vertigo

were of mild to moderate intensity
and were assessed as possibly
related to the study drug

• The events:

abnormal purple vaginal discharge
dysmenorrhea
fatigue
urinary abnormality

assessed as unlikely or not
related to study drug

The laboratory values at the beginning and at the end of the study were considered normal or the changes were not clinically significant for all subjects.

This reviewer agrees that the pharmacokinetic evaluation of FIV-ASA 500 mg suppository demonstrated good tolerance of the subjects to the study drug and revealed no new problems with the use of this (FIV-ASA) formulation.

B. Protocol MSN-PO-019 (as per the sponsor)

Title: Pharmacokinetic Evaluation of 5-ASA 500 mg Suppository Following a Single and a Multiple Dose Administration in Healthy Male Volunteers

a) Objectives

To evaluate the pharmacokinetic profile of 5-ASA and its metabolite (acetyl-5-ASA) in plasma and urine after a single and multiple rectal dose administration. To assess rectal tissue concentration of 5-ASA and Acetyl-5-ASA after the last dose of multiple dose administration.

b) Study Design

An open-label study of single and multiple-dosing of 5-ASA suppositories in healthy male volunteers, conducted at a Phase I research center.

c) Subjects

Sixteen healthy non-smoking male subjects (ages 22-50), within $\pm 15\%$ of ideal weight/height ratio, were included in this study, in order to complete 12 subjects. All laboratory tests had to be within 10% of the laboratory's normal range and of no clinical significance. Subjects could take no drugs for at least 17 days prior to and during the entire study period, except for ASA or NSAIDs, where the exclusion period was 14 days. No concomitant medications were allowed during the study.

d) Test Drug Schedule/Study Procedures

Single dose: Patients arrived at the clinical site the evening prior to first drug administration. The following morning, vital signs were measured and the first blood sample was taken.

Subjects then received a rectal dose of the test suppository. A retention time of at least 2 hours was recommended.

Blood samples were obtained pre-dose administration and at hourly intervals thereafter for the first 12 hours, then at 18 and 24 hours post dose. Urine was collected pre-dose administration and over the 24-hour period in four intervals (0-4 hr; 4-8 hr; 8-12 hr; 12-24 hr). Feces were collected once over the 24 hour period.

Multiple dose: Starting 24 hours after the single dose administration, a rectal dose of the suppository was administered at 8 hour intervals over five consecutive days; the last dose was administered on the morning of the sixth day. A retention time of 2 hours for each dose was recommended. Approximately 8 hours after the final drug administration, rectal biopsies (3-4 tissue collections) were taken in the first part of the rectum (5-10 cm). Approximately 24 hours after the last drug administration, subjects could leave the clinical site.

Blood and urine samples were obtained as above (for single dose) after the first and last suppository dosage. Feces were collected over the 24 hour period after the first and last drug administration.

C. Reviewer's Comments on Chemistry and PK/PD.

- The results of the dissolution test are important since this was the reason Rowasa[®] was taken off the market. Axcan's FIV-ASA level of dissolution meets the agency requirements and would assure that the medication will be available in sufficient quality at the site of action within the rectum.
- Since the therapeutic efficacy of mesalamine is thought to result from a predominantly topical effect, standard pharmacokinetic parameters bear little relationship to clinical efficacy. However, pharmacokinetic data may contribute to the characterization of safety. The PK levels of the parent drug and metabolites appear comparable to the levels observed in the Rowasa^R suppository preparation.
- This reviewer has no additional comments regarding the pharmacokinetic data (see Clinpharm/Biopharm review).

VI. SUPPORTIVE CLINICAL DATA

This submission contains the following clinical data:

1. Two historical clinical trials which were the basis of the approval of Rowasa[®] (Solvay).
2. An adequate and well controlled trial of the 27 patients submitted from Canadian

centers 301/302 which were originally part of NDA 19-919, Study 300 (Axcán).

The two placebo-controlled studies in NDA 19-919 (studies 300 and 330) and the Axcán sponsored centers from study 300 utilized the same Disease Activity Index described below.

A. Protocols of Clinical Trials

Both protocols 300 and 330 were of six weeks duration and included patients ≥ 18 years who were not pregnant and were to participate on an outpatient basis. All of the patients had their disease (active ulcerative proctitis) limited to 15 cm above the anal margin and a minimal score of 3 in two separate categories on a 12-point Disease Activity Index (DAI).

The DAI gives a score that equals the sum of four 0-3 point ordered scales assessing different aspects of disease activity:

- **Evacuation Frequency**

- 0 = normal consistency and frequency
- 1 = mild, 1-2 evacuations per day greater than normal
- 2 = moderate, 3-4 evacuations per day greater than normal
- 3 = severe, 5 or more evacuations per day greater than normal

- **Rectal Bleeding**

- 0 = no blood in stool
- 1 = blood in occasional evacuation
- 2 = blood in most evacuations
- 3 = blood in all evacuations

- **Mucosal Appearance on Sigmoidoscopy**

- 0 = mucosa appears normal
- 1 = mild inflammatory changes
- 2 = moderate inflammatory changes
- 3 = severe inflammatory changes

• **Physician's Overall Assessment of Disease Severity**

- 0 = normal
- 1 = mild disease
- 2 = moderate disease
- 3 = severe disease

PROTOCOLS 300 AND 330

a) *Study Design*

The following are Axcan scanned tables. Table 2 shows the side-by-side contrasts of the three studies.

