

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-751

Name: Mesalamine Rectal Suspension USP (Enema),
4 g/60 mL unit-dose bottle

Sponsor: Mfd by Agis Industries (1983), Ltd.
Dist by Clay-Park Labs, Inc.

Approval Date: September 17, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

APPROVAL LETTER

ANDA 76-751

SEP 17 2004

Clay-Park Labs, Inc.
Attention: Candis Edwards
U.S. Agent for: Agis Industries (1983), Ltd.
1701 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mesalamine Rectal Suspension, USP (Enema), 4 g/60 mL unit-dose bottle).

Reference is also made to your amendments dated April 6, May 5, June 17, July 23, and September 7, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Mesalamine Rectal Suspension, USP (Enema), 4 g/60 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Rowasa[®] Rectal Suspension, USP (Enema), 4 g/60 mL, of Solvay Pharmaceuticals. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with

applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler 9/17/01

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 76-751
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:

HFD-640/S.Read/ *Read 5/13/04*
HFD-645/B.Arnwine/5/13/04 *B.Arnwine 5/25/04*
HFD-617/N.Lee/ *nee 5/14/04*
HFD-613/K.Lee/ *KL 5/10/04*
HFD-613/L.Golson/ *mailed for L. Golson 5/17/04*

3/3/04 6/25/04
Robert West
9/17/2004

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F/T by: EW 5/13/04

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

APPROVED LABELING



Mesalamine Rectal Suspension, USP Enema

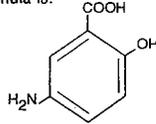
4.0 grams/unit (60 mL)

Rx only



DESCRIPTION: The active ingredient in mesalamine rectal suspension enema, a disposable (60 mL) unit, is mesalamine, also known as 5-aminosalicylic acid (5-ASA). Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid.

The empirical formula is $C_7H_7NO_3$, representing a molecular weight of 153.14. The structural formula is:



Each rectal suspension enema unit contains 4 grams of mesalamine. In addition to mesalamine the preparation contains the inactive ingredients carbomer 934P, edetate disodium, potassium acetate, potassium metabisulfite, purified water and xanthan gum. Sodium benzoate is added as a preservative. The disposable unit consists of an applicator tip protected by a polyethylene cover and lubricated with USP white petrolatum. The unit has a one-way valve to prevent back flow of the dispensed product.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). It is thought that the mesalamine component is therapeutically active in ulcerative colitis [A.K. Azad Khan *et al*, *Lancet* 2:892-895 (1977)]. The usual oral dose of sulfasalazine for active ulcerative colitis in adults is two to four grams per day in divided doses. Four grams of sulfasalazine provide 1.6 g of free mesalamine to the colon. Each mesalamine rectal suspension enema delivers up to 4 g of mesalamine to the left side of the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e., prostanooids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyicosatetraenoic acids (HETEs) is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Preclinical Toxicology

Preclinical studies have shown the kidney to be the major target organ for mesalamine toxicity. Adverse renal function changes were observed in rats after a single 600 mg/kg oral dose, but not after a 200 mg/kg dose. Gross kidney lesions, including papillary necrosis, were observed after a single oral 900 mg/kg dose, and after i.v. doses of > 214 mg/kg. Mice responded similarly. In a 13-week oral (gavage) dose study in rats, the high dose of 640 mg/kg/day mesalamine caused deaths, probably due to renal failure, and dose-related renal lesions (papillary necrosis and/or multifocal tubular injury) were seen in most rats given the high dose (males and females) as well as in males receiving lower doses 160 mg/kg/day. Renal lesions were not observed in the 160 mg/kg/day female rats. Minimal tubular epithelial damage was seen in the 40 mg/kg/day males and was reversible. In a six-month oral study in dogs, the no-observable dose level of mesalamine was 40 mg/kg/day and doses of 80 mg/kg/day and higher caused renal pathology similar to that described for the rat. In a combined 52-week toxicity and 127-week carcinogenicity study in rats, degeneration in kidneys was observed at doses of 100 mg/kg/day and above admixed with diet for 52 weeks, and at 127 weeks increased incidence of kidney degeneration and hyalinization of basement membranes and Bowman's capsule were seen at 100 mg/kg/day and above. In the 12 month eye toxicity study in dogs, Keratoconjunctivitis Sicca (KCS) occurred at oral doses of 40 mg/kg/day and above. The oral preclinical studies were done with a highly bioavailable suspension where absorption throughout the gastrointestinal tract occurred. The human dose of 4 grams represents approximately 80 mg/kg but when mesalamine is given rectally as a suspension, absorption is poor and limited to the distal colon (see **Pharmacokinetics**). Overt renal toxicity has not been observed (see **ADVERSE REACTIONS** and **PRECAUTIONS**), but the potential must be considered.

Pharmacokinetics

Mesalamine administered rectally as mesalamine rectal suspension enema is poorly absorbed from the colon and is excreted principally in the feces during subsequent bowel movements. The extent of absorption is dependent upon the retention time of the drug product, and there is considerable individual variation. At steady state, approximately 10 to 30% of the daily 4-gram dose can be recovered in cumulative 24-hour urine collections. Other than the kidney, the organ distribution and other bioavailability characteristics of absorbed mesalamine in man are not known. It is known that the compound undergoes acetylation but whether this process takes place at colonic or systemic sites has not been elucidated.

Whatever the metabolic site, most of the absorbed mesalamine is excreted in the urine as the N-acetyl-5-ASA metabolite. The poor colonic absorption of rectally administered mesalamine is substantiated by the low serum concentration of 5-ASA and N-acetyl-5-ASA seen in ulcerative colitis patients after dosage with mesalamine. Under clinical conditions patients demonstrated plasma levels 10 to 12 hours post mesalamine administration of 2 µg/mL, about two-thirds of which was the N-acetyl metabolite. While the elimination half-life of mesalamine is short (0.5 to 1.5 h), the acetylated metabolite exhibits a half-life of 5 to 10 hours [U. Klotz, *Clin. Pharmacokin.* 10:285-302 (1985)]. In addition, steady state

plasma levels demonstrated a lack of accumulation of either free or metabolized drug during repeated daily administrations.

Efficacy

In a placebo-controlled, international, multicenter trial of 153 patients with active distal ulcerative colitis, proctosigmoiditis or proctitis, mesalamine rectal suspension enema reduced the overall disease activity index (DAI) and individual components as follows:

EFFECT OF TREATMENT ON SEVERITY OF DISEASE DATA FROM U.S.-CANADA TRIAL COMBINED RESULTS OF EIGHT CENTERS

Activity Indices, mean

		N	Base-line	Day 22	End-Point	Change Baseline to End-Point †
Overall DAI	Mesalamine Rectal Suspension Enema	76	7.42	4.05**	3.37***	-55.07%***
	Placebo	77	7.40	6.03	5.83	-21.58%
Stool Frequency	Mesalamine Rectal Suspension Enema		1.58	1.11*	1.01**	-0.57*
	Placebo		1.92	1.47	1.50	-0.41
Rectal Bleeding	Mesalamine Rectal Suspension Enema		1.82	0.59***	0.51***	-1.30***
	Placebo		1.73	1.21	1.11	-0.61
Mucosal Inflammation	Mesalamine Rectal Suspension Enema		2.17	1.22**	0.96***	-1.21**
	Placebo		2.18	1.74	1.61	-0.56
Physician's Assessment of Disease Severity	Mesalamine Rectal Suspension Enema		1.86	1.13***	0.88***	-0.97***
	Placebo		1.87	1.62	1.55	-0.30

Each parameter has a 4-point scale with a numerical rating: 0 = normal, 1 = mild, 2 = moderate, 3 = severe. The four parameters are added together to produce a maximum overall DAI of 12.

†Percent change for overall DAI only (calculated by taking the average of the change for each individual patient).

* Significant mesalamine rectal suspension enema /placebo difference. p<0.05

** Significant mesalamine rectal suspension enema /placebo difference. p<0.01

*** Significant mesalamine rectal suspension enema /placebo difference. p<0.001

Differences between mesalamine rectal suspension enema and placebo were also statistically different in subgroups of patients on concurrent sulfasalazine and in those having an upper disease boundary between 5 and 20 or 20 and 40 cm. Significant differences between mesalamine rectal suspension enema and placebo were not achieved in those subgroups of patients on concurrent prednisone or with an upper disease boundary between 40 and 50 cm.

INDICATIONS AND USAGE

Mesalamine rectal suspension enema is indicated for the treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

CONTRAINDICATIONS

Mesalamine rectal suspension enema is contraindicated for patients known to have hypersensitivity to the drug or any component of this medication.

WARNINGS

Mesalamine rectal suspension enema contains potassium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown but probably low. Sulfite sensitivity is seen more frequently in asthmatic or in atopic nonasthmatic persons. Epinephrine is the preferred treatment for serious allergic or emergency situations even though epinephrine injection contains sodium or potassium metabisulfite with the above-mentioned potential liabilities. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in epinephrine injection should not deter the administration of the drug for treatment of serious allergic or other emergency situations.

PRECAUTIONS

Mesalamine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's history of sulfasalazine intolerance, if any, should be re-evaluated. If a rechallenge is performed later in order to validate the hypersensitivity it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. In the literature one patient previously sensitive to sulfasalazine was rechallenged with 400 mg oral mesalamine; within eight hours she experienced headache, fever, intensive abdominal colic, profuse diarrhea and was readmitted as an emergency. She responded poorly to steroid therapy and two weeks later a pancolectomy was required.

Although renal abnormalities were not noted in the clinical trials with

mesalamine rectal suspension enema, the possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on mesalamine rectal suspension enema, especially those on concurrent oral products which liberate mesalamine and those with preexisting renal disease, should be carefully monitored with urinalysis, BUN and creatinine studies.

In a clinical trial most patients who were hypersensitive to sulfasalazine were able to take mesalamine enemas without evidence of any allergic reaction. Nevertheless, caution should be exercised when mesalamine is initially used in patients known to be allergic to sulfasalazine. These patients should be instructed to discontinue therapy if signs of rash or fever become apparent.

While using mesalamine rectal suspension enema some patients have developed pancolitis. However, extension of upper disease boundary and/or flare-ups occurred less often in the mesalamine rectal suspension enema treated group than in the placebo-treated group.

Rare instances of pericarditis have been reported with mesalamine containing products including sulfasalazine. Cases of pericarditis have also been reported as manifestations of inflammatory bowel disease. In the cases reported with mesalamine rectal suspension enema there have been positive rechallenges with mesalamine or mesalamine containing products. In one of these cases, however, a second challenge with sulfasalazine was negative throughout a 2 month follow-up. Chest pain or dyspnea in patients treated with mesalamine rectal suspension enema should be investigated with this information in mind. Discontinuation of mesalamine rectal suspension enema may be warranted in some cases, but rechallenge with mesalamine can be performed under careful clinical observation should the continued therapeutic need for mesalamine be present.

Information for Patients: See patient information enclosed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mesalamine caused no increase in the incidence of neoplastic lesions over controls in a two-year study of Wistar rats fed up to 320 mg/kg/day of mesalamine admixed with diet. Mesalamine is not mutagenic to *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, TA1538. There were no reverse mutations in an assay using *E. coli* strain WP2UVRA. There were no effects in an *in vivo* mouse micronucleus assay at 600 mg/kg and in an *in vivo* sister chromatid exchange at doses up to 610 mg/kg. No effects on fertility were observed in rats receiving up to 320 mg/kg/day. The oligospermia and infertility in men associated with sulfasalazine have not been reported with mesalamine.

Pregnancy (Category B)

Teratologic studies have been performed in rats and rabbits at oral doses up to five and eight times respectively, the maximum recommended human dose, and have revealed no evidence of harm to the embryo or the fetus. There are, however, no adequate and well controlled studies in pregnant women for either sulfasalazine or 5-ASA. Because animal reproduction studies are not always predictive of human response, 5-ASA should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether mesalamine or its metabolite(s) are excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Adverse Experience

Mesalamine rectal suspension enema is usually well tolerated. Most adverse effects have been mild and transient.

ADVERSE REACTIONS OCCURRING IN MORE THAN 0.1 % OF MESALAMINE RECTAL SUSPENSION ENEMA TREATED PATIENTS (COMPARISON TO PLACEBO)

SYMPTOM	MESALAMINE RECTAL SUSPENSION ENEMA		PLACEBO	
	N=815		N=128	
	N	%	N	%
Abdominal Pain/Cramps/Discomfort	66	8.10	10	7.81
Headache	53	6.50	16	12.50
Gas/Flatulence	50	6.13	5	3.91
Nausea	47	5.77	12	9.38
Flu	43	5.28	1	0.78
Tired/Weak/Malaise/Fatigue	28	3.44	8	6.25
Fever	26	3.19	0	0.00
Rash/Spots	23	2.82	4	3.12
Cold/Sore Throat	19	2.33	9	7.03
Diarrhea	17	2.09	5	3.91
Leg/Joint Pain	17	2.09	1	0.78
Dizziness	15	1.84	3	2.34
Bloating	12	1.47	2	1.56
Back Pain	11	1.35	1	0.78
Pain on Insertion of Enema Tip	11	1.35	1	0.78
Hemorrhoids	11	1.35	0	0.00
Itching	10	1.23	1	0.78
Rectal Pain	10	1.23	0	0.00
Constipation	8	0.98	4	3.12
Hair Loss	7	0.86	0	0.00
Peripheral Edema	5	0.61	11	8.59
UTI/Urinary Burning	5	0.61	4	3.12
Rectal Pain/Soreness/Burning	5	0.61	3	2.34
Asthenia	1	0.12	4	3.12
Insomnia	1	0.12	3	2.34

In addition, the following adverse events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice: nephrotoxicity, pancreatitis, fibrosing alveolitis and elevated liver enzymes. Cases of pancreatitis and fibrosing alveolitis have been reported as manifestations of inflammatory bowel disease as well. Published case reports and/or spontaneous post marketing surveillance have described rare instances of aplastic anemia, agranulocytosis, thrombocytopenia, or eosinophilia. Anemia, leukocytosis and thrombocytosis can be part of the clinical presentation of inflammatory bowel disease.

