

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-841

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

Sponsor: Teva Pharmaceuticals USA

Approval Date: September 30, 2004

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APPLICATION NUMBER:
ANDA 76-841

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-841

APPROVAL LETTER

ANDA 76-841

SEP 30 2004

Teva Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated September 2, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Mesalamine Rectal Suspension, USP (Enema), packaged in a 4 gram/60 mL unit-dose bottle).

Reference is also made to your amendments dated April 9, May 14, June 4, September 8, September 20, and September 21, 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 gram/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.

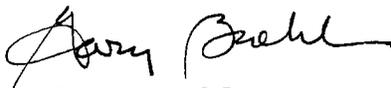
Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with

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 9/30/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-841
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Approved Electronic Labeling Located at:

Endorsements:

HFD-640/S. Basaran / *S. Basaran* 9/29/04

HFD-645/B. Arnwine / *B. Arnwine* 9/29/04

HFD-617/Y. Kong /

HFD-613/K. Lee / *K. Lee* 9/28/04

HFD-613/L. Golson / *L. Golson* 9/28/04

Bob West 9/30/04
Bob West
9/30/2004

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F/T by rad9/27/04

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-841

APPROVED LABELING

MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL

6888

Rx only

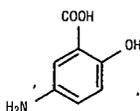
SEP 30 2004

ENLARGED TO 115%
BY FOIA STAFF

DESCRIPTION

The active ingredient in mesalamine rectal suspension USP, 4 g/60 mL, a disposable (60 mL) unit, is mesalamine, also known as 5-aminosalicylic acid (5-ASA). Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid.

The structural formula is:



C₇H₇NO₃

M.W. 153.14

Each rectal suspension USP 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 USP 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 USP 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 USP 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	Baseline	Day 22	EndPoint	Change Baseline to Endpoint†
Overall DAI	Mesalamine	76	7.42	4.05**	3.37***	-55.07%***
	Placebo	77	7.40	6.03	5.83	-21.58%
Stool Frequency	Mesalamine		1.58	1.11*	1.01**	-0.57*
	Placebo		1.92	1.47	1.50	-0.41
Rectal Bleeding	Mesalamine		1.82	0.59***	0.51***	-1.30***
	Placebo		1.73	1.21	1.11	-0.61
Mucosal Inflammation	Mesalamine		2.17	1.22**	0.96***	-1.21**
	Placebo		2.18	1.74	1.61	-0.56
Physician's Assessment of Disease Severity	Mesalamine		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/placebo difference. p<0.05

** Significant mesalamine/placebo difference. p<0.01

*** Significant mesalamine/placebo difference. p<0.001

Differences between mesalamine 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 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 USP, 4 g/60 mL is indicated for the treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

CONTRAINDICATIONS

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

WARNINGS

Mesalamine rectal suspension USP 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

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APPEARS ON PREVIOUS PAGE

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PATIENT INSTRUCTIONS

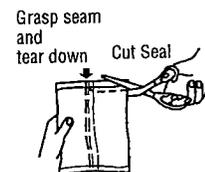
How to Use this Medication.

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

NOTE: Mesalamine Rectal Suspension USP, 4 g/60 mL 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.

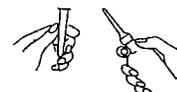
1 Remove the Bottles

- 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 USP, 4 g/60 mL is an off-white to tan colored suspension. Once the foilwrapped 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.



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 USP, 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 USP, 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 USP some patients have developed pancolitis. However, extension of upper disease boundary and/or flare-ups occurred less often in the mesalamine rectal suspension USP 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 USP there have been positive rechallenges with mesalamine or mesalamine containing products. In one of these cases, however, a second rechallenge with sulfasalazine was negative throughout a 2 month follow-up. Chest pain or dyspnea in patients treated with mesalamine rectal suspension USP should be investigated with this information in mind. Discontinuation of mesalamine rectal suspension USP 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.

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 USP is usually well tolerated. Most adverse effects have been mild and transient.