TABLE 2

Contrast in Study Designs

	Studies from NDA 19-919		Axcan-sponsored Canadian Centers
	Study 330 [n=94]	Study 300 [n=79]	301/302 ^a [n=27]
Dose per day	1.0 g	1.5 g	1.5 g
Frequency of administration	b.i.d.	t.i.d.	t.i.d.
Formulation500 mg suppository.....		
Admission Criteria	Ulcerative colitis ≤15 cm from anal verge		
Trial Execution:			
Pretreatment biopsy	Yes	No	No
Posttreatment biopsy	Yes	No	No
Global rating of improvement:			
Investigator assessment	Yes ^b	Yes ^c	Yes ^c
Patient assessment	Yes ^b	No	No
Efficacy Index	Yes ^b	No	No
Daily diary rating of improvement			
Blood in stool	Yes	Yes	Yes
Bowel frequency	Yes	Yes	Yes
Urgency to defecate	Yes	No	No
Number of Centers	9	7 ^a	2 ^a
Number of Patients	5-ASA: 50 Placebo: 44	5-ASA: 39 Placebo: 40	5-ASA: 14 Placebo: 13
a) Patients from the Axcan-sponsored Canadian centers were included in Protocol 300 from NDA 19-919 b) Weeks 3 and 6 c) Last visit All trials were six weeks in duration with sigmoidoscopy at weeks 3 and 6			

b) *Statistical Considerations*

All studies used similar statistical methods to assess group differences in efficacy outcome. The main measures of effectiveness subject to statistical analyses included the 12-point Disease Activity Index (DAI). Total score consisted of subscales: the cessation of rectal bleeding and bowel frequency as recorded on daily diary cards; and global rating of effectiveness. Percentage change score from baseline ($=$ [postdosing score minus baseline score/baseline score] x 100) was computed to incorporate pretreatment scores into the analyses.

c) *Results*

Table 3 through 6 summarize the results of the three studies.

Table 3 shows the effect of treatment on disease severity, Table 4 shows the effect of treatment on rectal bleeding and bowel frequency, Table 5 shows incidence of normalization of mucosal appearance and Table 6 demonstrates the global assessments.

TABLE 3

EFFECT OF TREATMENT ON DISEASE SEVERITY OVERALL DISEASE ACTIVITY INDEX: MEAN (PERCENT CHANGE FROM BASELINE)									
Studies from NDA 19-919							Axcan-sponsored Canadian Centers 301/302 ^a		
	Study 330			Study 300					
	5-ASA (n=48)	Placebo (n=41)	Est. of effect ^b	5-ASA (n=48)	Placebo (n=41)	Est. of effect ^b	5-ASA (n=48)	Placebo (n=41)	Est. of effect ^b
Baseline	6.36 (0.0)	7.74 (0.0)	-1.77, 0.15	7.03 (0.0)	7.35 (0.0)	-1.14, 0.45	5.29 (0.0)	5.46 (0.0)	-1.39, 1.05
Week 3	2.79 (-57.5)	7.46 (-15.1)	-3.57, -1.77	2.67 (-67.8)	5.75 (-18.1)	-2.47	1.14 (-78.4)	4.31 (-17.7)	-80.79, -40.67
Week 6	1.65 (-74.7)	4.79 (-34.2)	-4.087, -2.00				0.29 (-95.9)	3.73 (-27.7)	-100.24, -36.06
End-point^c	1.23 (-72.4)	5.19 (-25.9)	-4.77, -2.59				0.29 (-95.9)	3.69 (-29.4)	-94.04, -39.00

^a Patients from the Axcan-sponsored Canadian centers were included in Protocol 300 from NDA 19-919