Hair Loss

Mild hair loss characterized by "more hair in the comb" but no withdrawal from clinical trials has been observed in seven of 815 mesalamine patients but none of the placebo-treated patients. In the literature there are at least six additional patients with mild hair loss who received either mesalamine or sulfasalazine. Retreatment is not always associated with repeated hair loss.

OVERDOSAGE

There have been no documented reports of serious toxicity in man resulting from massive overdosing with mesalamine. Under ordinary circumstances, mesalamine absorption from the colon is limited.

DOSAGE AND ADMINISTRATION

The usual dosage of mesalamine rectal suspension enema in 60 mL units is one rectal instillation (4 grams) once a day, preferably at bedtime, and retained for approximately eight hours. While the effect of mesalamine rectal suspension enema may be seen within three to twenty-one days, the usual course of therapy would be from three to six weeks depending on symptoms and sigmoidoscopic findings. Studies available to date have not assessed if mesalamine rectal suspension enema will modify relapse rates after the 6-week short-term treatment.

Patients should be instructed to shake the bottle well to make sure the suspension is homogeneous. The patient should remove the protective sheath from the applicator tip. Holding the bottle at the neck will not cause any of the medication to be discharged. The position most often used is obtained by lying on the left side (to facilitate migration into the sigmoid colon); with the lower leg extended and the upper right leg flexed forward for balance. An alternative is the knee-chest position. The applicator tip should be gently inserted in the rectum pointing toward the umbilicus. A steady squeezing of the bottle will discharge most of the preparation. The preparation should be taken at bedtime with the objective of retaining it all night. Patient instructions are included with every seven units.

HOW SUPPLIED

Mesalamine rectal suspension, USP for rectal administration is an off-white to tan colored suspension. Each disposable enema bottle contains 4.0 grams of mesalamine in 60 mL aqueous suspension. Enema bottles are supplied in boxed, foil-wrapped trays of seven. Mesalamine rectal suspension, USP are for rectal use only.

Patient instructions are included.

Store at 20 to 25°C (68 to 77°F) (See USP Controlled Room Temperature). Once the foil-wrapped unit of seven bottles is opened, all enemas should be used promptly as directed by your physician. **Contents of enemas removed from the foil pouch may darken with time. Slight darkening will not affect potency, however, enemas with dark brown contents should be discarded.**

NOTE: Mesalamine rectal suspension enema will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel. Take care in choosing a suitable location for administration of this product.

Mfg. By: **Agis Industries (1983) Ltd.**
Yeruham, 80500 Israel

Dist. By: **CLAY-PARK LABS, INC.**
Bronx, NY 10457

1144-4X N0403

PATIENT INSTRUCTIONS

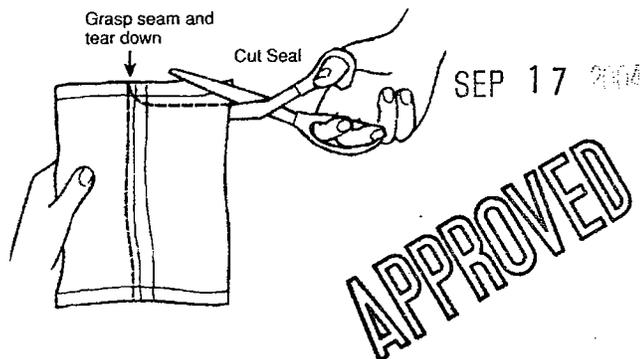
How to Use this Medication.

Best results are achieved if the bowel is emptied immediately before the medication is given.

NOTE: Mesalamine rectal suspension enema will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel. Take care in choosing a suitable location for administration of this product.

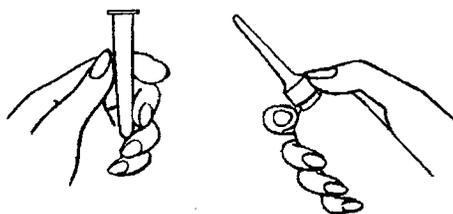
1 Remove the Bottles

- a. Remove the bottles from the protective foil pouch by tearing or by using scissors as shown, being careful not to squeeze or puncture bottles. Mesalamine rectal suspension enema is an off-white to tan colored suspension. Once the foil-wrapped unit of seven bottles is opened, all enemas should be used promptly as directed by your physician. **Contents of enemas removed from the foil pouch may darken with time. Slight darkening will not affect potency, however, enemas with dark brown contents should be discarded**



2 Prepare the Medication for Administration

- a. Shake the bottle well to make sure that the medication is thoroughly mixed.
- b. Remove the protective sheath from the applicator tip. Hold the bottle at the neck so as not to cause any of the medication to be discharged.

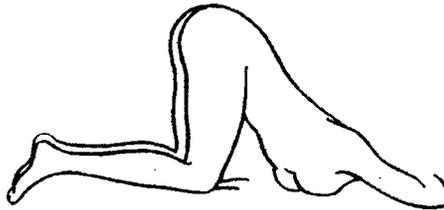


3 Assume the Correct Body Position

- a. Best results are obtained by lying on the left side with the left leg extended and the right leg flexed forward for balance.

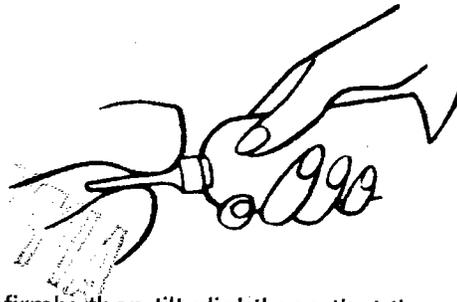


- b. An alternative to lying on the left side is the "knee-chest" position as shown here.



4 Administer the Medication

- a. Gently insert the lubricated applicator tip into the rectum to prevent damage to the rectal wall, pointed slightly toward the navel.



- b. Grasp the bottle firmly, then tilt slightly so that the nozzle is aimed toward the back, squeeze slowly to instill the medication. Steady hand pressure will discharge most of the medication. After administering, withdraw and discard the bottle.
- c. Remain in position for at least 30 minutes to allow thorough distribution of the medication internally. Retain the medication all night, if possible.

Mfg. By: **Agis Industries (1983) Ltd.**
Yeruham, 80500 Israel
Dist. By: **CLAY-PARK LABS, INC.**
Bronx, NY 10457

ORIG.

Each disposable unit-dose contains:
 Mesalamine.....4 gram
 in a suspension containing carbomer
 934P, edelate disodium, potassium
 acetate, potassium metabisulfite,
 purified water, sodium benzoate and
 xanthan gum.
SHAKE WELL BEFORE USE
 Store at 20° to 25°C (68° to 77°F)
 (See USP Controlled Room Temperature).
 Enema contents may darken with time.
 See package insert for complete
 information.
 Usual Dose: One unit-dose suspension
 daily before retiring. See enclosed
 directions.
 Mfg. By: Agis Industries (1983) Ltd.
 Yehulam, 80500 Israel
 Dist. By: CLAY-PARK LABS, INC.
 LCPL09846-4X N0204



NDC 45802-098-46

**MESALAMINE
 RECTAL
 SUSPENSION, USP
 ENEMA**

4 gram/9.8 mL Unit Dose
 For Rectal Use Only
 Rx only

60 mL

SEP 17 2006

APPROVED

ARTWORK SPECIFICATION • CLAY-PARK LABS, INC.		
1700 BATHGATE AVE., BRONX, NY 10457 U.S.A. P (718) 960.9967 • F (718) 960.9909		
ITEM NAME: Mesalamine Rectal Suspension, USP Enema	PRODUCT NO.: 144	
DIE # / SIZE: Silk Screen on bottle.	ITF / PHARMACODE: NA	
COLORS: Black	DESIGNER: Angel DATE: 4.8.03	
STATEMENT IDENTITY	SIZE	COMPARES TO...
NET WT	TAMPER EVIDENT	UPC
DISTRIBUTED BY	DISCLAIMER	

NDC 45802-098-51

MESALAMINE RECTAL SUSPENSION, USP ENEMA



4g/60 mL

For Rectal Use Only

Rx only

SEP 17

APPROVED

SHAKE WELL BEFORE USE

**DO NOT REMOVE FROM FOIL WRAP UNTIL
READY FOR USE. FOIL WRAP PROTECTS
PRODUCT FROM DISCOLORATION**

7 x 60 mL Unit-Dose Bottles

Each disposable unit contains:
Mesalamine (5-aminosalicylic acid).....4 gram
in a suspension containing carbomer 934P, edelate
disodium, potassium acetate, potassium metabisulfite,
purified water, sodium benzoate and xanthan gum.
USUAL DOSE: One unit-dose suspension before retiring.
See enclosed directions for use.
Dispense in original foil-wrapped package.
Store at 20° to 25°C (68° to 77°F) (See USP Controlled
Room Temperature).
Enema contents may darken with time. See package
insert for complete information.
NOTE: Product contents will cause staining of most
direct contact surfaces.

Mfg. By: Agis Industries (1983) Ltd.
Tel-Aviv, 60500 Israel
Dist. By: CLAY-PARK LABS, INC.
Bronx, NY 10457



3 45802-098-51 1

MESALAMINE RECTAL SUSPENSION, USP
ENEMA

NDC 45802-098-51

4g/60 mL
For Rectal Use Only

ARTWORK SPECIFICATION - CLAY PARK LABS, INC.	
1700 BATHURST AVE. BRONX, NY 10457 U.S.A. ☎ (718) 562-9909	
ITEM NAME: Mesalamine Rectal Suspension, USP, Enema	PRODUCT NO.: 098
DIE # / SIZE: (BT)	(T) / PHARMACODE: NA
COLORS: Pantone 285, 185 Red	DESIGNER: Angil DATE: 4.8.03
STATEMENT IDENTITY	SIZE
NET WT	TAMPER EVIDENT
	UPC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

LABELING REVIEW(S)

(3-1)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-751

Date of Submission: May 30, 2003

Applicant's Name: Agis Industries (1983) Ltd.

Established Name: Mesalamine Rectal Suspension USP, 4 g/60 mL

Labeling Deficiencies:

1. CONTAINER (60 mL unit-dose)
 - a. We encourage you to increase the prominence of "potassium metabisulfite".
 - b. Revise the storage temperature statement to "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".
 - c. Increase the prominence of "For Rectal Use Only".

2. CARTON (7 x 60 mL unit-dose bottles)

See CONTAINER comments

3. INSERT
 - a. We encourage you to add the full text of the patient instructions at the end of the labeling.
 - b. Although the reference listed drug does not refer to the patient instructions in the PRECAUTIONS section, we encourage you to add a statement to that section that refers to the patient instructions.

- b. HOW SUPPLIED

See CONTAINER comment (b).

4. PATIENT INSTRUCTIONS

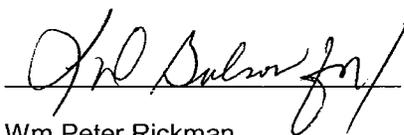
Please explain how the patient instructions will accompany the drug product.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm Peter Rickman", written over a horizontal line.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note:		x	

Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X See FTR 10		
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

- MODEL LABELING : ROWASA ® NDA 19-618/S-013, approved October 1, 2001
- INACTIVE INGREDIENTS (pages 42 and 2836)

Ingredient	Function	%w/w	AND A Batch
Mesalamine, USP*	Active	6.800	
Edetate Disodium, USP			
Carbomer 934P, NF			
Xanthan Gum, NF			

Potassium Acetate, USP					
Sodium Benzoate, NF					
Potassium Metabisulfite, NF					
Purified Water, USP					

preservative agent

3. PATENTS/EXCLUSIVITIES

Patent Data

represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Certification
019618	001	#4657900	APR 14,2004	PIII	None
019618	001	#RE33239	MAY 12,2004	PIII	None

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There is no unexpired exclusivity for this product	

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight, light-resistant containers.
- NDA: Store at controlled room temperature 20° to 25° C (68° to 77°F).
- ANDA: Store at controlled room temperature 20° to 25° C (68° to 77°F). (Chemistry comment -Accelerated (40 °C/75% RH) stability data are provided for packaged lot #ML002 and #ML003 tested at initial, 1, 2 and 3 months. Thermal cycling data has also been provided. The data are adequate and within the specified limits. The antimicrobial effectiveness testing on pages 4577-4594 show that the product passes the USP criteria for antimicrobial effectiveness at all concentrations of sodium benzoate 0% to 100%.)

