CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21252

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-252 SUBMISSION DATES: 07/03/00
08/15/00
08/30/00
10/11/00
10/23/00
11/02/00
11/09/00

MESALAMINE 500 MG SUPPOSITORY
CANASA® 500 MG SUPPOSITORY

AXCAN SCANDIPHARM, INC.
22 INVERNESS PARKWAY
BIRMINGHAM, AL 35242 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA SUBMISSION CODE: 3P

CONTENT PAGE

I. SYNOPSIS/BACKGROUND

What Is the Drug? The drug is mesalamine (Canasa®) 500 mg suppository.

What is the Pharmacologic Class of the Drug? Mesalamine is an anti-inflammatory agent.

What Is the Indication? Mesalamine 500 mg suppository is proposed for the treatment of active ulcerative proctitis.

What is the Mechanism of Drug Action? The sponsor states (i) that the exact mechanism of mesalamine action for the above indication "is unknown" and (ii) that for the above indication, mesalamine action "appears to be topical rather than systemic".

What Is the Scientific Rationale for the Use of Mesalamine for the Stated Indication? The sponsor feels (i) that for patients with distal ulcerative colitis, rectal drug application is more efficient than oral dosing, (ii) that tolerance and patient acceptability of rectally administered drugs have been evaluated and found to be practical and well accepted in long-term treatment and (iii) that rectal application of mesalamine suppository would be sufficient in remission maintenance of ulcerative colitis.

What Is the Drug Product Composition? The drug product contains mesalamine 500 mg and hard fat (Whitespool H-15, Suppository base) 1700 mg.

What Is the Labeling Recommended Dosage of the Drug? The labeling recommended dosage is **one** 500 mg suppository administered rectally **three times daily**. The labeling further recommends that the suppository be "retained [in the rectum] for one to three hours or longer, if possible, to achieve the maximum benefit".

What Is the Purpose of this NDA Submission? Mesalamine 500 mg suppository is an approved drug that was marketed by Solvay Pharmaceuticals under the trade name, Rowasa® Suppository. Recently, Solvay Pharmaceuticals voluntarily withdrew Rowasa® Suppository from the market due to dissolution failure. This NDA is submitted in order to make mesalamine suppository available on the market to meet the medical needs of the public hat has arisen from the withdrawal of Rowasa® Suppository from the market.

What Is the Nature of this NDA Submission? This NDA is submitted in accordance with the provisions of section 505(b)(2) of the Federal Food, Drug and Cosmetics Act (the Act).

What Is the Nature of the Pharmacokinetic Studies Submitted in the NDA? In this NDA, the sponsor submits pharmacokinetic studies conducted specifically to evaluate the single dose and steady state kinetics of rectally administered 500 mg mesalamine suppository in nine subjects with ulcerative proctitis (Protocol MSN-PO-083) and in 16 healthy subjects (Protocol MSN-PO-019). These studies are consistent with the Agency's bioiavailability study requirements set forth in the **CFR** under **"Guidelines for the conduct of an in vivo bioavailability study"** [CFR 320.25 (a) (2) and (3)].

What is the Adverse Event Profile of Drug Product? In the study assessing Canasa® 500 mg suppository in nine subjects with ulcerative colitis (Protocol MSN-PO-083) adverse events were observed in seven subjects as follows: headache (n=3), abdominal pain (n=3), nausea (n=2), vomiting (n=1), abnormal purple vaginal discharge (n=1), dysmenorrhea (n=1), constipation (n=1), diarrhea (with purple stool) (n=1), stool abnormality, fatigue (n=1), flatulence (n=1), melena (n=1), vertigo (n=1) and urinary abnormality (n=1). The sponsor states that of these adverse events, only headache, abdominal pain, nausea, vomiting, constipation, diarrhea (with purple stool), melena and vertigo were possibly related to the drug. Further evaluation of these safety aspects is referred to the reviewing medical officer (see **General Comment** [page 21]).

Were there any Changes in Clinical Laboratory Parameters? The sponsor states that in these studies (Protocols MSN-PO-083 and MSN-PO-019), there were no clinically significant changes in the clinical laboratory parameters of the study subjects.

Is Adequate Information Provided on the Methods of Sample Analysis? The submitted pharmacokinetic study utilized a validated

The analytical methods are adequately described.

Summary of Pharmacokinetic Findings: In ulcerative colitis patients treated with rectal mesalamine 500 mg suppository, systemic and rectal tissue drug exposure is highly variable. This could be related to differences between individuals in suppository location and/or retention time in the rectum. Since mesalamine acts locally in the rectum, its systemic exposure is related more to safety than to efficacy. Mesalamine is eliminated mainly in urine predominantly as its N-acetyl-5-ASA metabolite. In the majority of the study subjects, the elimination half-lives of both mesalamine and N-acetyl-5-ASA range from 1.0 h to 8 h. The single dose and steady state C_{max} of 5-ASA are similar suggesting that here is no systemic accumulation.

What is the Recommendation? Overall, the submitted pharmacokinetic information is deemed acceptable for consideration in the NDA approval process.

II. SUMMARY OF INFORMATION ON PHARMACOKINETICS AND PHARMACODYNAMICS

1. Is Adequate Information Provided on Pharmacokinetic Parameters of Mesalamine Administered as Rectal Suppository?

The single dose and multiple dose pharmacokinetic characteristics of mesalamine (Canasa®) 500 mg suppository, administered rectally, was evaluated in nine subjects (3 males and 6 females) with ulcerative proctitis in a Phase I, open label study (Protocol MSN-PO-083) conducted at a single center. In this study, each subject was to retain the suppository in the rectum for two hours. For the multiple dose regimen, FIV-ASA® 500 mg was administered to each patient every 8 h for 6 days. The washout period between the single dose and multiple dose treatments was 48 hours. In both the single dose and multiple dose components of the study, the concentration profiles of measlamine (5-ASA) were determined in plasma and urine. Rectal tissue concentrations of 5-ASA were also determined in the multiple dose portion of the study. In similar single dose and multiple dose studies (Protocol MSN-PO-019) submitted in Amendment BB to the NDA on August 30, 2000, 5-ASA was evaluated in 16 healthy subjects. Individual subject plots of plasma concentration profiles of 5-ASA in the patients and the healthy subjects are presented in Figs. 1 and 2, respectively. The single dose and steady state pharmacokinetic parameters of 5-ASA are summarized in Table 1. Individual subject plasma concentration data are presented in Appendix I (pages 22-23). Individual subject pharmacokinetic parameters are presented in Appendix I (pages 24-25).