^b 95% confidence interval of mean difference between 5-ASA and placebo

^c Last available score

TABLE 4

DAILY DIARY ASSESSMENT OF RECTAL BLEEDING AND BOWEL FREQUENCY NUMBER WITH EVENT / NUMBER POSSIBLE (PERCENT)									
	Studies from NDA 19-919						Axcen-sponsored Canadian Centers 301/302 ^a		
	Study 330			Study 300			S-ASA	Placebo	P value ^b
	S-ASA	Placebo	P value ^b	S-ASA	Placebo	P value ^b	S-ASA	Placebo	P value ^b
Cessation of rectal bleeding									
All Patients	33/47(79.2)	10/42 (23.8)	<0.001	31/37 (83.7)	10/42 (23.8)	<0.001	12/14 (85.7)	5/13 (38.5)	0.018
Female	12/30(79.9)	7/25 (28.0)	<0.001	17/21 (81.0)	7/25 (28.0)	<0.001	4/6 (66.7)		0.524
Male	12/17(73.6)	3/17 (17.6)	<0.001	14/16 (87.5)	3/17 (17.6)	<0.001	8/8 (100)	1/4 (25.0)	0.029
Patients on Prednisone	1/3 (33.3)	0/0 (0)	ns	7/10 (70.0)	0/0 (0)	ns	2/12 (16.7)	0/5 (0)	1.000
Patients not on prednisone	32/45(71.1)	10/42 (23.8)	<0.001	24/27 (88.8)	10/42 (23.8)	<0.001	10/12 (83.3)	5/5 (100)	
Patients on SASP	5/5 (100)	1/10 (10.0)	<0.001	8/11 (72.7)	1/10 (10.0)	<0.001	2/12 (16.7)	2/5 (40.0)	0.538
Patients not on SASP	7/40 (67.5)	9/32 (28.1)	<0.001	16/16 (100)	9/32 (23.1)	<0.001	10/12 (83.3)	3/5 (60.0)	
Stool Frequency ≤ 3/d	40/47(85.1)	22/42 (51.5)	0.053	30/37 (81.1)	22/42 (52.3)	0.053	7/12 (58.3)	2/5 (40.0)	0.620
Stool frequency ≤ 3/d and no rectal bleeding	29/47(61.7)	7/42 (16.7)	<0.001	27/37 (73.0)	7/42 (16.7)	<0.001	2/12 (16.7)	0/5 (0)	1.000

^a Patients from the Axcen-sponsored Canadian centers were included in Protocol 300 from NDA 19-919

^b P-value for the comparison of the two treatment groups based on a Fisher's Exact Chi-Square Test.

TABLE 5

INCIDENCE OF NORMALIZATION OF MUCOSAL APPEARANCE NUMBER BECOMING NORMAL / NUMBER ENTERED (PERCENT)									
	Studies from NDA 19-919						Axcen-sponsored Canadian Centers 301/302 ^a		
	Study 330			Study 300			S-ASA	Placebo	P value ^b
	S-ASA	Placebo	P value ^b	S-ASA	Placebo	P value ^b	S-ASA	Placebo	P value ^b
All Patients:	29/48 (60.4)	4/41 (0.0)	<0.001	22/37 (62.2)	10/40(25)	<0.001	12/14(85.7)	1/13(7.7)	<0.001
Female	20/31 (64.5)	3/24(12.5)	<0.001	12/21(57.1)	6/22(27.3)	0.003	4/6(66.7)	0/4 (0)	0.076
Male	9/17 (52.9)	1/17 (5.9)	0.003	11/16(68.8)	4/18(22.2)	0.031	8/8(100)	1/9(11.1)	<0.001
Upper Disease Boundary:									
< 10 cm	12/16 (75.0)	3/18(16.7)	0.001	7/12(58.3)	1/12(8.3)	0.032	5/12(41.7)	0/1(0)	1.000
10-20 cm	17/32 (53.1)	1/23 (4.4)	<0.001	16/25(64.0)	9/28(32.1)	0.004	7/12(58.3)	1/1(100)	1.000
Patients on Prednisone	1/2 (50.0)	0/0 (0.0)	ns	5/10(50.0)	1/5(20.0)	0.058	2/12(16.7)	0/1 (0)	1.000
Patients not on Prednisone	20/46 (60.9)	4/41(10.0)	<0.001	18/27(66.7)	9/35(25.7)	0.001	10/12(83.3)	1/1(100)	
Patients on SASP	2/5 (40.0)	0/0 (0)	ns	7/10(70.0)	2/9(22.2)	ns	3/12(25.0)	1/1 (100)	0.308
Patients not on SASP	26/41 (63.4)	4/31(12.9)	<0.001	11/17(64.7)	7/26(26.9)	0.010	9/12(75.0)	0/1(0)	

^a Patients from the Axcen-sponsored Canadian centers were included in Protocol 300 from NDA 19-919

^b P-value for the comparison of the two treatment groups based on a Fisher's Exact Chi-Square Test