5. DISPENSING STATEMENT COMPARISON

- NDA: Dispense in original foil-wrapped package.
- ANDA: Dispense in original foil-wrapped package.

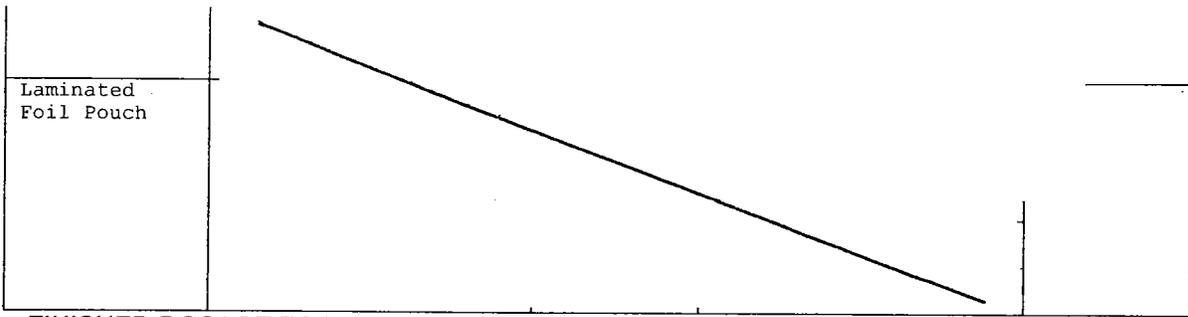
6. PACKAGE CONFIGURATION

- NDA: 7 X 60 mL Unit-Dose Bottles
- ANDA: 7 X 60 mL Unit-Dose Bottles

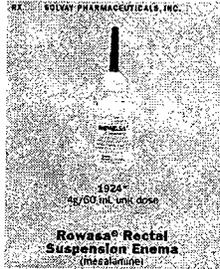
7. CONTAINER/CLOSURE

Summary of packaging systems (page 3361):

Component Description	Component Manufacturer	Materials of Construction	DMF #
60 mL Round bottle	/	/	/
Screw Cap Applicator Tip			
Tray			



8. FINISHED DOSAGE FORM



- NDA:
- ANDA: 60 mL round bottles with screw cap applicator tip wrapped in a laminated foil pouch.

9. The Manufacturer of this drug product is:

Agis Industries (1983) Ltd.
Industrial Zone
Yeruham 80500
Israel

10. This drug product contains potassium metabisulfate. The sulfite warning statement is included in the WARNINGS section per 21 CFR 201. 22.

Date of Review: 12/10/03

Date of Submission: May 30, 2003

Primary Reviewer: Koung Lee *KL*

Date: *02/24/03*

Team Leader: Lillie Golson *L Golson*

Date: *12/24/03*

cc:

ANDA: 76-751
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\Agis\LTRS&REV\76751.NA1.Labeling
Review

APPROVAL SUMMARY
(Only in effect after May 12, 2004)
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH

ANDA Number: 76-751

Date of Submission: May 30, 2003

Applicant's Name: Agis Industries (1983) Ltd.

Established Name: Mesalamine Rectal Suspension USP, 4 g/60 mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES

	Date Submitted	Code	Recommendation
Container (4gram/60 mL)	2/19./04	LCPL09846-4X N0204	Acceptable for Approval
Carton (7X60 mL Unit-Dose Bottles)	2/19./04		Acceptable for Approval
INSERT	2/19./04	I144-4X N0403	Acceptable for Approval
PATIENT INSTRUCTIONS	2/19./04	I098-4X N0403	Acceptable for Approval

- Revisions needed post-approval: Yes

Revise the title of the package insert to read "Mesalamine Rectal Suspension, USP (Enema) 4 grams/unit (60 mL)

BASIS OF APPROVAL:

- Was this approval based upon a petition? None
- What is the RLD on the 356(h) form: Rowasa
- NDA Number: 19-618
- NDA Drug Name: Rowasa
- NDA Firm: Solvay Pharmaceuticals, Inc.
- Date of Approval of NDA Insert and supplement #: October 1, 2001; S-013
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by Side
- Basis of Approval for the Carton Labeling: Side by Side

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x

Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X See FTR 10		

Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

- MODEL LABELING : ROWASA ® NDA 19-618/S-013, approved October 1, 2001
- INACTIVE INGREDIENTS (pages 42 and 2836) Consistent

Ingredient	Function	%w/w	ANDA Batch
Mesalamine, USP*	Active	6.800	
Edetate Disodium, USP			
Carbomer 934P, NF			
Xanthan Gum, NF			
Potassium Acetate, USP			
Sodium Benzoate, NF	preservative agent		
Potassium Metabisulfite, NF			
Purified Water, USP			

3. PATENTS/EXCLUSIVITIES

Patent Data

represents patent information submitted prior to August 18, 2003

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Certification
019618	001	#4657900	APR 14, 2004		PILL None

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There is no unexpired exclusivity for this product	

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight, light-resistant containers.
- NDA: Store at controlled room temperature 20° to 25° C (68° to 77°F).
- ANDA: Store at 20° to 25° C (68° to 77°F)(See USP Controlled Room Temperature).
(Chemistry comment - Accelerated (40 °C/75% RH) stability data are provided for packaged lot #ML002 and #ML003 tested at initial, 1, 2 and 3 months. Thermal cycling data has also been provided. The data are adequate and within the specified limits. The antimicrobial effectiveness testing on pages 4577-4594 show that the product passes the USP criteria for antimicrobial effectiveness at all concentrations of sodium benzoate 0% to 100%.)

5. DISPENSING STATEMENT COMPARISON

- NDA: Dispense in original foil-wrapped package.
- ANDA: Dispense in original foil-wrapped package.

6. PACKAGE CONFIGURATION

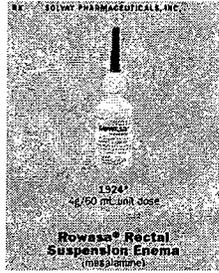
- NDA: 7 X 60 mL Unit-Dose Bottles
- ANDA: 7 X 60 mL Unit-Dose Bottles

7. CONTAINER/CLOSURE

Summary of packaging systems (page 3361):

Component Description	Component Manufacturer	Materials of Construction	DMF #
60 mL Round bottle	/	/	/
Screw Cap Applicator Tip			
Tray			
Laminated Foil Pouch			

8. FINISHED DOSAGE FORM



- NDA:
 - ANDA: 60 mL round bottles with screw cap applicator tip wrapped in a laminated foil pouch.
9. The Manufacturer of this drug product is:
Agis Industries (1983) Ltd.
Industrial Zone
Yeruham 80500
Israel
10. This drug product contains potassium metabisulfate. The sulfite warning statement is included in the WARNINGS section per 21 CFR 201. 22.

Date of Review: February 26, 2004

Date of Submission: February 19, 2004

Primary Reviewer: Koung Lee

Date: 3/4/04

Team Leader: Lillie Golson

Date: 3/4/04

cc:

ANDA: 76-751
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\Agis\LTRS&REV\76751.AP.Labeling
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

CHEMISTRY REVIEW(S)



ANDA #76-751

Mesalamine Rectal Suspension, USP

Agis Industries (1983) Ltd.

**Shahnaz Read
Office of Generic Drugs, Division of Chemistry II**

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Chemistry Review Data Sheet

1. ANDA # 76-751
2. REVIEW #: 1
3. REVIEW DATE: December 8, 2003
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS:

Previous Documents
Original Submission
Acknowledgement Letter

Document Date
May 30, 2003
August 25, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original Submission

Document Date
May 30, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Agis Industries (1983) Ltd.
Address:	Industrial Zone Yeruham, Israel 80500
Authorized U.S. Agent	Clay-Park Labs, Inc. 1701 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
- b) Non-Proprietary Name (USAN): Mesalamine Rectal Suspension, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Rowasa Rectal Suspension Enema the subject of NDA 19-618 manufactured by Solvay Pharmaceuticals containing mesalamine. There is no unexpired marketing exclusivity for Rowasa Rectal Suspension Enema under section 505(j)(4)(D) of the Act. There are two unexpired patents listed:

- U.S. Patent # 4657900, expiration date April 14, 2004
- U.S. Patent # RE33239, expiration date May 12, 2004

Agis has submitted a Paragraph III Certification Statement for these patents.

10. PHARMACOLOGICAL CATEGORY:

Treatment of mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 4 g/60 mL Unit Dose

13. ROUTE OF ADMINISTRATION: Rectal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note 17]:

SPOTS product – Form Completed

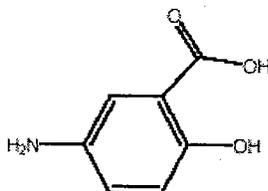
Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Mesalamine
 5-Aminosalicylic acid
 5-amino-2-hydroxybenzoic acid

Chemical Structure:



Molecular Formula: $C_7H_7NO_3$
 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Deficient	December 5, 2003	DMF holder has been notified
	III			4	NA		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or NA (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Rowasa Rectal Suspension Enema	NDA 19-618	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	Nov 4, 2003	S. Adams
Methods Validation	NA		
Labeling	Deficient	Dec 12, 2003	K. Lee
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA # 76-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active pharmaceutical ingredient, Mesalamine is believed to be the therapeutically active component of Sulfasalazine used in treatment of mild to moderate ulcerative colitis. The mechanism of action of Masalamine is unknown and appears to be topical rather than systemic. All the tests described for the drug substance are compendial tests.

The drug product is Mesalamine Rectal Suspension (Enema), packaged in unit-dose containers (4 g/60 mL). The manufacturing process involves _____

_____. The product is packaged as unit dose containers containing 4 g of Mesalamine in 60 mL suspension.

B. Description of How the Drug Product is Intended to be Used

The product is intended for rectal instillation once a day, preferably at bedtime and retained in the body for eight hours. Detailed instructions are provided in the patient instructions which are included along with the insert.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues related to drug substance and stability specifications, and bulk testing.



III. Administrative

A. Reviewer's Signature

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/12/8/03
HFD-645/BTArnwine/1/15/04
HFD-617/NLee/1/15/04

C. CC Block

ANDA 76-751
DIV FILE
Field Copy

APPEARS THIS WAY
ON ORIGINAL

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1



Chemistry Assessment Section

2. Please acknowledge that Mesalamine Rectal Suspension is an official monograph in the United States Pharmacopeia (USP). The approval to use an analytical procedure that may differ from that in the USP does not release your firm from any obligation to comply with the method and procedure in the USP specified for that product. Therefore, in the event of a dispute, only the results obtained by the official method and procedures in the USP will be considered conclusive.

Sincerely yours,

Brenda J. Gennine / for
1/22/04

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



Chemistry Assessment Section

cc: ANDA 76-751
ANANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/12/8/03 *Read 1/16/04*
HFD-645/BTArnwine/1/15/04 *(BT) Arnwine 1/20/04*
HFD-617/NLee/1/15/04 *ML 1/22/04*

F/T by: EW 1/16/04
\\cds013\ogds11\FIRMSAM\AGIS\LTRS&REV\76751R1

TYPE OF LETTER: Not Approvable (Minor)

**APPEARS THIS WAY
ON ORIGINAL**



ANDA #76-751

Mesalamine Rectal Suspension, USP

Agis Industries (1983) Ltd.

**Shahnaz Read
Office of Generic Drugs, Division of Chemistry II**

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B. Endorsement Block	8
C. CC Block.....	8
Chemistry Assessment	9



Chemistry Review Data Sheet

1. ANDA # 76-751
2. REVIEW #: 2
3. REVIEW DATE: March 1, 2004
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS:

Previous Documents

Original Submission
Acknowledgement Letter

Document Date

May 30, 2003
August 25, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Minor Amendment

Document Date

February 19, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Agis Industries (1983) Ltd.
Address:	Industrial Zone Yeruham, Israel 80500
Authorized U.S. Agent	Clay-Park Labs, Inc. 1701 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
- b) Non-Proprietary Name (USAN): Mesalamine Rectal Suspension, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Rowasa Rectal Suspension Enema the subject of NDA 19-618 manufactured by Solvay Pharmaceuticals containing mesalamine. There is no unexpired marketing exclusivity for Rowasa Rectal Suspension Enema under section 505(j)(4)(D) of the Act. There are two unexpired patents listed:

- U.S. Patent # 4657900, expiration date April 14, 2004
- U.S. Patent # RE33239, expiration date May 12, 2004

Agis has submitted a Paragraph III Certification Statement for these patents.

10. PHARMACOLOGICAL CATEGORY:

Treatment of mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 4 g/60 mL Unit Dose

13. ROUTE OF ADMINISTRATION: Rectal

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note17]:

SPOTS product – Form Completed

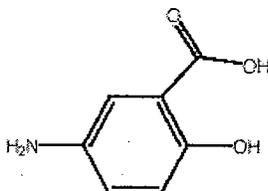
Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Mesalamine
 5-Aminosalicylic acid
 5-amino-2-hydroxybenzoic acid

Chemical Structure:



Molecular Formula: $C_7H_7NO_3$
 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Inadequate	3/1/04	
/	III	/	/	4	NA		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or NA (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Rowasa Rectal Suspension Enema	NDA 19-618	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	Nov 4, 2003	S. Adams
Methods Validation	NA		
Labeling	Acceptable(only after May 12, 2004)	3/4/04	K. Lee
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA # 76-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active pharmaceutical ingredient, Mesalamine is believed to be the therapeutically active component of Sulfasalazine used in treatment of mild to moderate ulcerative colitis. The mechanism of action of Masalamine is unknown and appears to be topical rather than systemic. All the tests described for the drug substance are compendial tests.