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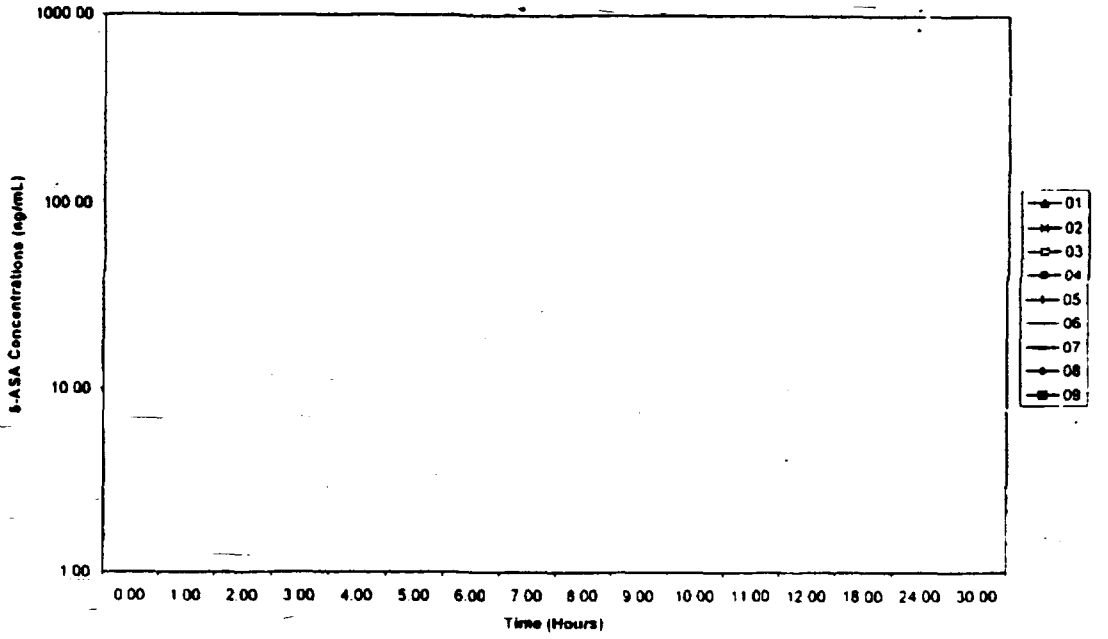
Fig. 1. Individual Subject Plots of Plasma Concentration Profiles of 5-ASA in Patients with Ulcerative Proctitis Following the Administration of Mesalamine 500 mg Rectal Suppository as a Single Dose (A) and Following the Last Dose of Multiple Dose Administration Every Eight Hours for Six Days (B)

A


1000 00
100 00
10 00
1 00
5-ASA Concentrations (ng/mL)
0 00 1 00 2 00 3 00 4 00 5 00 6 00 7 00 8 00 9 00 10 00 11 00 12 00 18 00 24 00 30 00
Time (Hours)
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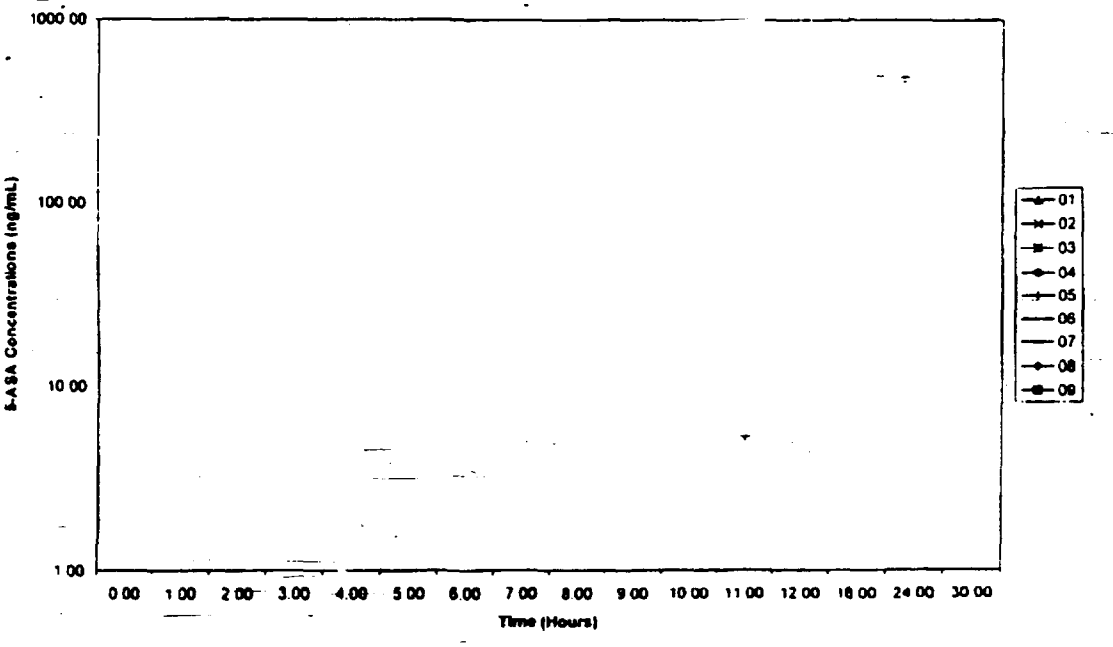
B