TABLE 6

GLOBAL ASSESSMENTS OF IMPROVEMENT NUMBER "MUCH IMPROVED" / NUMBER ENTERED (PERCENT) ^a									
Protocol 330				Protocol 300			Axcen-sponsored Canadian Centers 301/302 ^b		
	5-ASA	Placebo	P	5-ASA	Placebo	P	5-ASA	Placebo	P ^c
Physician's Global Assessment									
All Patients	38/48(79.2)	11/42(26.2)	<0.001	32/38 (84.2)	16/39(41.0)	0.002	13/14(92.9)	2/13(15.4)	<0.001
Females	28/31(83.9)	7/25 (28.0)	<0.001	18/23 (78.1)	8/21 (38.0)	0.042	5/6(83.3)	0/4(0)	0.048
Males	12/17(70.6)	4/17 (23.5)	0.006	14/15 (93.3)	8/18 (44.4)	0.029	8/8(100)	2/9(22.4)	<0.001
Upper Disease Boundary									
< 10 cm	12/16(75.0)	3/18 (38.9)	0.008	7/12 (58.3)	4/12 (33.3)	0.036	6/13(46.2)	1/2 (50)	1.000
10 - 20 cm	17/32(53.1)	4/23 (17.4)	<0.001	16/25 (64.0)	12/27(44.4)	0.004	7/13(53.8)	1/2 (50)	1.000
Patient's Global Assessment				Not done in Protocol 300			Not done		
All Patients	38/48(79.2)	14/42(26.2)	<0.001						
Females	28/31(83.9)	8/25 (32.0)	<0.001						
Males	12/17(70.6)	6/17 (35.3)	0.006						
Upper Disease Boundary									
< 10 cm	12/16(75.0)	8/18 (44.4)	ns						
10 - 20 cm	28/32 (87.3)	5/23 (21.7)	<0.001						

^a Includes patients rated "Very much improved" or "Much improved" at last visit for protocol 330.
^b Patients from the Axcen-sponsored Canadian centers were included in Protocol 300 from NDA 19-919
^c P-value for the comparison of the two treatment groups based on a Fisher's Exact Chi-Square Test.

- In addition to the above tables, the reviewer has assembled tables 7 through 9 that clearly show the therapeutic difference between 5-ASA and placebo:

TABLE 7
Study 300

Parameter	5-ASA	PL	Therapeutic Difference	p-value
% Mean Reduction in 12-point DAI	80.4	36.8	43.6	<0.001
% Cessation of Bleeding	84.0	41	43.0	<0.001
Physicians Global Assessment	84.2	41	43.2	<0.001

TABLE 8
Study 330

Parameter	5-ASA	PL	Therapeutic Difference	p-value
% Mean Reduction in 12-point DAI	72	26	46	<0.001
Physicians Global Assessment	79	26	53	<0.001
Mucosal Biopsies	60	10	50	<0.001

TABLE 9
Study 300 (centers 301/302)

Parameter	5-ASA	PL	Therapeutic Difference	p-value
% Mean Reduction in 12-point DAI	94.5	31.6	62.9	<0.001
Cessation of Rectal Bleeding	93	36	57	<0.001
Physicians Global Assessment	93	15	78	<0.001

Therapeutic differences range from 43% to 78%.

d) Disposition of Patients

As seen in Table 10 the information lost due to either dropouts or missing data was minimal.

TABLE 10

**Number of Patients Participating in Efficacy Summaries
(Protocols 300 and 330)**

Protocol	Number Randomised	Disease Activity Index				Diary DI rating Record	Global Rating of Improvement
		Base-line	Week 3	Week 6	End-Point ^a		
300							
5-ASA	39	39	37	37	37	37	38
Placebo	40	40	40	34	40	37	39
Total	79	79	77	71	77	74	77
330							
5-ASA	50	50	47	46	48	47	48
Placebo	44	43	41	33	41	43	42
Total	94	93	88	79	89	90	90

^a last available assessment

^b physician assessment for protocol 300. physician and patient assessments at last visit for protocol 330

As listed in Table 11, the major reason for early termination in either of the main studies was lack of effect and all except one were in the placebo groups.

TABLE 11

Reasons for Early Termination (Protocols 300 and 330)
Number with Result/Number Entered

	Protocol 300	Protocol 330
<u>a) Observation Completed</u>		
5-ASA	35/39	44/50
Placebo	34/40	33/44
<u>b) Lack of Effectiveness</u>		
5-ASA	1/39	0/50
Placebo	5/40	8/44
<u>c) Adverse Experiences</u>		
5-ASA	1/39	2/50
Placebo	0/40	0/44
<u>d) Concurrent Illness</u>		
5-ASA	1/39	1/50
Placebo	0/40	0/44
<u>e) Positive Stool Culture</u>		
5-ASA	1/39	0/50
Placebo	1/40	0/44
<u>f) Administrative Withdrawal</u>		
5-ASA	0/39	3/50
Placebo	0/40	3/44
<u>TOTAL</u>		
5-ASA	4/39	6/50
Placebo	6/40	11/44

B. Historical Clinical Literature on FIV-ASA Formulation

What follows are summaries of results of two trials from the literature utilizing Axcan suppositories in ulcerative proctitis study (sponsor's material).

STUDY 1

Authors. Campieri M; Gionchetti P, Belluzzi A, Brignola C, Tampieie M, Lannone P, Brunetti G, Miglioli M, Barbara L.

Title. Topical treatment with 5-aminosalicylic acid in distal ulcerative colitis by using a new suppository preparation.

Publication. Int J Colorectal Dis 1990 May; 5(2):79-81

Purpose. To compare the efficacy of 500 mg 5-ASA suppositories administered three times a day vs a placebo in a double-blind clinical trial.