The drug product is Mesalamine Rectal Suspension (Enema), packaged in unit-dose containers (4 g/60 mL). The manufacturing process involves _____

_____ The product is packaged as unit dose containers containing 4 g of Mesalamine in 60 mL suspension.

B. Description of How the Drug Product is Intended to be Used

The product is intended for rectal instillation once a day, preferably at bedtime and retained in the body for eight hours. Detailed instructions are provided in the patient instructions which are included along with the insert.

C. Basis for Approvability or Not-Approval Recommendation

A couple of minor issues remain to be resolved.



III. Administrative

A. Reviewer's Signature

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/Review Chemist
HFD-645/BTArnwine/Team Leader
HFD-617/NLee/Project Manager

C. CC Block

ANDA 76-751
DIV FILE
Field Copy

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 11 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2



33. ESTABLISHMENT INSPECTION

Acceptable by S. Adams, November 4, 2003

34. BIOEQUIVALENCE

Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The firm claims a categorical exclusion from the requirement of an Environmental Impact Analysis statement under 21 CFR sec §25.31(a).

**APPEARS THIS WAY
ON ORIGINAL**



36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-751

APPLICANT: Agis Industries (1983) Ltd.

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 g/60 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. _____

2. Since Mesalamine Rectal Suspension is a USP product, stability specifications for Impurities should match USP limits for the product.
3. _____

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-751
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/3/1/04

HFD-645/BTArnwine/3/24/04

HFD-617/NLee/3/24/04

Read 3/25/04
B. Arnwine 3/25/04
N. Lee 3/26/04

F/T by: EW 3/25/04

\\cds013\ogds11\FIRMSAM\AGIS\LTRS&REV\76751R2

TYPE OF LETTER: Not Approvable (Minor)

**APPEARS THIS WAY
ON ORIGINAL**

APPEARS THIS WAY
ON ORIGINAL

~~ANDA #76-751~~

Mesalamine Rectal Suspension, USP

Agis Industries (1983) Ltd.

**Shahnaz Read
Office of Generic Drugs, Division of Chemistry II**

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B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation	7
III. Administrative.....	8
A. Reviewer's Signature	8
B. Endorsement Block	8
C. CC Block.....	8
Chemistry Assessment	9



Chemistry Review Data Sheet

1. ANDA # 76-751
2. REVIEW #: 3
3. REVIEW DATE: May 6, 2004, revised June 18, 2004
4. REVIEWER: Shahnaz Read
5. PREVIOUS DOCUMENTS:

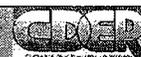
<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	May 30, 2003
Acknowledgement Letter	August 25, 2003
Minor Amendment	February 19, 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	April 6, 2004
Telephone Amendment	May 5, 2004
Telephone Amendment	June 17, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Agis Industries (1983) Ltd.
Address:	Industrial Zone Yeruham, Israel 80500
Authorized U.S. Agent	Clay-Park Labs, Inc. 1701 Bathgate Avenue Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	718-960-9976



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Mesalamine Rectal Suspension, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA submission is the RLD Rowasa Rectal Suspension Enema the subject of NDA 19-618 manufactured by Solvay Pharmaceuticals containing mesalamine. There is no unexpired marketing exclusivity for Rowasa Rectal Suspension Enema under section 505(j)(4)(D) of the Act. There are two unexpired patents listed:

- U.S. Patent # 4657900, expiration date April 14, 2004
- U.S. Patent # RE33239, expiration date May 12, 2004

Agis has submitted a Paragraph III Certification Statement for these patents.

10. PHARMACOLOGICAL CATEGORY:

Treatment of mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 4 g/60 mL Unit Dose

13. ROUTE OF ADMINISTRATION: Rectal

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note17]:

SPOTS product – Form Completed

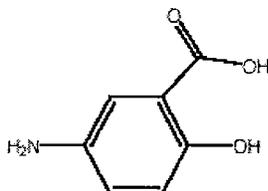
Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Mesalamine
 5-Aminosalicylic acid
 5-amino-2-hydroxybenzoic acid

Chemical Structure:



Molecular Formula: $C_7H_7NO_3$
 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	I	Adequate	4/27/2004	
/	III	/	/	4	NA		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or NA (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Rowasa Rectal Suspension Enema	NDA 19-618	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	Nov 4, 2003	S. Adams
Methods Validation	NA		
Labeling	Acceptable(only after May 12, 2004)	3/4/04	K. Lee
Bioequivalence	Acceptable	3/23/2004	M. Makary
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for ANDA # 76-751

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approve

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active pharmaceutical ingredient, Mesalamine is believed to be the therapeutically active component of Sulfasalazine used in treatment of mild to moderate ulcerative colitis. The mechanism of action of Mesalamine is unknown and appears to be topical rather than systemic. All the tests described for the drug substance are compendial tests.

The drug product is Mesalamine Rectal Suspension (Enema), packaged in unit-dose containers (4 g/60 mL). The manufacturing process involves _____

_____. The product is packaged as unit dose containers containing 4 g of Mesalamine in 60 mL suspension.

B. Description of How the Drug Product is Intended to be Used

The product is intended for rectal instillation once a day, preferably at bedtime and retained in the body for eight hours. Detailed instructions are provided in the patient instructions which are included along with the insert.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

Shahnaz Read

B. Endorsement Block

HFD-645/SRead/Review Chemist
HFD-645/BTArnwine/Team Leader
HFD-617/NLee/Project Manager

C. CC Block

ANDA 76-751
DIV FILE
Field Copy

**APPEARS THIS WAY
ON ORIGINAL**

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information from

CHEMISTRY REVIEW #3



CHEMISTRY REVIEW



Chemistry Assessment Section

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

The firm claims a categorical exclusion from the requirement of an Environmental Impact Analysis statement under 21 CFR sec §25.31(a).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

None.

APPEARS THIS WAY
ON ORIGINAL



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-751
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/5/6/04, revised 6/18/04 *Read 6/22/04*
HFD-645/BTArnwine/5/13/04/ 6/21/04 *(B) Arnwine 6/22/04*
HFD-617/NLee/5/10/04; 6/18/04

F/T by: EW 5/13/04

\\cdsnas\ogds11\FIRMSAM\AGIS\LTRS&REV\76751R3

TYPE OF LETTER: Approvable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-751
Drug Product Name	Mesalamine Rectal Suspension, USP
Strength	4 gm/60 mL
Applicant Name	Agis Industries (1983) LTD
Address	Bnei-Brak, Israel
Submission Date(s)	May 30, 2003 August 5, 2003
Amendment Date(s)	N/A
Reviewer	Moheb H. Makary
First Generic	Yes
File Location	V:\FIRMSAM\AGIS\LTRS&REV\76751N0503.doc

I. Executive Summary

This submission consisted of a BE study and dissolution data. The study was conducted on the 4 gm/60 mL test product, comparing it with Rowasa^R Rectal Suspension, 4 gm/60 mL, manufactured by Solvay Pharmaceuticals. The study design for the BE study is a two-way, crossover study in normal male and female subjects (n=47).

Statistical analyses of the plasma concentration data for mesalamine demonstrate bioequivalence. Mesalamine results (point estimate, 90% CI) are: LAUC_t of 107, 92-124%, LAUC_i 102, 85-122 and LC_{max} of 107, 95-120%.

The firm submitted acceptable dissolution testing. The dissolution specification submitted by the firm is acceptable. The application is acceptable with no deficiencies.

APPEARS THIS WAY
ON ORIGINAL

II. Table of Contents

I.	Executive Summary	1
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1.	Single-dose Fasting Bioequivalence Study	8
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III. Submission Summary

A. Drug Product Information

Test Product	Mesalamine Rectal Suspension USP, 4 gm/60 mL
Reference Product	Rowasa [®] (mesalamine) Rectal Suspension USP, 4 gm/60 mL
RLD Manufacturer:	Solvay Pharmaceuticals
NDA No.	19618
RLD Approval Date	December 24, 1987
Indication	ROWASA [®] (Mesalamine) Rectal Suspension Enema is indicated for the treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

APPEARS THIS WAY
ON ORIGINAL

B. PK/PD Information

Bioavailability	It is poorly absorbed from the colon and is excreted principally in the feces during subsequent bowel movements.
Food Effect	N/A
T_{max}	5-6 hours
Metabolism	It is known that the compound undergoes acetylation but whether this process takes place at colonic or systemic sites has not been elucidated.
Excretion	Whatever the metabolic site, most of the absorbed mesalamine is excreted in the urine as the N-acetyl-5-ASA metabolite.
Half-life	While the elimination half-life of mesalamine is short (0.5 to 1.5 h), the acetylated metabolite exhibits a half-life of 5 to 10 hours.
Relevant OGD or DBE History	The Division File contains the reviews of the following relevant documents: A. Protocol #02-014 submitted 4/1/02 B. Control #02-230 submitted 4/29/01.
	The DBE recommends that ANDA sponsors for Mesalamine Rectal Suspension USP, 4 gm/60 mL to conduct the following:
	1. A single dose, two-way crossover bioequivalence on Mesalamine Rectal Enema, 4 gm/60 mL.
	2. The Division requests that mesalamine be assayed in plasma and analyzed using a confidence interval approach. However, if mesalamine (5-ASA) can not be reliably measured in plasma, N-acetylsalicylic acid (Ac-5-ASA) should be assayed in plasma and analyzed using a confidence interval approach.
Agency Guidance	CDER 2000 BA/BE Guidance
Drug Specific Issues (if any)	No

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose BE Study	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Mesalamine
Internal Standard	4-aminosalicylic acid
Method description	HPLC/Fluorescence Detection
QC range	E J
Standard curve range	40 to 4000 ng/mL
Limit of quantitation	40 ng/mL
Average recovery of Drug (%)	71.5%
Average Recovery of Int. Std (%)	94.9%
Intraday precision range (% CV)	1.9 to 4.6%
Intraday accuracy range (%)	99.1 to 111%
Interday precision range (% CV)	2.8 to 4.3%
Interday accuracy range (%)	104 to 111%
Bench-top stability (hrs)	4
Stock stability (days)	30
Processed stability (hrs)	24
Freeze-thaw stability (cycles)	4
Long-term storage stability (days)	65 at -20°C
Dilution integrity	2-fold, 101%
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Chromatograms included (Y/N)	Yes
Random Selection of Serial Chrom	Yes

E. In Vivo Studies

1. Single-dose Bioequivalence Study

Study Summary	
Study No.	10216928
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	48
No. of subjects completing	47
No. of subjects analyzed	47
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 43 Female: 5
Test product	Mesalamine Rectal Suspension, USP
Reference product	Rowasa [®] (mesalamine) Rectal Suspension USP
Strength tested	4 gm/60 mL
Dose	1x4 gm/60 mL

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	Point Estimate	90% Confidence Interval
LAUC _t	107%	92-124%
LAUC _i	102%	85-122%
LC _{max}	107%	95-120%

Reanalysis of Study Samples Additional information in Appendix, Table 6				
Reason why assay was repeated	Number of samples reanalyzed		Number of recalculated values used after reanalysis	
	Actual number	% of total assays	Actual number	% of total assays
Unacceptable chromatography	31	1.5	Same	Same
Unknown process error	24	1.16	Same	Same
Sample concentration above upper limit of quantitation	16	0.77	Same	Same
Low IS	11	0.53	Same	Same
Interference from endogenous peak	2	0.09	Same	Same
High IS	1	0.05	Same	Same
Peak at zero hour	1	0.05	Same	Same
Total	86	4.1	Same	Same

Did use of recalculated plasma concentration data change study outcome? No

Comments on Fasting Study:

The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC_t, AUC_i and C_{max} for mesalamine. The reviewer's calculations are similar to those submitted by the firm.

F. Formulation

Location in appendix	Section IV.B, Page 15
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	Phosphate Buffer, pH 7.2
Volume (mL)	900
USP Apparatus type	USP 27 apparatus 2 (paddle)
Rotation (rpm)	50
Firm's proposed specifications	NLT \bar{x} (Q) in 15 minutes
FDA-recommended specifications	NLT \bar{x} (Q) in 15 minutes
F2 metric calculated (yes or no)	N/A
If no, reason why F2 not calculated	N/A
Method is acceptable (yes or no)	Yes

H. Waiver Request(s)

None

I. Deficiency Comments

None

J. Recommendations

1. The single-dose bioequivalence study conducted by Agis Industries (1983) LTD., on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #ML002, comparing it to Rowasa[®] (mesalamine) Rectal Suspension USP, 4 gm/60 mL, Lot #92451, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Agis' Mesalamine Rectal Suspension USP, 4 gm/60 mL, is bioequivalent to the

reference product Rowasa^R Rectal Suspension, 4 gm/60 mL, manufactured by Solvay Pharmaceuticals, Inc.

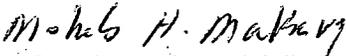
2. The dissolution testing conducted by Agis Industries (1983) LTD., on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #ML002, is acceptable.