1000 00
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5-ASA Concentrations (ng/mL)
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Time (Hours)
01
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05
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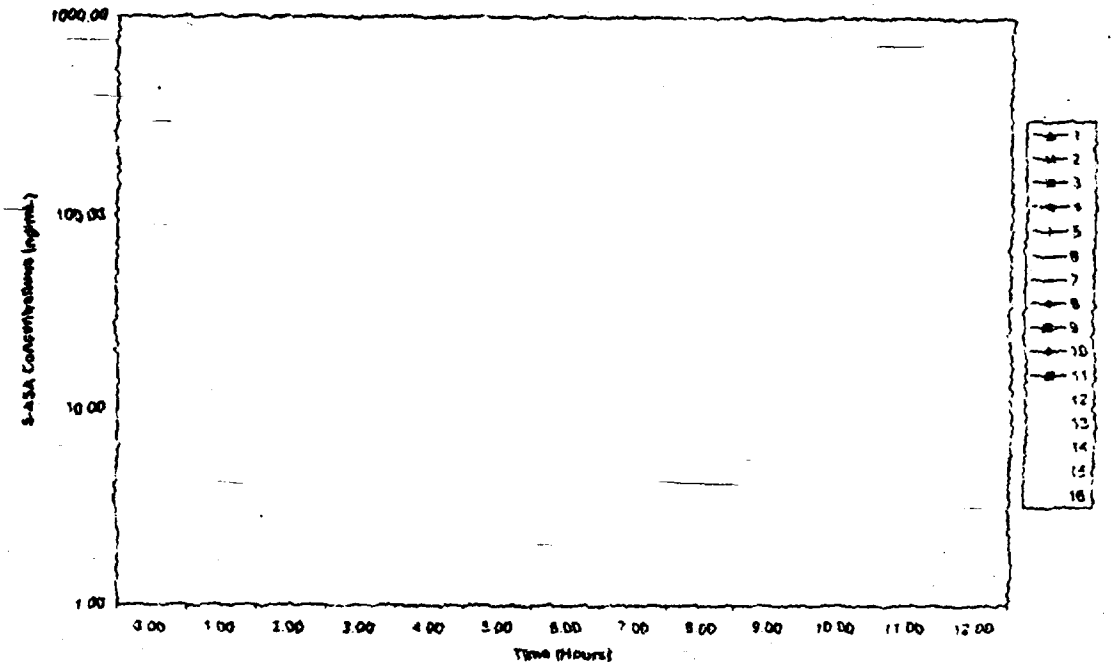
09

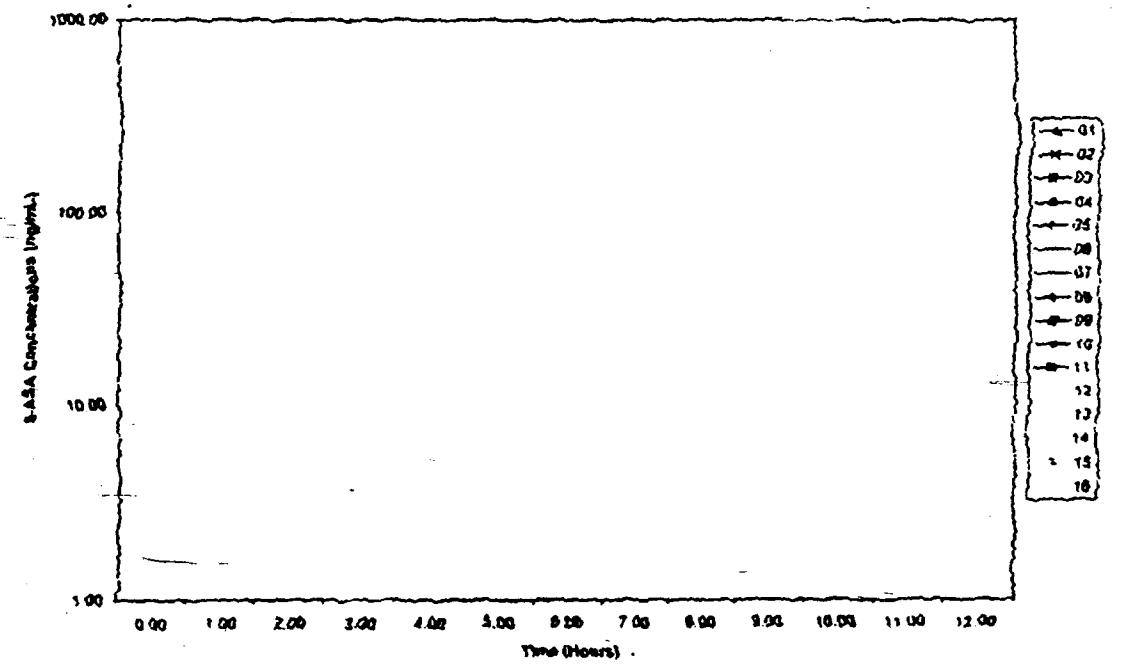
Fig. 2. Individual Subject Plot of Plasma Concentration Profiles of 5-ASA in Healthy Subjects Following the Administration of Mesalamine 500 mg Rectal Suppository as a single Dose (A) and Following the Last Dose of Multiple Dose Administration Every Eight Hours for Six Days (B)

Table 1. Summary of Pharmacokinetic Parameters of 5-ASA in Patients with Ulcerative Colitis

A



B



and Healthy Subjects Treated with Mesalamine 500 mg Rectal Suppository as a Single Dose and on the Last day of Multiple Dose Administration Every Eight Hours for Six Days.