Methods. Sixty-two patients with mild to moderate attacks of ulcerative colitis limited to within 20 cm from the anal verge participated in this study of one month duration. Clinical, sigmoidoscopic and histologic assessments were carried out at the beginning, at 15 days and at one month. Physicians who performed assessments were unaware of the treatment each patient was taking. Patients had a daily diary to record the number of stools and presence of blood and/or mucus. Patients were judged to be improved on each measure if there was improvement of at least one grade from baseline. Patients were judged to be in remission when there was a complete disappearance of symptoms; sigmoidoscopic remission was declared when the rectal mucosal appeared repaired.

Efficacy. The following table summarizes the clinical, sigmoidoscopic and histologic results.

	5-ASA (n=12)		Placebo (n=30)	
	15 days	30 days	15 days	30 days
Clinical				
No change	19	4	24	20
Improvement	14	10	5	8
Remission	8	18	1	2
Sigmoidoscopic				
No change	13	7	26	23
Improvement	14	12	3	5
Remission	5	13	1	2
Histological				
No change	16	11	27	26
Improvement	13	12	3	3
Remission	1	9	0	1

After 15 days of treatment, 22/32 patients in the 5-ASA group were either in remission (n=8) or improved (n=14), while in the placebo group, only 6/30 were improved. At one month, 28 (87%) of the 5-ASA patients were either in clinical remission (n=18) or improved (n=10), compared with 10 (33%) in the placebo group, 2 in remission and 8 improved (p<0.01).

There was a significant difference (p<0.01) in sigmoidoscopic appearance between the two groups favoring the 5-ASA group both at 15 days and one month. In the 5-ASA group 19 patients (59%) were either improved or in remission at 15 days, vs only 3 (10%) in the placebo group. At one month, 21 patients (65%) in the 5-ASA group were improved or in remission, vs only 11 patients (39%) receiving placebo.

There was a significant difference between the groups in histological assessments: after one month, 21 patients (65%) in the 5-ASA group were either improved (n=12) or in remission (n=9) while there were only four placebo patients with an improved histological appearance.

Safety. No side effects were observed.

Author's Conclusion. Suppositories should be the first choice treatment for patients with distal sigmoiditis.

STUDY 2

Authors. Farup PG, Holvde O, Halvorsan FA, Raknerud N, Brodin U.

Title. Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis

Publication. Scan J Gastroenterol 1995 Feb; 30(2):164-70

Purpose. To compare the efficacy, safety and practicality of mesalazine suppositories, 500 mg twice daily, with those of hydrocortisone foam, 178 mg twice daily, in patients with ulcerative proctitis and proctosigmoiditis.

Methods. This was a randomized, open, multicenter trial with parallel-groups. Patients were stratified into two groups: Group 1 consisted of patients with proctitis (disease activity 5-15 cm from the anus), Group 2 consisted of patients with proctosigmoiditis (no disease proximal to the sigmoid). A total of 179 patients were randomized to treatment with either mesalazine suppositories (500 mg bid) or hydrocortisone foam enemas (178 mg bid). Patients had to have a DAI >6. Examinations were performed at baseline, and after 14 days and 28 days of treatment. At each assessment, symptoms and side effects were recorded, a routine laboratory screen was performed, and an endoscopy with biopsy specimens was done. **Patients were classified as "complete responders" if the DAI was <2; as "partial responders" if the DAI was >2 but had decreased from the previous treatment value and "non-responders" if the DAI was unchanged or had increased. Patients classified as complete responders or non-responders after 2 weeks terminated the study.** Histologic assessment by degree of inflammation in the mucosa was scored 0 (normal mucosa), 1 (chronic inflammatory infiltration, none or mild architectural disorder), 2 (mild crypt injury with acute inflammatory cell infiltrate), or 3 (extensive crypt injury with crypt abscesses and ulceration). Patients evaluated ease of use on a visual analog scale.

Efficacy. Complete responders in the different groups of patients are displayed in Table 12 below. Twenty-seven patients reached the endpoint after two weeks (17 complete responders) and fifty-two patients reached the four weeks (30 complete responders).

TABLE 12
Complete Responders

	Treatment Duration			
	2 weeks		4 weeks	
	n	%	n	%
All patients				
Mesalazine	11	27	17	42
Hydrocortisone	6	16	13	34
Proctitis				
Mesalazine	10	42	14	58
Hydrocortisone	5	19	9	35
Proctosigmoiditis				
Mesalazine	1	6	3	18
Hydrocortisone	1	8	4	33

(Sponsor's Table)

There was a non-significant trend toward a higher proportion of responders in the mesalazine group than in the hydrocortisone group, and a statistically significant higher response rate in patients with proctitis than those with proctosigmoiditis ($p < 0.05$). The median DAI in the mesalamine and hydrocortisone group at pretreatment and after 2 and 4 weeks of treatment were 14, 6, and 4 vs 13, 8, and 6, respectively, which gave a statistically significant relative treatment effect in favor of mesalazine ($p = 0.022$).