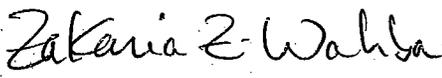
The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.2, at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than $\frac{1}{Q}$ (Q) of the labeled amount of Mesalamine in the dosage form is dissolved in 15 minutes.

From the bioequivalence point of view, the firm has met the requirements of the *in vivo* bioequivalence and the *in vitro* dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.


Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence


for GJP SINGH, Ph.D.
Team Leader Review Branch III
Division of Bioequivalence


for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

IV. Appendix

A. Individual Study Reviews

1. Single-dose Bioequivalence Study

Study Information	
Study Number	10216928
Study Title	A Study to Evaluate the Relative Bioavailability of Two Mesalamine 4 gm/60 mL Rectal Enema Formulations
Clinical Site	_____
Principal Investigator	_____
Study/Dosing Dates	Period I: 2/22/2003 Period II 3/01/2003
Analytical Site	_____
Analytical Director	_____, M.S.
Analysis Dates	March 8, 2003 and April 14, 2003
Storage Period (no. of days from first sample to final analysis)	50 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Mesalamine Rectal Suspension, USP	Rowasa [®] (mesalamine) Rectal Suspension
Manufacturer	Agis Industries (1983) LTD.	Solvay Pharmaceuticals, Inc.
Batch/Lot No.	ML002	92451
Manufacture Date	December, 2002	N/A
Expiration Date	N/A	June, 2004
Strength	4 gm/60 mL	4 gm/60 mL
Dosage Form	Suspension	Suspension
Batch Size	_____	N/A
Production Batch Size	Not Reported	N/A
Potency	105.3%	102.3%
Content Uniformity	99.5%	Not Reported
Formulation	See Appendix Section B	
Dose Administered	1x4 gm/60 mL	1x4 gm/60 mL
Route of Administration	Rectal	Rectal

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	N/A
Washout Period	7 days
Randomization Scheme	AB for subjects #1, 3, 6, 8, 10, 11, 13, 16, 18, 20, 22, 24, 26, 28, 30, 31, 33, 36, 38, 39, 41, 43, 45, 48 and BA for the rest of subjects.
Blood Sampling Times	0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, 48 and 60 hours post-dose.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics Administration	See Table 1
	Approximately ninety minutes prior to dosing with the study drug the nursing staff administered to each subject a Fleet ^R saline enema (1 bottle equivalent to approximately 118 mL delivered dose) in order that subjects empty their bowel prior to study drug administration. The study drug (one 4 gm/60 mL mesalamine rectal suspension enema) was administered according to the manufacturer's instructions for the reference product (Rowasa ^R). The weight of each enema bottle was measured prior to and after dosing to determine the total weight of drug administered. The mean weight of Treatment A was 56.2 gm (N=47) and Treatment B was 55.0 (N=47). For at least the first 30 minutes after dosing, the study subjects remained lying on their left side and remained in bed for at least 8 hours after dosing in order to minimize any leakage of study drug. All subjects retained the enema for at least 8 hours after dosing.
Length of Fasting	2 hours pre-dose and 8 hours post-dose (a light breakfast was provided approximately two hours prior to dosing).
Length of Confinement	From at least 11 hours pre-dose to 34 hours post-dose.

Table 1 Demographics of Study Subjects

Age		Weight(lbs)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	47.92
Mean	32	Mean	173	18-40	81.25	Male	89.6	Afr. Amer.	43.75
SD	10	SD	9.7	41-64	18.7	Female	10.4	Hispanic	4.17
Range	20-55	Range	119-241	65-75	0			Asian	0
				>75	0			Others	4.17

Study Results

Table 2 Dropout Information

Subject No	19
Reason	Subject #19 withdrew from study participation, as he did not return for period II check-in due to adverse events of stomach cramps, emesis and diarrhea.
Replacement	No

Was there a difference in side effects for the test versus the reference? No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Elevated blood pressure	2	
Scratchy throat	0	1
Diarrhea	0	1
Vomiting	0	1
Discomfort, right eye	1	0
Headache	2	2
Sore area, top of left wrist	1	0
Swelling, lower lid right eye	0	1
Scratchy throat	0	1
Elevated glucose	1	0
Elevated WBC	1	0
Elevated neutrophils	1	0
Elevated ALT	0	2
Itchy, right upper arm	2	0
Upset Stomach	0	2
Light headed	1	0
Elevated AST	1	0
Total:	13	11

Comments: No serious adverse events occurred during the conduct of the study.

Was there a difference in protocol deviations for the test versus the reference? No

Table 4 Protocol Deviations

No significant deviations from the protocol were documented. The reported protocol deviations were judged unlikely to affect the study integrity.

Table 5 Assay Validation – Within Study

	Parent							
QC Conc. (ng/mL)	100	600	3000					
Inter day Precision (% CV)	6.4	6.4	6.5					
Inter day Accuracy (%)	99.9	105	103					
Cal. Standards Conc. (ng/mL)	40	80	200	500	1000	2000	3200	4000
Inter day Precision (% CV)	7.5	5.8	3.7	4.9	4.6	3.4	2.5	2.6
Inter day Accuracy (%)	100	100	101	103	95.9	97.2	102	100
Linearity Range (range of R ² values)	0.999							

Chromatograms: Any interfering peaks? No

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
ANI 156.07	04/26/2001	Sample Reassays and Reporting of Final Concentrations

Comments on repeat assays.

- Did recalculation of plasma concentrations change the study outcome? No
- Does the reviewer agree with the outcome of the repeat assays? Yes
- There were no pharmacokinetic repeats.

Comments on Within-Study Validation: The analytical method and data for mesalamine are acceptable.

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figure 1.

Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC _{0-t}	hr-ng/mL	17432.7	68.0	17139.0	77.0	1.02
AUC _∞	hr-ng/mL	26139.9	81.2	22193.4	88.0	1.18
C _{max}	ng/mL	1350.9	55.6	1252.6	45.6	1.08
T _{max}	hr	5.9		5.9		
T _{1/2}	hr	12.9		7.6		
kel	1/hr	0.197		0.235		

Table 8 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	13978	13119	1.07	92-124%
AUC _∞	15840	15593	1.02	85-122%
C _{max}	1186	1108	1.07	95-120%

Table 9 Additional Study Information

Root mean square error, AUC _{0-t}	0.438		
Root mean square error, AUC _∞	0.371		
Root mean square error, C _{max}	0.339		
mean ratio AUC _{0-t} /AUC _∞	T =0.67	R =0.77	

Comments:

- kel and AUC_∞ were determined for 29 and 38 subjects for the test and reference products, respectively.
- If there are cases in which kel cannot be calculated, indicate if you agree or disagree with firm's decision. Yes
- Indicate the number of subjects with the following:
 - a. measurable drug concentrations at 0 hr. None
 - b. first scheduled post-dose sampling time as T_{max}. None
 - c. first measurable drug concentration as C_{max}. None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? No
- Are the 90% confidence intervals for AUC_{0-t}, AUC_∞, C_{max} within the acceptable limits of 80-125%. Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. N/A

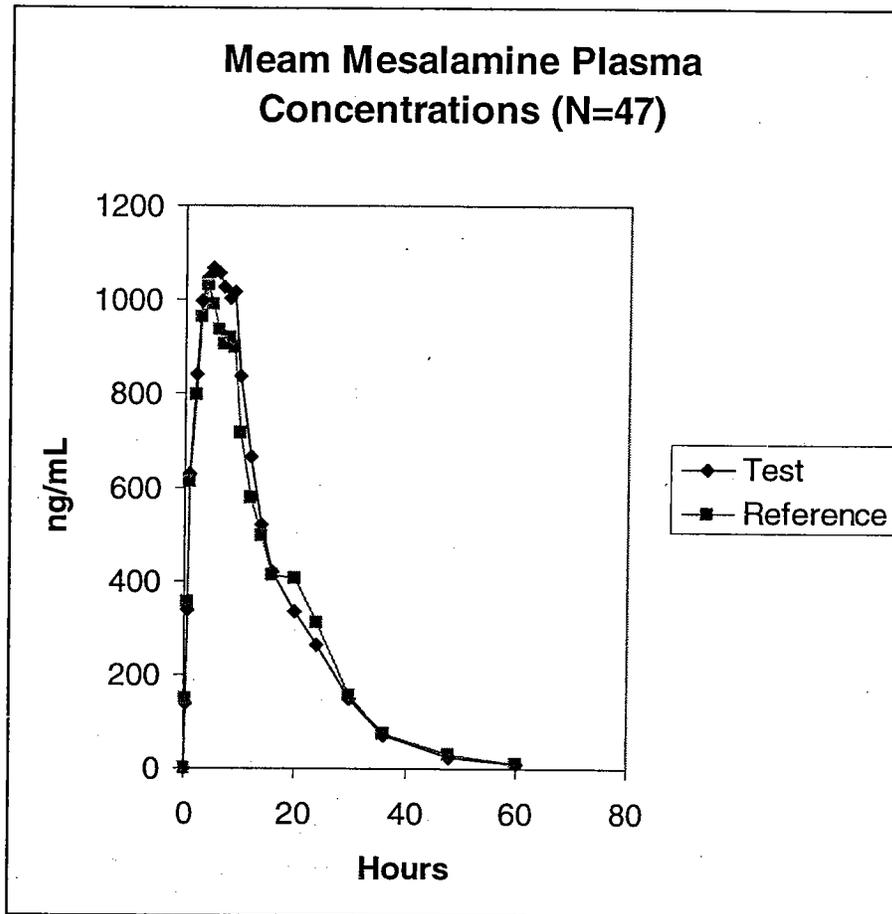
Conclusion: The single-dose bioequivalence study is acceptable.

Table 10 Mean Plasma concentration (ng/mL) of Mesalamine, Single-Dose Bioequivalence Study

Time (hr)	Test (n=47)		Reference (n=47)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0		0		
0.25	139.44	68.07	148.11	50.55	0.94
0.5	338.97	66.09	353.62	59.50	0.96
1	629.17	51.64	611.66	52.09	1.03
2	842.06	45.55	797.98	50.57	1.06
3	996.81	47.21	961.72	48.78	1.04
4	1046.47	48.91	1030.17	45.40	1.02
5	1068.79	46.54	989.55	48.04	1.08
6	1059.68	49.01	937.11	48.88	1.13
7	1028.57	54.43	906.49	51.00	1.13
8	1003.87	58.49	920.98	53.69	1.09
9	1018.51	62.56	898.83	65.84	1.13
10	836.93	89.63	716.69	87.70	1.17
12	666.46	119.86	578.70	102.72	1.15
14	520.73	110.29	495.37	115.11	1.05
16	418.22	119.45	413.29	117.72	1.01
20	333.28	119.03	404.61	122.94	0.82
24	262.70	120.04	312.59	127.13	0.84
30	149.86	156.07	155.68	167.97	0.96
36	72.66	200.79	75.56	271.22	0.96
48	24.76	370.00	30.26	356.67	0.82
60	10.81	501.95	11.21	482.60	0.96

**APPEARS THIS WAY
ON ORIGINAL**

Figure 1



APPEARS THIS WAY
ON ORIGINAL

B. Formulation Data

Ingredient	Mg/gm	% w/w	— ANDA Batch
Mesalamine, USP*		6.800	
Edetate Disodium, USP			
Carbomer 934P, NF			
Xanthan Gum, NF			
Potassium Acetate, USP			
Sodium Benzoate, NF			
Potassium Metabisulfite, NF			
Purified Water, USP			

* Includes an overage of 2.0%

**APPEARS THIS WAY
ON ORIGINAL**

C. Dissolution Data

Table 1

Sampling Time (min)	Test Product, Strength 4 gm/60 mL Lot No. ML002			Reference Product, Strength 4 gm/60 mL Lot No. 92451		
	Mean	% CV	Range	Mean	% CV	Range
5	94.9	2.8	/	97.4	1.1	/
10	99.5	2.4		97.3	1.0	
15	100.8	3.1		96.7	0.8	
20	99.9	2.8		96.6	1.1	
30	100.0	3.2		97.0	1.1	

APPEARS THIS WAY
ON ORIGINAL

Figure 2 Dissolution Profiles (*optional*)

**APPEARS THIS WAY
ON ORIGINAL**

D. SAS Output

Study	Data	Sas Code	SAS Output
Fasting Study	 mes.prn	 mesalaminecod.t xt	 mesalamineoutpu t.txt

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-751

APPLICANT: Agis Industries (1983) LTD

DRUG PRODUCT: Mesalamine Rectal Suspension, 4 gm/60 mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

We agree with your proposed dissolution method and specification as follows:

The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.2, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than ~~—~~% (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



for

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-751
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

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Printed in final on 3/23/04

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary *MM*

for HFD-658/ Bio team Leader G. Singh *ZZW* 3/29/04

for HFD-650/ D. Conner *BCD* 3/29/04

8/5/03

BIOEQUIVALENCE - ACCEPTABLE

submission date: ~~5-30-03~~

1. Bioequivalence STUDY (STF)

Strengths: 4 gm/60 mL

Clinical: _____

Outcome: AC

Analytical: _____

Outcome Decisions: AC - ACCEPTABLE

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-751

SPONSOR : Agis Industries (1983) LTD

DRUG AND DOSAGE FORM : Mesalamine Rectal Suspension, USP

STRENGTH(S) : 4 gm/60 mL

TYPES OF STUDIES : A single-dose bioequivalence study

CINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Acceptable

DISSOLUTION : Acceptable.