Parameter	Single Dose Regimen				Multiple Dose Regimen			
	Patients		Healthy Subjects		Patients		Healthy Subjects	
n	9		16		9		16	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{min} (ng/mL)	NC[1]	NC[1]	NC	NC	89.05	88.56	22.40	274.94
C_{max} (ng/mL)	352.89	56.48	192.75	53.33	361.11	66.68	359.36	166.29
T_{max} (h)	6.78	43.51	2.30	60.90	5.89	59.76	2.40	79.20
AUC_{0-T}[a]	3969.7	65.36	1111.6	78.4	NC[1]	NC[1]	NC[1]	NC[1]
AUC_{inf}[ab]	4185.2	60.96	1697.7	96.3	NC[1]	NC[1]	NC[1]	NC[1]
AUC_{0-8}[a]	NC[1]	NC[1]	NC	NC	1813.2	65.2	1614.8	64.7
AUC_{0-12}[a]	NC[1]	NC[1]	NC	NC	2455.7	63.0	1789.5	67.9
$t_{1/2}$ (h)	4.98	72.82	3.96	119.81	7.08	102.48	0.93	50.39
Fluctuation (%)	NC[1]	NC[1]	NC	NC	149.68	51.36	296.66	49.98

[1]Not calculated, [a]ng/mL*h, [b]$AUC_{0\text{-infinity}}$

Based on these data, following rectal administration of mesalamine (FIV-ASA®) 500 mg suppository to subjects with ulcerative colitis, systemic drug exposure is highly variable between individuals as evidenced by high variability in AUC and C_{max}. This could be related to variability in bioavailability secondary to differences between individuals in suppository location and/or retention time in the rectum. In subjects with ulcerative proctitis, single dose and steady state C_{max} appear to be comparable suggesting no systemic accumulation of absorbed mesalamine. Steady state C_{min} and AUC and single dose C_{max} and AUC appear to be greater for subjects with ulcerative colitis as compared to healthy subjects suggesting greater drug exposure in the ulcerative colitis patients. Since mesalamine acts locally in the rectum, its systemic exposure relates more to safety than to efficacy. However, safety-exposure relationship was not assessed in the submitted studies. Due to high inter-individual pharmacokinetic variability, the range of individual subject pharmacokinetic parameters is considered more useful to the clinician then the mean values and will be used in the labeling.

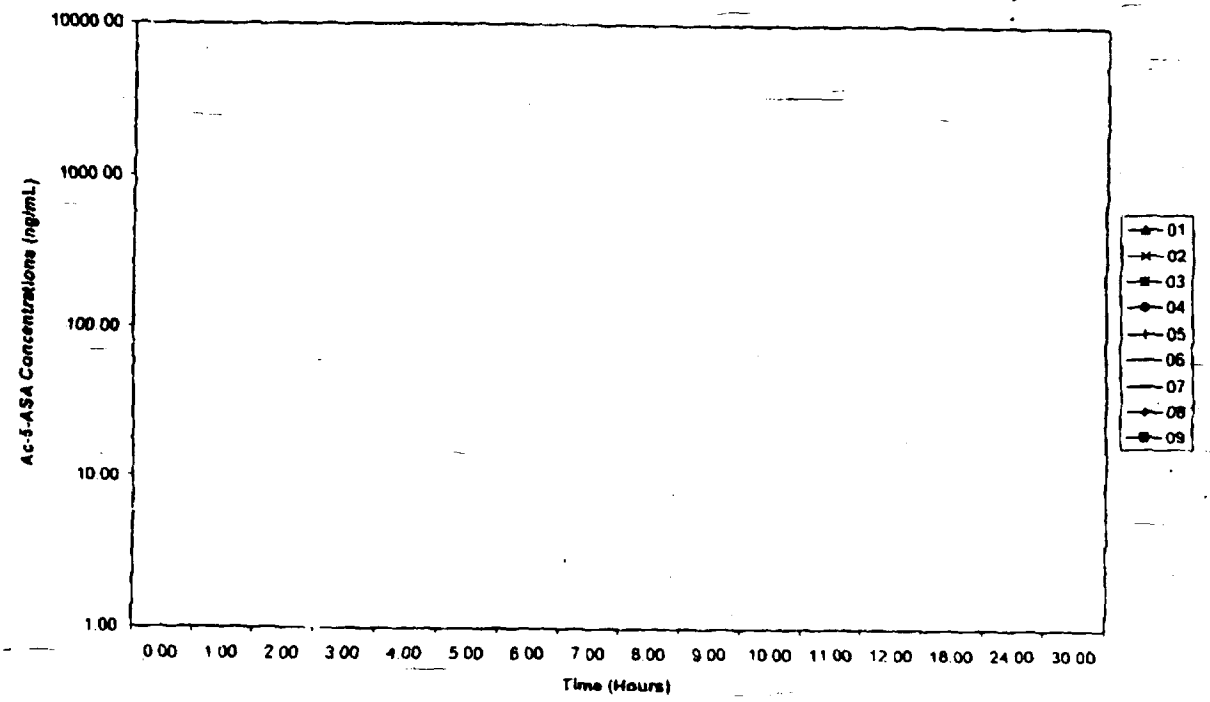
2. Is Adequate Information Provided on Metabolism of Mesalamine Administered as Rectal Suppository?

The metabolism of mesalamine 500 mg rectal suppository was evaluated in the studies described in item 1 above (Protocols MSN-PO-083 and MSN-PO-019). Mesalamine was metabolized to N-acetyl-5-ASA. Plots of individual subject profiles of N-acetyl-5-ASA obtained in the study are presented in Figs. 3 and 4. A summary of the pharmacokinetic parameters of N-acetyl-5-ASA is presented in Table 2 (see Appendix I [pages 26-29] for individual subject plasma concentration and pharmacokinetic data).

Fig. 3. Individual Subject Plots of Plasma Concentration Profiles of N-acetyl-5-ASA in Patients with Ulcerative Proctitis Following the Administration of Mesalamine 500 mg Rectal Suppository Administered

as a Single Dose (A) and Following the Last Dose of Multiple Dose Administration Every Eight Hours for Six Days (B)