Patient diary cards showed no statistically significant difference between the treatment groups with respect to mean score, but patients with proctitis reported less symptoms than patients with proctosigmoiditis ($p = 0.02$). Patient evaluation of ease of use of the treatment regimens after 2 and 4 weeks on a 100 mm VAS was 4 and 5 mm in the mesalazine group and 12 and 12.5 mm in the hydrocortisone group, respectively ($p < 0.05$).

Safety. One serious side effect (erythema multiform-like exanthema and fever) occurred in a patient receiving mesalazine. Another two patients, one in each treatment group complained of transient exanthema. Four patients, three taking mesalazine and one taking hydrocortisone, reported a slight burning sensation in the anus. Six patients in each treatment group reported the above side effects. No clinically significant changes in laboratory test results were reported.

Author's Conclusion. Both mesalazine suppositories and hydrocortisone foam are effective for patients with proctitis and proctosigmoiditis. When topical treatment is given for distal ulcerative colitis, mesalamine suppositories seem to be the first choice due to its practical use, high patient compliance, and lack of potential side-effects due to adrenal suppression during long-term treatment.

Reviewer's Comments:

- These two randomized trials, one with placebo control and one with local hydrocortisone therapy as active control comparator showed significant superiority of Axcan FIV-ASA in symptomatic improvement and mucosal healing of ulcerative proctitis.
- Although these two trials were not prospectively designed for 6-weeks treatment the four week efficacy superiority exhibited by the Axcan FIV-ASA appears to be in line with the other 5-ASA formulations (i.e., Rowasa®).
- The presented efficacy results show superiority of the mesalamine suppository formulation over placebo in the symptomatic improvement of active ulcerative proctitis.
- A cardinal symptom of active ulcerative proctitis is rectal bleeding. The mesalamine suppositories greatly and highly statistically significantly treated this symptom. Also, the number of bowel movements, another key feature of active proctitis, was similarly affected by the mesalamine suppositories. In addition, the mucosal biopsies in study 330 showed a 50% therapeutic difference from placebo.
- Overall the efficacy demonstrated with the twice daily regimen (study 330) was comparable to that observed with the three times daily dosing (study 300).
- It is the view of this reviewer that the results of the Canadian multicenter study sponsored by Axcan confirm the results from NDA 19-919. Although the numbers were small in the Axcan sponsored trial, it appears that the efficacy in females was not as robust as in males.
- Patients in studies (300 and 330) who were taking oral sulfasalazine or prednisone greatly benefited from the addition of 5-ASA. This further benefit was not seen in the Axcan study patients.
- It is concluded that the results from the historical controlled trials which used the 5-ASA suppositories to treat ulcerative proctitis show similar efficacy and safety as that obtained by Solvay with the Rowasa® suppository formulation.

VII. OVERALL SUMMARY OF SAFETY

Mesalamine suppositories have been marketed in the U.S. since 1990. What will be reviewed in this section includes:

- Safety-related data on FIV-ASA suppositories (mesalamine 500 mg) from Axcan-sponsored clinical trials. Axcan has been marketing FIV-ASA suppositories (under the name Salofalk®) in Canada since 1986.

- A brief recap of the safety data from NDA 19-919 (Rowasa® [mesalamine 500 mg] suppositories).
- Axcan's experience with adverse events reported for suppositories in Canada.
- A review of the medical literature with highlights on mesalamine suppositories.

NDA 19-919 contained data on a total of 258 subjects from clinical trials (252 patients, 6 healthy volunteers). The 27 Axcan sponsored patients were included in the NDA 19-919. Additionally, Axcan has performed two pharmacokinetic studies utilizing 9 proctitis patients and 16 healthy volunteers. The numerical breakdown of these studies are provided in Table 13.

TABLE 13

TOTAL NUMBER OF PATIENTS AND HEALTHY SUBJECTS IN MESALAMINE SUPPOSITORY CLINICAL TRIALS ^a			
Study	Mesalamine	Placebo	Total
PATIENTS/SUBJECTS FROM NDA 19-919			
Protocol 300 (double-blind)	39	40	79
Protocol 330 (double-blind)	50	44	94
Protocol 304 (Open-label)	13	0	13
Protocol 334 (Open-label)	23	0	23
Compassionate Use	79	0	79
Protocol 51 (Healthy Volunteers)	6	0	6
TOTAL FROM NDA 19-919	174	84	258
PATIENTS/SUBJECTS FROM AXCAN-SPONSORED CLINICAL TRIALS			
Protocol 301/302 (double-blind)	14 ^b	13 ^b	27 ^b
Protocol 083 (Proctitis Patients)	9	0	9
Protocol 019 (Healthy Volunteers)	16	0	16
TOTAL FROM AXCAN-SPONSORED TRIALS	39	13	52
TOTAL HUMAN SUBJECTS	199^c	84^c	283^c
a) Includes both Axcan-sponsored trials and trials from NDA 19-919			
b) The 27 Patients from the Axcan-sponsored clinical study were included in NDA 19-919 as patients in Protocol 300			
c) Patients whose data were in both Axcan studies and in NDA 19-919 were not counted twice			

A. Exposure

- The 27 patients from Axcan studies 301/302 were exposed to study drug for six weeks.
- NDA 19-919 included data on 75 patients treated up to 2 months
 - 45 patients treated 2-4 months
 - 49 patients who were treated for ≥ 4 months.