WAIVER REQUEST: N/A

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
NO		
First Generic <u>Yes</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D BRANCH : III

INITIAL : mhm DATE : 3/29/04

TEAM LEADER : GJP SINGH, Ph.D

BRANCH : III

INITIAL : ZZW

DATE : 3/29/04

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Barbara M. Sawit DATE : 3/29/04

Mesalamine Rectal Suspension, USP
4 gm/60 mL
ANDA #76-751
Reviewer: Moheb H. Makary
W 76751O0804.doc

Agis Industries (1983) LTD
Bnei-Brak, Israel
Submission Date:
August 5, 2003

Addendum to the August 5, 2003 Review

This application was found acceptable by the Division of Bioequivalence (review dated March 29, 2004) based on an acceptable bioequivalence (BE) study and dissolution data.

Staff members from the Immediate Office of Generic Drugs and the Division of Bioequivalence met on August 12 to discuss this application. For certain types of mesalamine products, the OGD is discussing with the DCGIDP whether to conduct a BE study with clinical endpoints.

For the rectal suspension mesalamine drug products, the OGD has decided that it is not appropriate to request a BE study with clinical endpoints if the following criteria are met (see attachment):

- (1) The proposed generic product is BE to the RLD in an in vivo study with PK endpoints.
- (2) The proposed generic and RLD formulations are Q1 and Q2 essentially the same.
- (3) The proposed generic and RLD formulations have comparable particle size.
- (4) It may be necessary to use a more discriminating dissolution method for this product than the one currently used for the RLD.

The firm has already met criteria #1 and 2. The particle size for Agis' mesalamine rectal suspension will be compared with the RLD. The firm is requested to provide additional dissolution data.

Recommendation:

The firm should submit comparative dissolution testing in the following media (900 mL): 0.1N HCl, and USP buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. The firm may modify the filtration method in the dissolution testing, if necessary.

The firm should be informed of the above recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch IV

Kuldeep R. Dhariwal, Ph.D. *Mohariwal.* Date *8/18/2004*
Team Leader, Branch IV

Concur: *Dale P. Conner* Date: *8/19/04*
DC Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

MMakary/ 8-17-04, 76751O0804.doc

cc: ANDA #76-751, original, HFD-658 (Makary), Drug File, Division File.

**APPEARS THIS WAY
ON ORIGINAL**

Attachment

From: Davit, Barbara M
Sent: Monday, August 16, 2004 12:20 PM
To: Dhariwal, Kuldeep R
Cc: Conner, Dale P
Subject: Mesalamine rectal suspension products -- updated email

Kuldeep:

This email supercedes the previous email. Please include this updated email as part of Moheb's review.

Staff members from the Immediate Office of Generic Drugs and the Division of Bioequivalence met on August 12 to discuss this application. For certain types of mesalamine products, the OGD is discussing with the DCGIDP whether to conduct a BE study with clinical endpoints.

However, for the rectal suspension mesalamine drug products, the OGD has decided that it is not appropriate to request a BE study with clinical endpoints if the following criteria are met.

- (1) The proposed generic product is BE to the RLD in an in vivo study with PK endpoints.
- (2) The proposed generic and RLD formulations are Q1 and Q2 essentially the same.
- (3) The proposed generic and RLD formulations have comparable particle size.
- (4) It may be necessary to use a more discriminating dissolution method for this product than the one currently used for the RLD.

Please ask Moheb to

- (1) Compare Teva's formulation with that of the RLD. Rob Lionberger has a copy of the innovator's formulation.
- (2) Request particle size information from Teva if it is not already in the CMC data or review.
- (3) Request to see dissolution testing at a pH range (in addition to the method that Moheb suggests in his review). What we specify in the BA/BE guidance (3 pH's) is OK.

Thanks,

Barbara

Formulation Data

Agis' Formulation

Ingredient	Mg/gm	%w/w	Gm/Unit	— ANDA Batch
Mesalamine, USP*		6.800	4.08	
Edetate Disodium, USP				
Carbomer 934P, NF				
Xanthan Gum, NF				
Potassium Acetate, USP				
Sodium Benzoate, NF				
Potassium Metabisulfite, NF				
Purified Water, USP				

* Includes an overage of 2.0%

RLD's Formulation* (Solvay Pharmaceuticals)

INGREDIENT	grams/unit	% w/w
Mesalamine, USP	4.080	
Sodium Benzoate, NF		
Carbomer 934P, NF		
Edetate Disodium, USP		
Potassium Metabisulfite, NF		
Potassium Acetate, USP		
Xanthum Gum, NF		
Purified Water, USP q.s.		

*(Ref, NDA #19-618, Review of Chemistry Manufacturing, and Controls Supplement, July 26, 2002).

The formulation is qualitatively and quantitatively the same as that of the RLD.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-751

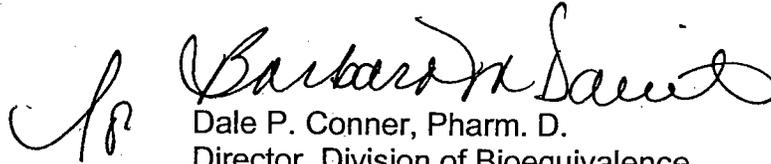
APPLICANT: Agis Industries LTD

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 gm/60 mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Please submit comparative dissolution testing in the following media (900 mL): 0.1N HCl, and buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. Please ensure that your dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Dale P. Conner". The signature is written in a cursive style with a large initial "D" and "C".

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-751
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

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Printed in final on 8/18/04

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary *M M*

HFD-658/ Bio team Leader K. Dhariwal *MD* 8/18/04

HFD-650/ D. Conner *DC* 8/19/04

for

BIOEQUIVALENCE - DEFICIENCIES

- ✓ 1. Other
U.S. document

Submission Date: 8/5/2003

Strength: 4 gm/60 mL

Outcome: IC

Mesalamine Rectal Suspension, USP
4 gm/60 mL
ANDA #76-751
Reviewer: Moheb H. Makary
W 76751A0904.doc

Agis Industries (1983) LTD
Bnei-Brak, Israel
Submission Date:
September 7, 2004

Review of an Amendment

Executive Summary

This amendment is a response to the Division of Bioequivalence (DBE) deficiency letter of August 27, 2004. The fasting bioequivalence (BE) study submitted in the original application was found acceptable (review dated March 29, 2004). However, for the rectal suspension mesalamine drug products, the DBE decided to request comparative dissolution testing in multiple media in addition to the BE study. In this amendment the firm submitted the requested dissolution data. The response is acceptable. The application is acceptable with no deficiencies.

Background

For the rectal suspension mesalamine drug products, on August 12, 2004, the OGD decided that it is not appropriate to request a BE study with clinical endpoints if the following criteria are met (see attachment):

- (1) The proposed generic product is BE to the RLD in an in vivo study with PK endpoints.
- (2) The proposed generic and RLD formulations are Q1 and Q2 essentially the same.
- (3) It may be necessary to use a more discriminating dissolution method for this product than the one currently used for the RLD.

The firm already met criteria #1 and 2 (previous submissions). The firm was requested to provide additional dissolution data.

DBE Comment

Please submit comparative dissolution testing in the following media (900 mL): 0.1N HCl, and buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. Please ensure that your dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.

Firm's Response

The firm has submitted comparative dissolution results using the above recommended dissolution media and rotation speeds. It emptied the contents of one rectal suspension container to each of the twelve dissolution vessels. The results are shown in Table I. The results indicate that the average percentage release of the active ingredient from Agis' Mesalamine Rectal Suspension, USP and Solvay's Rowasa (mesalamine) Rectal Suspension Enema in various pH media and rotation speeds are comparable.

The firm's reply to the comment is acceptable.

Recommendation:

1. The single-dose bioequivalence study conducted by Agis Industries (1983) LTD., on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #ML002, comparing it to Rowasa[®] (mesalamine) Rectal Suspension USP, 4 gm/60 mL, Lot #92451, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Agis' Mesalamine Rectal Suspension USP, 4 gm/60 mL, is bioequivalent to the reference product Rowasa^R Rectal Suspension, 4 gm/60 mL, manufactured by Solvay Pharmaceuticals, Inc.
2. The dissolution testing conducted by Agis Industries (1983) LTD., on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #ML002, is acceptable.

The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.2, at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than — % (Q) of the labeled amount of Mesalamine in the dosage form is dissolved in 15 minutes.

From the bioequivalence point of view, the firm has met the requirements of the *in vivo* bioequivalence and the *in vitro* dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.

Moheb H. Makary
Moheb H. Makary, Ph.D.
Review Branch IV
Division of Bioequivalence

9/9/04

Kuldeep Dhariwal
Kuldeep Dhariwal, Ph.D.
Team Leader Review Branch IV
Division of Bioequivalence

9/9/04

Dale P. Conner
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

9/10/04

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-751

APPLICANT: Agis Industries (1983)
LTD

DRUG PRODUCT: Mesalamine Rectal Suspension, 4 gm/60 mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

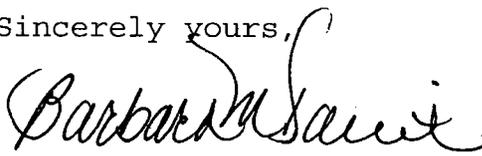
We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 900 mL of phosphate buffer pH 7.2, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less than $\bar{\alpha}$ % (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for 

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-751
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader K. Dhariwal

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Printed in final on 9/9/04

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary *MHM 9/9/04*
HFD-658/ Bio team Leader K. Dhariwal *MD 9/9/04*
HFD-650/ D. Conner *BD 9/10/04*

AK

BIOEQUIVALENCE - ACCEPTABLE

submission date: 9-7-04

- ✓ 1. STUDY AMENDMENT (STA)

Strengths: 4 gm/60 mL
Outcome: AC

Outcome Decisions: AC -- ACCEPTABLE

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-751

SPONSOR : Agis Industries (1983) LTD

DRUG AND DOSAGE FORM : Mesalamine Rectal Suspension, USP

STRENGTH(S) : 4 gm/60 mL

TYPES OF STUDIES : A single-dose bioequivalence study

CINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : Acceptable

DISSOLUTION : Acceptable.

WAIVER REQUEST: N/A

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic <u>Yes</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D

BRANCH : IV

INITIAL : MHM

DATE : 9/9/04

TEAM LEADER : Kuldeep Dhariwal, Ph.D

BRANCH : IV

INITIAL : KD

DATE : 9/9/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Barbara D. Savitt DATE : 9/10/04

Table I

1. pH = 7.2 and 50 RPM

Table 1 - Comparative Dissolution Results for Test Product and Reference Product at pH 7.2 and 50RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92451				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1										
2										
3										
4										
5										
6										
Average, %	93.8	101.1	103.3	102.5	102.3	97.7	97.3	97.1	96.9	97.6
RSD, %	3.6	2.1	2.1	1.1	1.2	1.0	0.9	0.5	1.4	0.8

2. pH = 7.2, 25 RPM

Table 2 - Comparative Dissolution Results for Test Product and Reference Product at pH 7.2 and 25 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92451				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1										
2										
3										
4										
5										
6										
Average, %	84.3	86.1	86.9	86.7	87.2	91.2	90.6	90.6	91.1	91.5
RSD, %	6.6	7.4	6.4	5.7	6.3	2.7	2.2	2.9	3.3	2.5

3. pH = 6.8 and 50 RPM

Table 3 - Comparative Dissolution Results for Test Product and Reference Product at pH 6.8 and 50 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92873				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1										
2										
3										
4										
5										
6										
Average, %	94.5	97.3	96.9	97.5	98.9	96.9	97.1	97.9	98.1	98.7
RSD, %	2.6	2.3	2.4	2.9	2.7	0.7	1.4	6.8	1.0	1.4

4. pH = 6.8 and 25 RPM

Table 4 - Comparative Dissolution Results for Test Product and Reference Product at pH 6.8 and 25 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92873				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1										
2										
3										
4										
5										
6										
Average, %	89.9	91.5	92.1	92.8	93.1	87.0	87.5	88.5	88.0	88.4
RSD, %	1.1	1.5	1.9	2.3	2.0	1.7	1.3	0.6	1.0	0.7

5. pH = 4.5 and 50 RPM

Table 5 - Comparative Dissolution Results for Test Product and Reference Product at pH 4.5 and 50 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92873				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1										
2										
3										
4										
5										
6										
Average, %	33.8	36.1	36.8	36.4	36.1	32.6	34.8	35.4	35.7	35.8
RSD, %	1.0	0.2	2.3	1.0	1.1	7.9	0.9	1.3	1.5	1.0

6. pH = 4.5 and 25 RPM

Table 6 - Comparative Dissolution Results for Test Product and Reference Product at pH 4.5 and 25 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92873				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1										
2										
3										
4										
5										
6										
Average, %	35.3	35.1	35.6	35.9	35.9	34.6	35.1	35.8	35.5	35.9
RSD, %	1.6	0.7	1.1	1.1	0.9	1.0	0.4	1.1	1.2	0.6

7. 0.1 N HCl and 50 RPM

Table 7 - Comparative Dissolution Results for Test Product and Reference Product at 0.1 N HCl, and 50 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92873				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1	/									
2										
3										
4										
5										
6										
Average, %	101.6	102.0	101.3	100.8	101.2	99.3	100.0	100.1	99.1	100.4
RSD, %	3.3	4.0	1.8	2.0	1.6	1.5	1.1	1.2	0.8	2.7

8. 0.1 N HCl and 25 RPM

Table 8 - Comparative Dissolution Results for Test Product and Reference Product at 0.1 N HCl and 25 RPM

Container #	Test Product, Lot # ML002					Reference Product, Lot #92873				
	5 min.	10 min.	15 min.	20 min.	30 min.	5 min.	10 min.	15 min.	20 min.	30 min.
1	/									
2										
3										
4										
5										
6										
Average, %	95.1	96.4	96.8	98.8	98.6	99.2	96.9	96.9	98.2	98.0
RSD, %	2.7	1.6	2.5	3.3	2.8	1.0	1.2	1.2	2.0	0.6

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

ATTACHMENT FROM BIOEQUIVALENCE REVIEW OF 9/7/04 SUBMISSION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-751

ADMINISTRATIVE DOCUMENTS

JUN 13 2003

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 76-751 FIRM NAME Agis Industries (1983) LTD.