A



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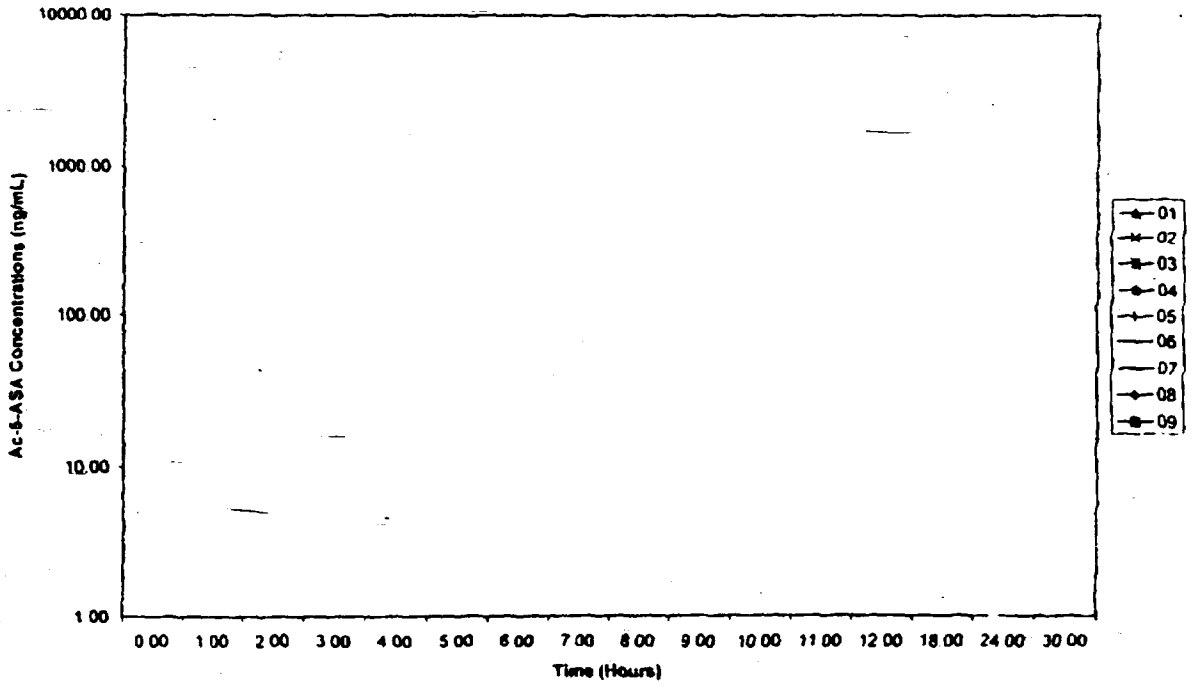
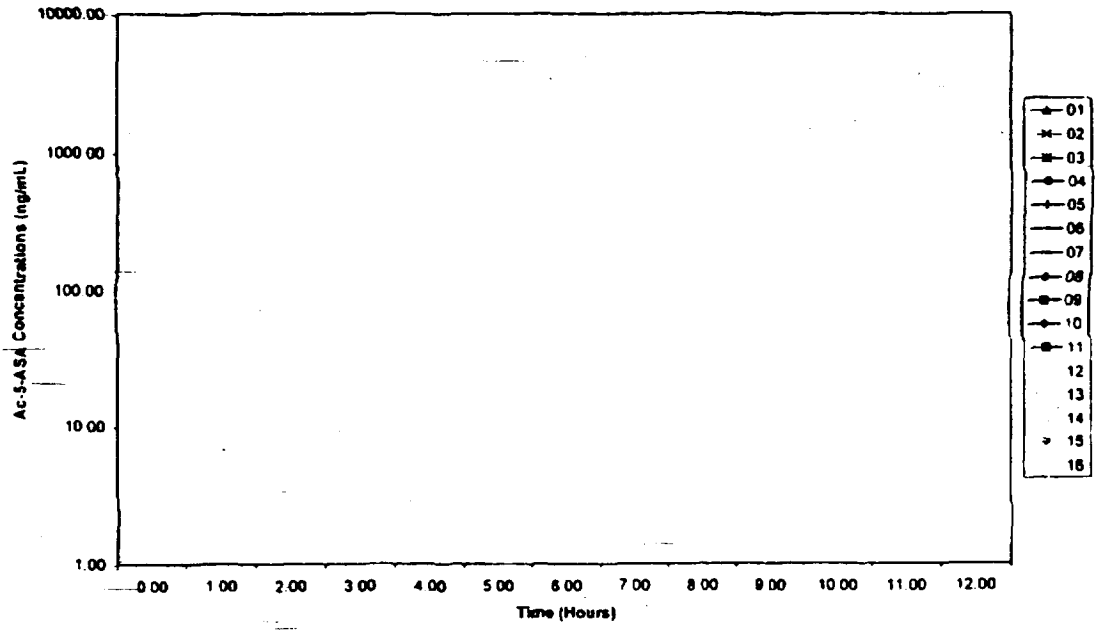


Fig. 4. Individual Subject Plots of Plasma Concentration Profiles of N-acetyl-5-ASA in Healthy Subjects Following the Administration of Mesalamine 500 mg Rectal Suppository as a Single Dose (A) and Following the Last Dose of Multiple Dose Administration Every Eight Hours for Six Days (B)

A



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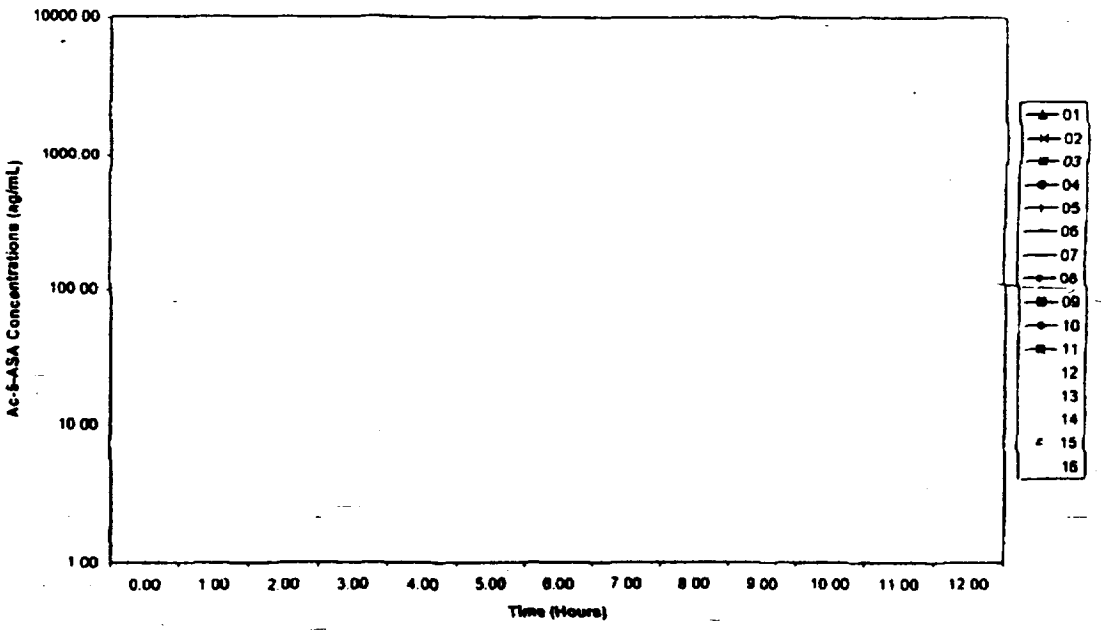