B. Deaths

- There were no deaths in the mesalamine suppository studies.

- Axcan has received **no** reports of death since the marketing of its 5-ASA suppository in 1981.
- An extensive review of the medical literature up to May 4, 2000; contains **no** reports of death that can be attributed to mesalamine.

C. Adverse Events

Overall the frequency of adverse events was not significantly different between the 5-ASA and placebo treatment groups, and no individual adverse symptom occurred significantly more often in mesalamine-treated patients compared to placebo-treated patients. Table 14 lists the most common side effects.

TABLE 14

Adverse Event	5-ASA	Placebo
Headache	11.2%	11.9%
Flatulence	6.7%	6-8 %
Diarrhea	6.7%	6-8%
Abdominal Pain	6.7%	6-8%

- Notably, the last three adverse events are also common symptoms of ulcerative proctitis.
- There were only 3 adverse events reported on more than one occasion in mesalamine-treated patients but not reported in placebo-treated patients:
 - Rectal pain (3 times)
 - Fever (2 times)
 - Rash (2 times)
- No adverse events occurred more often in placebo-treated patients than in patients receiving the mesalamine suppository.

The frequency of adverse events by body system is shown in Table 15.

TABLE 15

ADVERSE EVENTS BY BODY SYSTEM (DOUBLE-BLIND TRIALS)^a				
Body System	Mesalamine (n=89)		Placebo (n=94)	
	n	%	n	%
Body as a Whole	19	21.3	22	23.8
Cardiovascular	2	2.2	1	1.2
Digestive	20	22.5	18	21.4
Endocrine	0	0.0	0	0.0
Hemic and Lymphatic	0	0.0	0	0.0
Metabolic and Nutritional Disorders	3	3.4	2	2.4
Musculoskeletal	3	3.4	1	1.2
Nervous	4	4.5	2	2.4
Respiratory	4	4.5	5	6.0
Skin and Appendages	4	4.5	3	3.6
Special Senses	1	1.1	1	1.1
Urogenital	1	1.1	4	4.8

a) The 27 patients from the Axcan-sponsored clinical study were included in NDA 19-919 as patients in Protocol 300.

The digestive system and body as a whole had the highest incidence of adverse events in both treatment groups. Importantly, the distribution of adverse events by body system is not significantly different between mesalamine-treated and placebo-treated patients.

D. Severe Adverse Events

Severe adverse events (SAE) from the controlled mesalamine trials (Study 300, Study 330) are shown in Table 16.

**TABLE 16
SEVERE ADVERSE EVENTS**

Treatment	Headache	Body Aches	Rectal Bleed
5-ASA	2	0	0
Placebo	1	1	1

The only severe adverse events were headaches and these were self-limiting.

E. Adverse Events Leading to Discontinuation

- Of the 168 5-ASA-treated patients, three discontinued due to an adverse event
 - One patient with rectal burning and itching
 - One patient with skin rash
 - One patient who had worsening of colitis

- No early terminations due to adverse events occurred in the placebo group.

F. Clinical Laboratory Evaluations

In the two large trials reported in NDA 19-919, in which the patients from the Axcan-sponsored study were included, standard clinical laboratory tests were performed prior to randomization and again at the end of the double-blind drug treatment. The battery of tests included:

- a complete blood count
- serum chemistry
- urinalysis with microscopic analysis of sediment

Reviewer comments on Clinical Laboratory Evaluation

- No clinically significant drug-related alteration was seen in any of the parameters tested. No patients were withdrawn from treatment because of an abnormal clinical laboratory finding.
- Additionally, an analyses of renal function and possible kidney toxicity was performed on lab data from NDA 19-919. Because animal toxicology studies had demonstrated that the kidney was the major target organ for mesalamine.
- The tests analyzed included an analyses of urea nitrogen and creatinine data from serum chemistry, and observation of abnormal results from urinalysis data. The incidence of abnormal findings in either of these two analyses was not increased in patients treated with mesalamine suppositories and was not different from placebo suppository-treated patients.

G. Post-Marketing Surveillance

Mesalamine has replaced sulfasalazine as first-line therapy for inflammatory bowel disease since its introduction worldwide in 1985.