DRUG NAME Mesalamine Rectal Suspension USP

DOSAGE FORM Rectal Suspension USP, 4 gram/60 mL

SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence	
<input type="checkbox"/>	Study meets statutory requirements
<input checked="" type="checkbox"/>	Study does NOT meet statutory requirements
	Reason: Lack of in vitro dissolution data
<input type="checkbox"/>	Waiver meets statutory requirements
<input type="checkbox"/>	Waiver does NOT meet statutory requirements
	Reason: N/A

RECOMMENDATION: COMPLETE INCOMPLETE

Reviewed by:

Zakaria Wahba Zakaria Z. Wahba Date: 6/13/03
Reviewer

Gur-Jai Pal Singh Gur-Jai Pal Singh Date: 6-13-03
Team Leader

sa Dale Conner Date: Barbara M. DeWitt
Director, Division of Bioequivalence

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Assay Methodology	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Procedure SOP	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Study Results Ln/Lin	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Adverse Events	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
IRB Approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Dissolution Data	<input type="checkbox"/>	<input checked="" type="checkbox"/>			required
Pre-screening of Patients	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Chromatograms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Consent Forms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Composition	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Summary of Study	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Individual Data & Graphs, Linear & Ln	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
PK/PD Data Disk Submitted)	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Randomization Schedule	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Protocol Deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Clinical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Analytical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Study Investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>			

Medical Records	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Clinical Raw Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Test Article Inventory	<input type="checkbox"/>	<input checked="" type="checkbox"/>			required
BIO Batch Size	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Assay of Active Content Drug	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Content Uniformity	<input type="checkbox"/>	<input checked="" type="checkbox"/>			required
Date of Manufacture	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Exp. Date of RLD	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
BioStudy Lot Numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Statistics	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Summary results provided by the firm indicate studies pass BE criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Waiver requests for other strengths / supporting data	<input type="checkbox"/>	<input checked="" type="checkbox"/>			N/A

Additional Comments regarding the ANDA:

The RLD is Solvay's Rowasa Rectal Enema (NDA #19-618)

The following items are not provided in the submission

- 1. In vitro Dissolution data on the test and RLD product.**
- 2. Test article inventory.**
- 3. Content uniformity**

RECORD OF TELEPHONE CONVERSATION

<p>This call was made to relay the following deficiency:</p> <p>It is required for the drug product stability specifications to meet the USP requirements. The data presented does not provide justification for _____.</p> <p>The firm has agreed to revise and send in new spec sheets.</p>	DATE: 5-4-2004
	ANDA NUMBER: 76-751
	PRODUCT NAME: Mesalamine Rectal Suspension
	Firm Name: <i>Clay Park</i>
	FIRM REPRESENTATIVE: Candice Edwards
	PHONE NUMBER: 718-960-9976
	FDA REPRESENTATIVES: Brenda Arnwine Shahnaz Read Nicole Lee
SIGNATURES:	

CC: ANDA
Telecon Binder

V:firmsnz/Watson/telecons/76751.5-4-2004
agis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-751

CORRESPONDENCE



TEL. EXTENSION
03-5773 -

DIRECT FAX:
03-5773 -

Handwritten notes:
- No dissolution data
- Presently
- 10/11/03
- July 2003
- Concur.
- 01-JUL-2003
- [Signature]

May 30, 2003

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room # 150
Rockville, MD 20855-2773

Re: ANDA for Mesalamine Rectal Suspension, USP

Dear Mr. Buehler:

Agis Industries (1983) Ltd. hereby submits an original abbreviated new drug application (ANDA) in hard copy format, to seek approval to market Mesalamine Rectal Suspension, USP, that is bioequivalent to the reference listed drug, Rowasa® (Mesalamine) Rectal Suspension Enema, manufactured by Solvay Pharmaceuticals, pursuant to NDA #019618.

This ANDA consists of 9 volumes. Agis Industries (1983) Ltd. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) that contains all the information in archival copy with the exception of the bioequivalence **Section (VI)**. A separate copy of the bioequivalence section is provided in orange folders.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical section of the ANDA (including a copy of the FDA 356h form and a certification that the contents are the true copy of those filed with the Office of Generic Drugs) is being sent to our local district office. This "field copy" is contained in burgundy folders.

For a more detailed information on the organization of this ANDA, please refer to the "Executive Summary" attached after the field copy certification statement.

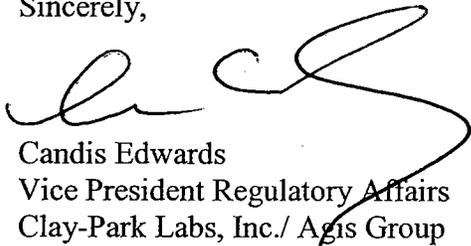
RECEIVED
MAY 30 2003
OGD / CDER

Should you have any comments or require any further clarification on this ANDA, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', with a large, sweeping flourish extending to the right.

Candis Edwards
Vice President Regulatory Affairs
Clay-Park Labs, Inc./ Agis Group
On behalf of Agis Industries (1983) Ltd.

ANDA 76-751

Clay-Park Labs, Inc.
U.S. Agent for: Agis Industries (1983) Ltd.
Attention: Candis Edwards
1701 Bathgate Avenue
Bronx, NY 10457

JUL 1 2004

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated May 30, 2003, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d) (3) for the following reasons:

You have failed to submit complete comparative *in vitro* dissolution profiles comparing your proposed drug product, Lot #ML002, and the reference listed drug. You have also failed to submit content uniformity data for the reference listed drug and your test product. Please provide this data.

You have failed to provide authorization from the holders of the Drug Master Files (DMFs), _____ and _____, for the Agency to access their DMFs in support of your application. Please provide authorization from the holder of the DMFs granting the Agency access to the DMFs.

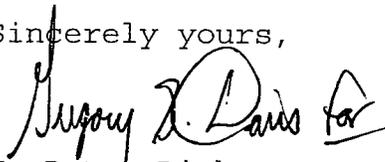
In addition, for any future submissions please provide the U.S. Agent's firm name as well as contact person on the 356h.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Christine Bina
Project Manager
(301) 827-5862

Sincerely yours,

A handwritten signature in black ink, appearing to read "Wm Peter Rickman". The signature is written in a cursive style with a large, stylized initial "W".

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-751

cc: DUP/Jacket

Division File

HFD-92

Field Copy

HFD-610/R.West

HFD-610/P.Rickman

HFD-615/MBennett

Endorsement: HFD-615/GDavis, Chief, RSB *Davis* 01-JUL-2003 date

HFD-615/CBina, CSO *Marie M. Bina* 6-30-03 date

Word File

V:/FIRMSAM\AGIS\LTRS&REV\76751.RTF

F/T File

ANDA Refuse to Receive!



August 5, 2003

TEL. EXTENSION
03-5773 -

DIRECT FAX:
03-5773 -

Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER
Food and Drug Administration
Document Center Room
Metro Park North II
7500 Standish Place – Room 150
Rockville, MD 20855

ORIGINAL AMENDMENT
N/AC

**Re: Response to Refusal to File Letter
Mesalamine Rectal Suspension, USP, 4 g/60 mL
ANDA # 76-751**

Dear Mr. Rickman:

In response to the Refusal to File Letter dated July, 7 2003 (**See Attachment 1**) for Mesalamine Rectal Suspension, USP ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the requested information in order to render the file sufficiently complete to merit a technical review.

Regarding the comparative *in vitro* dissolution profiles comparing our proposed drug product, Lot # ML002 and the reference listed drug, the following Analytical Documentation is provided:

- **Attachment 2:** R & D Document # 26822-v2: Protocol Comparative In-Vitro Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa® (mesalamine) Rectal Suspension Enema, versus Agis Industries (1983) Ltd.'s Mesalamine Rectal Suspension, USP
- **Attachment 2:** R & D Document # 26863-v1: Report Comparative In-Vitro Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa® (mesalamine) Rectal Suspension Enema, versus Agis Industries (1983) Ltd.'s Mesalamine Rectal Suspension, USP
- **Attachment 3:** R & D Document # 26761-v2 Validation Protocol of HPLC Dissolution Test Method for Mesalamine Rectal Suspension, USP

RECEIVED

AUG 06 2003

OGD/CDER

- **Attachment 3:** R & D Document # 26840-v1
Validation Report of HPLC Dissolution Test Method for Mesalamine Rectal Suspension, USP
- **Attachment 4:** R & D Document # 14913-v2
Dissolution Test Method

On the subject of the content uniformity data for the reference listed drug and Agis Industries (1983) Ltd.'s test product, the average results of the content uniformity test for Agis Industries (1983) Ltd.'s proposed drug product were provided on **pages 3502** (Lot # ML002) and **3612** (Lot # ML003) of the original application. The Certificates of Analysis have been revised to include the individual tests results and are presented in **Attachment 5**. The test results for the reference listed drug, as requested by the Agency are also presented in **Attachment 5**.

*Finished
Dose of CC*

Relating to the Agency's request for authorization from the holder of the Drug Master File (DMF), _____, the letter of authorization was included in the original application on **page 3435**. The Agency acknowledged that they were able to locate the document during a telephone conversation between the US Agent and the FDA Project Manager.

Pertaining to the letter of authorization from _____, Agis Industries (1983) Ltd inadvertently listed _____ as the manufacturer of the _____ in the Table on **page 3440** of the original application. Agis Industries (1983) Ltd. herein uses this correspondence to correct the file and states that _____ is the manufacturer and _____, is the supplier of the _____. Hence, a corrected cGMP certification from _____ is attached herewith (see **Attachment 6**). The Table presented on **page 3440** of the original application, has been revised to incorporate the above-mentioned correction (see **Attachment 7**).

Since _____ does not have a DMF on file with the Agency, Agis Industries (1983) Ltd. submits test results for the USP _____ (see **Attachment 8**). This data supplements the results for USP _____, USP _____ and USP _____ previously submitted on **pages 3419 – 3431** of the original application.

Agis Industries (1983) Ltd. would like to take this opportunity to revise the printer's proof labeling submitted in the original application with regard to the color of the ink. The printer's proof labeling submitted on **page 0073** of the original application is printed using _____ and black ink. Since this labeling will be printed directly onto the bottles and the Stability Study for Lot # ML003 (Printed Bottles) was conducted using black ink only, the labeling has been revised from _____ and black to black only. Twelve (12) copies of the revised draft labeling are presented in **Attachment 9**.

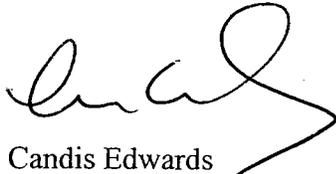
Based on the information provided with this correspondence, we anticipate that sufficient justification has been submitted to warrant a critical technical review for approval.

Should you require any further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', with a long, sweeping tail that extends to the right and then loops back down.

Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

ANDA 76-751

AUG 25 2003

Clay-Park Labs, Inc.
U.S. Agent for: Agis Industries (1983) Ltd.
Attention: Candis Edwards
1701 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made our "Refuse to Receive" letter dated July 1, 2003 and to your amendment dated August 5, 2003.

NAME OF DRUG: Mesalamine Rectal Suspension USP, 4 g/60 mL.

DATE OF APPLICATION: May 30, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 5, 200³7

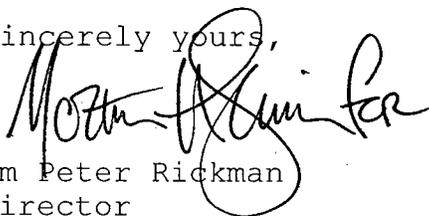
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Nicole Park
Project Manager
(301) 827-5849

Sincerely yours,



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-751

cc: DUP/Jackets

HFD-600/Division File

Field Copy

HFD-610/G. Davis

HFD-92

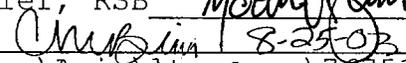
Endorsement:

HFD-615/MShimer, Chief, RSB



date 25 Aug 2003

HFD-615/CBina, CSO



date

Word File V:\Firmsam\Agis\ltrs&rev\76751.ACK

F/T CMB 8-25-03

ANDA Acknowledgment Letter!