Table 2. Summary of Pharmacokinetic Parameters of N-acetyl-ASA in Patients with Ulcerative Proctitis and Healthy Subjects Following the Administration of Mesalamine 500 mg Rectal Suppository as a Single Dose and Following the Last Dose of Multiple Dose Administration Every eight Hours for Six Days.

N-acetyl-5-ASA

Parameter	Single Dose Regimen				Multiple Dose Regimen			
	Patients		Healthy Subjects		Patients		Healthy Subjects	
n	9		16		9		16	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{min} (ng/mL)	NC[1]	NC[1]	NC	NC	208.88	71.74	84.26	192.77
C_{max} (ng/mL)	713.43	39.47	475.90	56.65	623.74	53.94	779.07	34.33
T_{max} (h)	7.78	44.86	4.10	43.90	6.75	49.33	3.40	82.40
AUC_{0-T}[a]	8538.5	41.69	3203.0	67.7	NC[1]	NC[1]	NC[1]	NC[1]
AUC_{inf}[a,b]	9437.0	48.23	4487.4	95.29	NC[1]	NC[1]	NC[1]	NC[1]
AUC_{0-8}[a]	NC[1]	NC[1]	NC	NC	3391.6	51.7	4140.0	46.2
AUC_{0-12}[a]	NC[1]	NC[1]	NC	NC	4776.9	55.8	4778.0	52.8
$t_{1/2}$ (h)	5.80	63.21	3.48	99.31	7.56	82.29	1.79	75.50
Fluctuation (%)	NC[1]	NC[1]	NC	NC	117.15	53.52	211.60	44.62

[1]Not calculated, [a]ng/mL*h, [b]$AUC_{0\text{-infinity}}$

Based on these results, the ratios, N-acetyl-5-ASA/5-ASA of the exposure parameters (AUC, C_{max} and C_{min}) approximate 2.0 or greater. These findings suggest that following rectal administration of mesalamine 500 mg suppository, mesalamine is extensively metabolized to N-acetyl-5-ASA, its major metabolite. The values of the single dose AUC and steady state C_{min} of N-acetyl-5-ASA appear to be greater for patients with ulcerative colitis as compared to healthy individuals but its steady state AUC values for ulcerative colitis patients and healthy individuals appear to be comparable. In general, inter-individual variability in N-acetyl-5-ASA kinetics is high.

3. Is Adequate Information Provided on Urinary Excretion of Mesalamine Administered as Rectal Suppository?

In the studies of mesalamine 500 mg rectal suppository in ulcerative proctitis patients and in healthy subjects described in item 1 above (Protocols MSN-PO-083 and MSN-PO-019), the 30-hour urinary excretion of 5-ASA and N-acetyl-5- ASA was evaluated following the single dose treatment and the last dose of the multiple dose treatment regimen. The results are summarized in Table 2.

Table 3. Percentage of 5-ASA Eliminated in Urine unchanged and as N-acetyl 5-ASA Over Thirty Hours in Patients with Ulcerative Proctitis and Healthy Subjects Following the

Administration of Mesalamine 500 mg Rectal Suppository as a Single Dose and Following the Last Dose of Multiple Dose Administration Every Eight Hours for Six Days.

Moiety 5-ASA		Percentage of 5-ASA Dose Single Dose Regimen		Percentage of 5-ASA Dose Multiple Dose Regimen	
		Patients	Healthy Subjects	Patients	Healthy Subjects
	n	9	16	9	16
	Mean	1.90	0.17	2.34	0.55
	CV (%)	205.26	111.8	152.14	152.7
	Minimum	0.15	0.02	0	0.05
	Maximum	12.26	7.37	11.15	3.45
N-Acety-5-ASA					
	Mean	39.40	16.95	28.64	23.6
	CV (%)	71.80	80.59	55.90	59.96
	Minimum	15.02	2.55	3.77	7.58
	Maximum	107.5	50.86	49.84	59.38

These findings suggest that, in ulcerative colitis patients or healthy individuals treated with mesalamine 500 mg rectal suppository, less than 13% of the dose of mesalamine is eliminated unchanged in urine in 30 h following a single dose or under steady state conditions. In the same time interval and under the under the same conditions, the fraction of mesalamine eliminated in urine as N-acetyl-5-ASA is 50% or greater. These data suggest that in ulcerative patients or healthy individuals treated with mesalamine 500 mg suppository, mesalamine is eliminated mainly in urine, predominantly as N-acetyl-5-ASA.

4. Is any Information Provided on Rectal Tissue Kinetics of Mesalamine Administered as Rectal Suppository?

In the multiple dosage portions of the studies described in item 1 above (Protocols MSN-PO-083 and MSN-PO-019), rectal biopsy was performed on each subject 8 h following the last dose of Canasa® 500 mg suppository (i.e., 152 h from initiation of treatment).