The majority of adverse events to mesalamine have been reported after use of an oral formulation. These have included: fever and rash, pancreatitis, myocarditis, hepatotoxicity, renal toxicity and neuropathy. These adverse events appear to be idiosyncratic, affecting only the rare patient. More to the point, since this submission deals with the suppository formulation, adverse events with the suppository are even rarer than with the oral formulation. In the clinical trials, side effects are generally limited to peri-anal irritation. Recently, there have been two reports in the literature of more serious side effects: one patient who developed leukopenia and

thrombocytopenia after seven months of treatment with one 500 mg suppository nightly,⁶ one patient with rash and fever which was a similar reaction to sulfasalazine.⁷

In this reviewer's opinion, mesalamine suppositories have a remarkable record of safety. The adverse reactions appear to be idiosyncratic and rare.

VIII. BENEFIT-RISK RATIO

Ulcerative proctitis is an idiopathic inflammatory bowel disease limited to the distal colon or rectum. In general, ulcerative proctitis is considered a milder form of ulcerative colitis; nonetheless, ulcerative proctitis is often chronic and very disruptive to a patient's lifestyle, with prominent abdominal pain, frequent stools and rectal bleeding.

Mesalamine is regarded as effective therapy for ulcerative colitis, and for patients with ulcerative proctosigmoiditis the rectal drug application is more effective than oral dosing.⁸

Also, mesalamine suppositories may be practical and well accepted for long-term remission maintenance.⁹

Therefore, the benefits of mesalamine suppositories have been established in the control of acute symptoms of ulcerative proctitis, and in the prevention of recurrence once the disease is in remission. This benefit allows patients to have a life with fewer disruptions due to disease manifestations. There is reduced time lost from work or school and reduced hospitalization.

As stated earlier, the serious side effects of mesalamine appear to be idiosyncratic affecting only the rare patient. The benefit/risk ratio for use of FIV-ASA suppositories is strongly in favor of utilizing this compound in affected patients. The medical benefits (cessation of bleeding, decreased diarrhea and tenesmus) and the favorable effects on lifestyle far outweigh any risk associated with FIV-ASA usage.

IX. FINANCIAL DISCLOSURE

The sponsor certified that no investigator of any of the covered clinical studies had any financial interests to disclose.

⁶ Cassilas R et al. Leukopenia and Thrombocytopenia as adverse effects of treatment with 5-aminosalicylic suppositories. *J Clin Gastroenterol* 1996; 2:160-161.

⁷ Bell C. Safety of topical 5-ASA in pregnancy. *Am. J. Gastroenterol* 1999; 92:12

⁸ Campieri M et al. A controlled randomized trial comparing oral versus rectal mesalamine in the treatment of ulcerative proctitis. *Gastroenterol* 1996; A876

⁹ Hanauer S et al. Maintenance treatment of ulcerative proctitis: results of a multicenter two year controlled trial. *Gastroenterol* 1992; 102:A634

Cistillas F et al. Practicality of 5-aminosalicylic suppositories for long-term treatment of inactive distal ulcerative colitis. *Hepatogastroenterol* 1999; 46(28):2343-2346.

X. CONCLUSIONS AND RECOMMENDATIONS FOR REGULATORY ACTION

1. The sponsor submitted efficacy and safety data included in Solvay's NDA 19-919, i.e. Rowasa[®] suppository formulation. In addition, the sponsor submitted historical published literature from randomized clinical trials using FIV-ASA suppositories in the treatment of ulcerative proctitis. With exception of duration of treatment (4 weeks for FIV-ASA vs 6 weeks for Rowasa[®]) efficacy results revealed similarity in the two preparations over placebo or comparability in healing with topical hydrocortisone enemas as approved treatment for ulcerative proctitis.
2. Since the therapeutic efficacy of mesalamine is thought to result from a predominantly topical effect, standard pharmacokinetic parameters bear little relationship to clinical efficacy. However, pharmacokinetic data may contribute to the characterization of safety. The PK levels of the parent drug and metabolites appear comparable to the levels observed in the Rowasa^R suppository preparation.
3. With regard to the safety of the suppository formulation, Rowasa[®] and the proposed FIV-ASA are comparable and allow for an acceptable margin of safety risks.
4. Based on the aforementioned safety and efficacy results this reviewer concludes that the efficacy and safety of the proposed Axcan suppository preparation is comparable to the previously approved Rowasa[®] formulation.

**APPEARS THIS WAY
ON ORIGINAL**

5 The following are my recommended changes in the wording of the proposed label:

- 6 Approval of the 5-ASA formulation (FIV-ASA) for the proposed indication of treatment of active ulcerative proctitis is recommended

Raymond E. Joseph, M.D., F.A.C.P.

cc:

NDA 21-252

HFD-180

HFD-180/LTalarico

HFD-180/HGallo-Torres

HFD-180/RJoseph

HFD-181/MMcNeil

HFD-180/JChoudary

HFD-180/LZhou

r/d 10/5/00 jgw

r/d 11/30/00 jgw

N/21252010.0RJ

/s/

Raymond Joseph
12/21/00 02:26:27 PM
MEDICAL OFFICER

Hugo Gallo Torres
12/26/00 08:57:30 AM
MEDICAL OFFICER

Lilia Talarico
1/2/01 02:06:18 PM
MEDICAL OFFICER