MODE = MEMORY TRANSMISSION

START=DEC-29 10:23

END=DEC-29 10:24

FILE NO.=757

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	a	917189609907	003/003	00:00:39

-FDA CDER OGD DLPS -

***** - ***** - *****

Fax Cover Sheet

Department of Health and Human Services
 Public Health Service
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Generic Drugs
 Rockville, Maryland 20855

To: Candis Edwards

DATE: December 24, 2003

Phone: 718-960-9976

Fax: 718-960-~~0111~~

9907

SUBJECT: Labeling Comments for ANDA 76-751

From: Koung Lee

Phone: (301) 827-5846

Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments:

*This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

(3-1)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-751

Date of Submission: May 30, 2003

Applicant's Name: Agis Industries (1983) Ltd.

Established Name: Mesalamine Rectal Suspension USP, 4 g/60 mL

Labeling Deficiencies:

1. CONTAINER (60 mL unit-dose)

- a. We encourage you to increase the prominence of "potassium metabisulfite".
- b. Revise the storage temperature statement to "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".
- c. Increase the prominence of "For Rectal Use Only".

2. CARTON (7 x 60 mL unit-dose bottles)

See CONTAINER comments

3. INSERT

- a. We encourage you to add the full text of the patient instructions at the end of the labeling.
- b. Although the reference listed drug does not refer to the patient instructions in the PRECAUTIONS section, we encourage you to add a statement to that section that refers to the patient instructions.

b. HOW SUPPLIED

See CONTAINER comment (b).

4. PATIENT INSTRUCTIONS

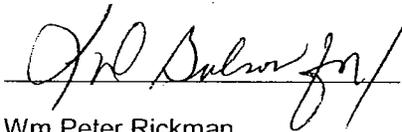
Please explain how the patient instructions will accompany the drug product.

Please revise your labeling as instructed above and submit 4 draft labels and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Wm Peter Rickman", written over a horizontal line.

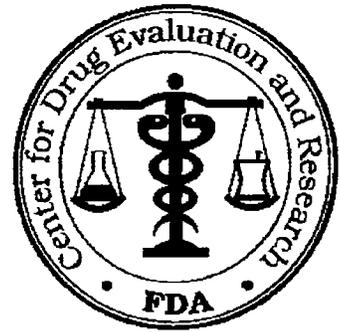
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

MINOR AMENDMENT

ANDA 76-751

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



JAN 22 2004

APPLICANT: Clay-Park Labs, Inc., U.S. Agent for
Agis Industries (1983) Ltd.

TEL: 718-960-9976

FAX: 718-960-0111

ATTN: Candis Edwards

PROJECT MANAGER: (301) 827-5849

FROM: Nicole Lee

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

Reference is also made to your amendment(s) dated: August 5, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

2. Please acknowledge that Mesalamine Rectal Suspension is an official monograph in the United States Pharmacopeia (USP). The approval to use an analytical procedure that may differ from that in the USP does not release your firm from any obligation to comply with the method and procedure in the USP specified for that product. Therefore, in the event of a dispute, only the results obtained by the official method and procedures in the USP will be considered conclusive.

Sincerely yours,



Florence S. Fang

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research



February 19, 2004

TEL. EXTENSION
03-5773 -DIRECT FAX:
03-5773 -

Nicole Lee
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

RE: ANDA 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Lee,

In reference to the deficiency letter for the Chemistry section dated January 22, 2004 (**Attachment 1**) on our abbreviated new drug application for Mesalamine Rectal Suspension, USP 4 g/60 mL ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response for the Chemistry section designated as a Minor Amendment.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

RECEIVED

FEB 19 2004

OGD/CDER



February 19, 2004

TEL. EXTENSION
03-5773

DIRECT FAX:
03-5773-

William Peter Rickman, Director
Division of Labeling and Program Support
Office of Generic Drugs, CDER
Document Control room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF
FPL

LABELING AMENDMENT

RE: ANDA # 76-751 Mesalamine Rectal Suspension USP

Dear Mr. Rickman:

In reference to the deficiency letter of the Labeling Section, dated December 24, 2003 (Attachment A), on our abbreviated new drug application for Mesalamine Rectal Suspension, USP, ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response, designated as a Labeling Amendment.

Should you have any comments or require any further clarification, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

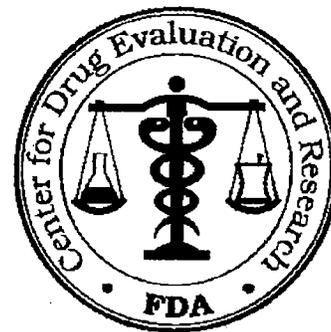
Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

RECEIVED
FEB 19 2004
OGD/CDER

MINOR AMENDMENT

ANDA 76-751

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



MAR 26 2004

APPLICANT: Agis Industries (1983) Ltd. (U.S. Agent
:Clay-Park Labs, Inc.)

TEL: 718-960-9976

FAX: 718-960-0111

ATTN: Candis Edwards

PROJECT MANAGER: (301) 827-5849

FROM: Nicole Lee

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated May 30, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

Reference is also made to your amendment(s) dated: February 19, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (/ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

h

6

MAR 26 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-751

APPLICANT: Agis Industries (1983) Ltd.

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 g/60 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. _____

2. Since Mesalamine Rectal Suspension is a USP product, stability specifications for Impurities should match USP limits for the product.
3. _____

Sincerely yours,



Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research



April 6, 2004

TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

Nicole Lee
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/A M

MINOR AMENDMENT

RE: ANDA 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Lee,

In reference to the deficiency letter for the Chemistry section dated March 26, 2004 (**Attachment 1**) on our abbreviated new drug application for Mesalamine Rectal Suspension, USP 4 g/60 mL ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response for the Chemistry section designated as a Minor Amendment.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.

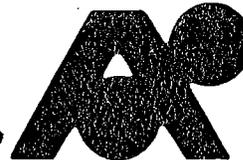
On behalf of Agis Industries (1983) Ltd.

RECEIVED

APR 08 2004

OGD / CDER

ORIGINAL



May 5, 2004

TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

Nicole Lee
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A M

**TELEPHONE AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW**

RE: ANDA # 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Lee,

In response to our telephone conversation with the Agency yesterday, May 4, 2004, in reference to ANDA # 76-751 for Mesalamine Rectal Suspension, USP 4 g/ 60 mL, as requested, Agis Industries (1983) Ltd. hereby submits the revised Stability Monograph (see **Attachment 1**) for the drug product. The stability specifications for the impurities have been revised to match the USP limits for the product.

The change in specifications is summarized below:

Stability Evaluation		
Impurities	Old Specifications	New Specifications
Individual Known	NMT —%	NMT 0.2%
Individual Unknown	NMT —%	NMT 0.2%
Total Impurities	NMT —%	NMT 1.0%

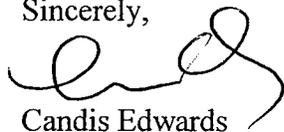
RECEIVED
MAY 06 2004
OGD/CDER

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', with a large, stylized flourish at the end.

Candis Edwards

VP Regulatory Affairs

Clay-Park Labs, Inc.

On behalf of Agis Industries (1983) Ltd.

ORIGINAL



TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

June 17, 2004

Nicole Lee, Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A M

**TELEPHONE AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW**

**RE: ANDA # 76-751 Mesalamine Rectal Suspension USP,
4 g/60 mL**

Dear Ms. Lee,

As requested in a telephone conversation with the Agency on June 15, 2004, Agis Industries (1983) Ltd. has revised the finished product and stability test monographs for Mesalamine Rectal Suspension USP, 4 g/60 mL, ANDA # 76-751, to add a dissolution test. The dissolution test method includes the testing parameters and specifications indicated in the OGD correspondence dated June 15, 2004 (see **Attachment A**). The revised finished product and stability test monographs are presented in **Attachment B**.

Also, as requested, dissolution testing was performed on the 18 month Controlled Room Temperature (CRT) stability testing interval for Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # ML002 (bio batch). **Attachment C** presents the updated Stability Summary Report and the Certificate of Analysis for the 18 month CRT testing interval.

We hope that this information satisfies the Agency's requirements for product approval.

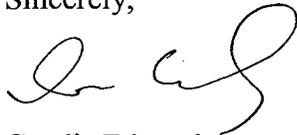
RECEIVED
JUN 18 2004
OGD/CDEH

Should you require any further information please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

A handwritten signature in black ink, appearing to read 'Candis Edwards', written in a cursive style.

Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.



July 23, 2004

TEL. EXTENSION
03-5773-

DIRECT FAX:
03-5773-

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N / AB

INFORMATIONAL AMENDMENT - BIOEQUIVALENCE

RE: ANDA 76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Mr. Buehler:

Agis Industries (1983) Ltd. hereby submits the enclosed document regarding our Abbreviated New Drug Application # 76-751 for Mesalamine Rectal Suspension, USP 4 g/60 mL, designated as an Informational Amendment. The Amendment sets forth our current position regarding the status of the Agency's review and approval of our ANDA.

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,

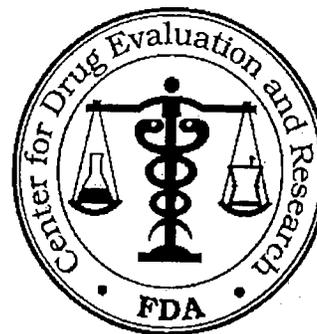
Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.

RECEIVED
JUL 26 2004
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-751

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



AUG 27 2004

APPLICANT: Agis Industries (1983) Ltd.
(U.S. Agent :Clay-Park Labs, Inc.)

TEL: 718-960-9976

ATTN: Candis Edwards

FAX: 718-960-0111

FROM: Beth Fabian-Fritsch *BFF*

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 5, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/60 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

AUG 27 2004

AUG 27 2004

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-751

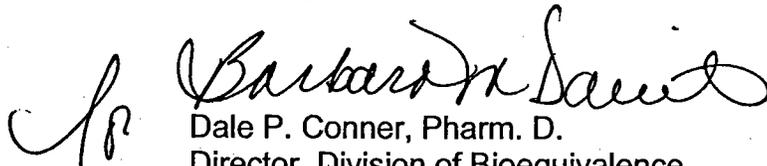
APPLICANT: Agis Industries LTD

DRUG PRODUCT: Mesalamine Rectal Suspension USP, 4 gm/60 mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Please submit comparative dissolution testing in the following media (900 mL): 0.1N HCl, and buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. Please ensure that your dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

31

AGIS INDUSTRIES (1983) LTD.



ORIGINAL

September 07, 2004

TEL. EXTENSION
972-3-5773

DIRECT FAX:
972-3-5773

Beth Fabian-Fritsch
Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

**BIOEQUIVALENCY AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW**

RE: ANDA #76-751 Mesalamine Rectal Suspension USP, 4 g/60 mL

Dear Ms. Fabian-Fritsch,

In reference to the deficiency letter for the Bioequivalence section dated August 27, 2004 (**Attachment 1**), on our abbreviated new drug application for Mesalamine Rectal Suspension, USP 4 g/60 mL ANDA # 76-751, Agis Industries (1983) Ltd. hereby submits the deficiency response for the Bioequivalence section, designated as a Bioequivalency Amendment.

The Agency has requested the following:

“Please submit comparative dissolution testing in the following media (900 mL): 0.1 N HCl, and buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 and 25 rpm. Please ensure that your dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.”

As requested by the Agency, Agis Industries (1983) Ltd. has completed the comparative *in vitro* dissolution profile testing on Mesalamine Rectal Suspension USP, 4 g/ 60 mL. The testing was performed using Agis Industries (1983) Ltd.’s validated methodology, Dissolution Test Method # 14913, submitted to the Agency on 08/05/03 in Response to the Refusal to File letter dated 07/01/03, for this ANDA.

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Comparative dissolution testing was performed on Agis Industries (1983) Ltd.'s drug product, Bio batch # ML002, and on the innovator's drug product, Solvay Pharmaceutical Inc.'s Rowasa[®] (Mesalamine) Rectal Suspension Enema, Lot # 92451, and Lot # 92873 using the dissolution conditions specified. The results from the comparative *in vitro* dissolution testing were found to be comparable.

The study protocol and corresponding study report are presented in **Attachment 2** as follows:

Protocol R&D Document #33195-v1: Comparative *In-Vitro* Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa[®] (mesalamine) Rectal Suspension Enema – Versus Agis Industries (1983) Ltd. Mesalamine Rectal Suspension, USP

Report R&D Document #: 33195-v1: Comparative *In-Vitro* Dissolution Testing of Solvay Pharmaceuticals Inc.'s Rowasa[®] (mesalamine) Rectal Suspension Enema – Versus Agis Industries (1983) Ltd. Mesalamine Rectal Suspension, USP

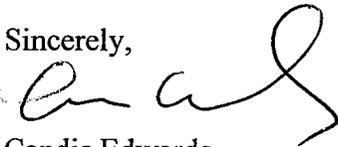
Please note that there are two binders enclosed: one Archival Copy (Blue Folder) and one Bioequivalence Copy (Orange Folder).

Should you have any comments or require any further clarification on this amendment, please contact the undersigned as follows:

Telephone: (718) 960-9976

Fax: (718) 960-0111

Sincerely,



Candis Edwards
VP Regulatory Affairs
Clay-Park Labs, Inc.
On behalf of Agis Industries (1983) Ltd.