Table 4. Rectal tissue Concentration of 5-ASA and N-acetyl 5-ASA (ng/mg of Tissue) in Subjects with Ulcerative Proctitis and in Healthy Subjects 152 Hours Following Initiation of Treatment with Mesalamine Rectal Suppository in a Multiple Dosage Regimen of 500 mg Every Eight Hours for Six Days

Moiety	Concentration (ng/mg of Tissue)

		Patients	Healthy Subjects
5-ASA			
	n	5	16
	Mean	19.44	22.33
	CV (%)	136.66	178.71
	Minimum	1.44	0.01
	Maximum	63.45	139.31
N-Acety-5-ASA			
	n	9	16
	Mean	19.41	6.17
	CV (%)	79.59	83.85
	Minimum	3.17	0.12
	Maximum	51.45	16.19

In patients with ulcerative colitis, the rectal tissue concentrations (ng/mg of tissue) ranged from 1.44 to 63.45 (mean=19.49, CV=135.66, n=5) for 5-ASA and from 3.17 to 51.45 (mean=19.41, CV=79.59, n=9) for N-acetyl-5-ASA. For 4 of 9 patients, "extrapolated" values ranging to 66.38 ng/mg of tissue to 541.56 ng/mg of tissue are stated. What these values were extrapolated from and the reason(s) for extrapolation were not stated in the NDA. Accordingly, the extrapolated values are considered unacceptable. In healthy subjects, the rectal tissue concentrations (ng/mg of tissue) ranged from 0.01 to 139.31 (mean=22.33, CV=178.71%, n=16) for 5-ASA and 0.12 to 16.19 (mean=6.17, CV=83.86%, n=16) for N-acetyl-5-ASA. These data suggest high inter-individual variability in 5-ASA and N-acetyl-5-ASA concentrations in rectal tissues following rectal administration of mesalamine 500 mg suppository. Safetyor efficacy information that would allow an exploration of a relationship between rectal tissue concentration of mesalamine and safety or efficacy is not provided in the NDA.

On November 9, 2000, the sponsor submitted Amendment BB to the NDA in response to the Agency's request for a description of, and the validation data for, the analysis of 5-ASA and N-acetyl-5-ASA in rectal tissue samples (see Appendix I [pages 30-31]). In this amendment, the sponsor states (i) that there was no validated method for the analysis of these analytes in rectal tissue samples since blank rectal tissue samples were not obtained in the study, (ii) that the reason for not obtaining blank rectal tissue samples was to spare the patients the inconvenience of undergoing unnecessary biopsies, (iii) that such "unnecessary" biopsies could possibly have interfered with the study, (iv) that the rectal tissue concentrations of 5-ASA and N-acetyl-5-ASA submitted in the original NDA were estimated using the plasma standard curves for these analytes and (iv) that the rectal tissue concentrations of 5-ASA and N-acetyl-5-ASA estimated using their plasma standard curves, though not rigorously exact, do indicate that there is uptake of 5-ASA and N-acetyl-5-ASA into rectal tissue following administration of Canasa® 500 mg rectal suppository to patients with ulcerative proctitis or healthy individuals.

Since the Agency does not usually ask for drug concentrations at the site of drug action as a requirement for NDA approval, it is considered that further comments related to the analysis of 5-ASA and N-acetyl-5ASA in rectal tissue samples are not necessary. In the drug product labeling, rectal tissue uptake of mesalamine from Canasa® 500 mg rectal suppository will be expressed qualitatively rather than quantitatively.

5. ***Is Adequate Information Provided on Drug-Drug Interactions?***

No information is provided on the potential of interactions of mesalamine administered as the 500 mg rectal suppository with other drugs.

6. *Is Adequate Pharmacokinetic Provided in Special Populations (Patients with Renal or Hepatic Impairment)?*

No information is provided on the effect of renal or hepatic impairment on elimination of mesalamine in patients treated with Canasa® 500 mg rectal suppository. N-acetyl 5-ASA and 5-ASA elimination is likely to be prolonged in patients with renal impairment. In patients with hepatic impairment, there is a potential of 5-ASA systemic accumulation due to reduced metabolism.

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Analytical methods

9. *Is Adequate Information Provided on Dissolution of 5-ASA?*

The following dissolution information is provided for 5-ASA 500 mg suppository.

(a) Dissolution Method and Specification:

Apparatus: USP Apparatus 2
Dissolution Medium: Phosphate Buffer (Volume = 900 mL, pH = 7.5, Temperature = 37°C)
Speed of Paddle Rotation: 100 rpm
Duration of Sampling: 120 minutes
Dissolution specification: Not less than (NLT) % in 120 min

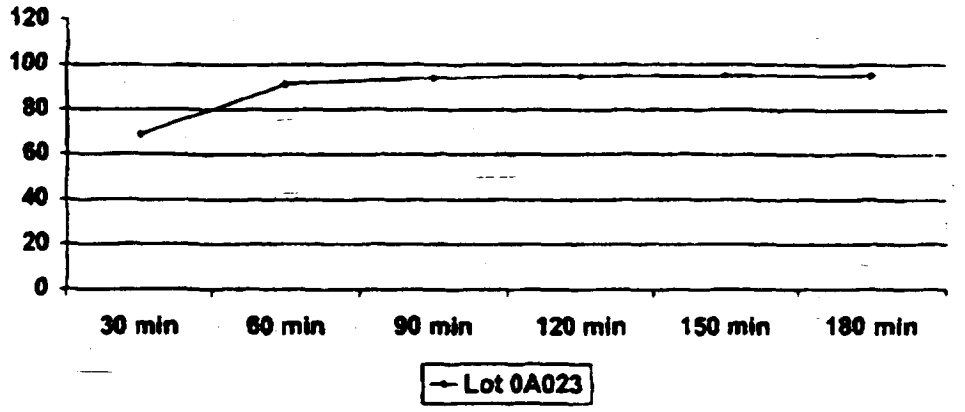
(b) Summary of Dissolution Data for Three Lots of 5-ASA 500 mg Suppositories (Six Suppositories per Lot) Tested Using the above Dissolution Method):

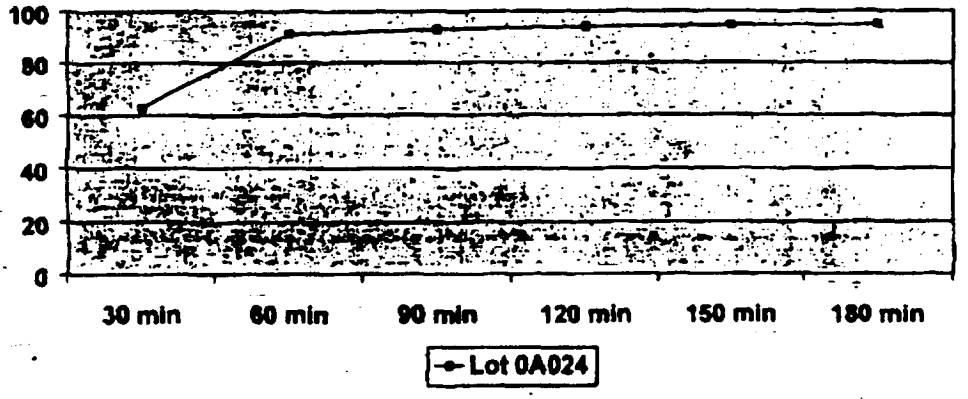
	% of 5-ASA Dissolved		
Lot Number	Range:	Mean	CV (%)
OA025		98.0	1.6
OA024		97.7	1.8
OA023		98.7	2.1

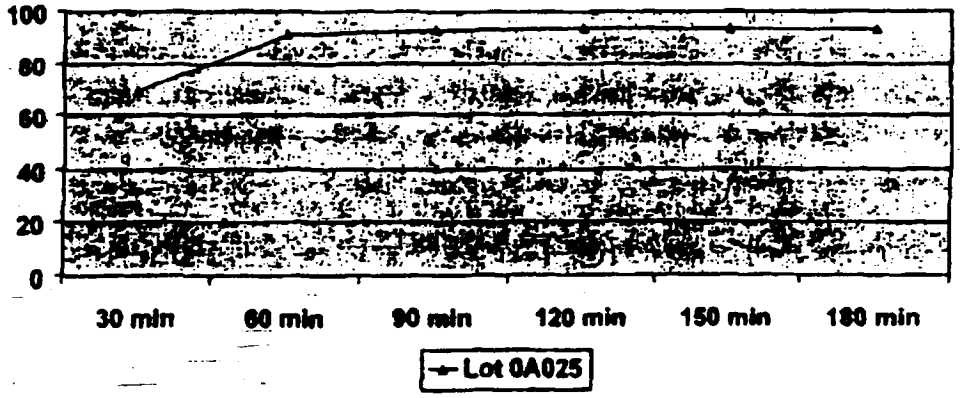
(c) Plots of Dissolution Profiles for Lots OA023, OA024 and OA025 with Dissolved 5-ASA analyzed at 30, 60, 90, 120, 150 and 180 min from Onset of Test:

Plots of the dissolution profile summary in item (b) above are presented in Fig. 5.

Fig 5. Mean Plots of Percentage of 5-ASA Dissolved in 900 mL of Acetate Buffer at pH of 7.5 and Temperature of 25°C using USP Apparatus 2 (Paddle) at 100 rpm for 5-ASA Lots OA023, OA024 and OA025







(d) Summary of Dissolution Data for Three Six-month Stability Lots of 5-ASA 500 mg Suppositories Tested at 25°C and a Paddle Speeds of 75 rpm and 100 rpm:

The following data were provided in Amendment BC submitted to the NDA on August 15, 2000.

		% of 5-ASA Dissolved	
Lot Number	n	at 75 rpm	at 100 rpm
9H26	6	70.7-90.0	93.9-99.9
9H27	5	84.7-102.3	100.2-100.9
9H28	5	89.5-99.7	100.1-100.8

Dissolution testing of mesalamine 500 mg suppository at 25°C was not acceptable. The sponsor was requested to further evaluate the drug product dissolution at 37°C using Apparatus 2 (paddle) speeds of 50 and 75 rpm and submit the individual dose unit tabulated and graphical dissolution profiles for review. The sponsor submitted the requested data, plus data for a paddle speed of 100 rpm at 37°C, in Amendment BB to the NDA, on October 11, 2000 (see Appendix I [pages 32-35]). The data submitted by the sponsor are considered acceptable.

Based on the data submitted in the aforestated Amendment BB to the NDA, the following Dissolution Method and Specification are recommended:

Apparatus:	USP Apparatus 2 (Paddle)
Speed of Paddle Rotation:	75 rpm
Dissolution Medium:	Phosphate Buffer (Volume = 900 mL, pH = 7.5, Temperature = 37°C)
Duration of Sampling:	120 minutes
Dissolution specification:	Not less than (NLT) % in 120 min

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III. LABELING COMMENTS

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IV. GENERAL COMMENT

In the study evaluating the bioavailability of mesalamine 500 mg suppository in nine patients with ulcerative proctitis, the adverse events observed were headache (n=3), abdominal pain (n=3), nausea (n=2), vomiting (n=1), abnormal purple vaginal discharge (n=1), dysmenorrhea (n=1), constipation (n=1), diarrhea (with purple stool) (n=1), stool abnormality, fatigue (n=1), flatulence (n=1), melena (n=1), vertigo (n=1) and urinary abnormality (n=1). The sponsor states that only headache, abdominal pain, nausea,

vomiting, constipation, diarrhea (with purple stool), melena and vertigo were possibly related to the drug. Are these adverse events of any clinical significance?

V. RECOMMENDATION

NDA 21-252 submitted for mesalamine (Canasa®) 500 mg suppository, by the sponsor, on October 29, 1999, and the amendments to the NDA submitted on August 15, 2000, August 30, 2000 and October 11, 2000, October 23, 2000, November 2, 2000 and November 9, 2000 have been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The mesalamine pharmacokinetic information provided in the NDA is acceptable for consideration in the process of making the NDA approval decision. However, the issues raised in Labeling Comments 1 and 2 (pages 19-20) need to be satisfactorily addressed by the sponsor prior to NDA approval.

Please convey this Recommendation and Labeling Comments 1 and 2 (pages 19-20), as appropriate, to the sponsor. The General Comment above should be brought to the attention of the reviewing medical officer.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

Clinpharm/Biopharm Briefing: 11/22/00 (Attendees: Malinowski, Hunt, Doddapaneni and Roy [HFD-870]).

cc: NDA 21-252, HFD-180, HFD-180 (McNeil), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).