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

SYMPTOM	MESALAMINE N=815		PLACEBO 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
Fiu	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 USP 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 USP 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 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, 4 g/60 mL for rectal administration is a off-white to tan colored suspension. Each disposable enema bottle contains 4 grams of mesalamine in 60 mL aqueous suspension. Enema bottles are supplied in boxed, foil-wrapped trays of seven. Mesalamine Rectal Suspension USP, 4 g/60 mL is 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 USP, 4 g/60 mL 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.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

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

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

SYMPTOM	MESALAMINE N=815		PLACEBO 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	9	7.03
Cold/Sore Throat	19	2.33	4	3.12
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	11	8.59
Peripheral Edema	5	0.61	4	3.12
UTI/Urinary Burning	5	0.61	3	2.34
Rectal Pain/Soreness/Burning	5	0.61	4	3.12
Asthenia	1	0.12	3	2.34
Insomnia	1	0.12	3	2.34

APPEARS ON PREVIOUS PAGE

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 USP 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 USP 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 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, 4 g/60 mL for rectal administration is a off-white to tan colored suspension. Each disposable enema bottle contains 4 grams of mesalamine in 60 mL aqueous suspension. Enema bottles are supplied in boxed, foil-wrapped trays of seven. Mesalamine Rectal Suspension USP, 4 g/60 mL is 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 USP, 4 g/60 mL 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.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. A 3/2004

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.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. A 3/2004

NDC 0093-6888-71

MESALAMINE
RECTAL
SUSPENSION USP
4 g/60 mL
Unit-Dose



FOR RECTAL USE ONLY

Rx only

60 mL

SEP 30 2004

Each disposable unit-dose contains:
Mesalamine, 4 g
In a suspension containing carbomer 934P, edetate sodium, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum. **SHAKE WELL BEFORE USE**

Enema contents may darken with time. See package insert for complete instructions.
USUAL DOSAGE: Dip unit-dose into rectum before reinserting. See enclosed directions.

Store at 20° to 25° C. (68° to 77° F)
(See USP Controlled Room Temperature).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

C21209 Rev. A 3/2004
TEVA PHARMACEUTICALS USA
Sellerville, PA 10960



82

NDC 0093-6888-71

MESALAMINE RECTAL SUSPENSION, USP 4g/60 mL

7x60 mL UNIT-DOSE BOTTLES

TEVA

APPROVED
SEP 30 2004

FOR RECTAL USE ONLY

Patient Instructions Enclosed.

Each disposable unit contains:

Mesalamine (5-aminosalicylic acid) 4 grams
In a suspension containing carbomer 934P, edetate disodium, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum.

USUAL DOSAGE: 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.

**SHAKE WELL BEFORE USE
DO NOT REMOVE FROM FOIL WRAP UNTIL READY TO USE.
FOIL WRAP PROTECTS PRODUCT FROM DISCOLORATION.**

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Rx only

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



NDC 0093-6888-71

MESALAMINE
RECTAL SUSPENSION, USP
4g/60 mL

FOR RECTAL USE ONLY

7x60 mL UNIT-DOSE BOTTLES

TEVA

NDC 0093-6888-71

MESALAMINE RECTAL SUSPENSION, USP 4g/60 mL

7x60 mL UNIT-DOSE BOTTLES

TEVA

FOR RECTAL USE ONLY

REDUCED TO 50%
BY FOIA STAFF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-841

LABELING REVIEW(S)

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". The signature is written in a cursive style and is positioned above 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)			
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 (page 3711, Red vol. 1.2)

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

- 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). Packaged product stored at both accelerated condition (40°C/75% RH) and controlled room temperature conditions (25°C/60% RH) and also at 30° C/60% RH.

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 3936, Red Vol. 1.2)

2 oz _____ bottle, 20 mm Enema Nozzle screw-on, Enema Nozzle Cap, valve: _____ white petrolatum, _____ Absorbing Packet, Tray -7 Cavity Hips, and Foil Pouch 286 mm X 173 mm.

8. FINISHED DOSAGE FORM



- NDA: FOIL POUCH HAS NO TEXT ON IT.
 - ANDA: 60 mL round bottles with screw cap applicator tip wrapped in a plain laminated foil pouch.
9. The Manufacturer of this drug product is:
TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960
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: 1/8/03

Date of Submission: September 2, 2003

Primary Reviewer: Koung Lee *[Signature]*

Date: 1/16/04

Team Leader: Lillie Golson *[Signature]*

Date: 1/16/04

cc:

ANDA: 76-841
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76841.NA1.Labeling
Review

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

ANDA Number: 76-841

Date of Submission: April 9, 2004

Applicant's Name: TEVA Pharmaceuticals USA

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	Vol. #	Revised	Recommendation
Container (60 mL)	April 9, 2004	2.1	A 3/2004	Acceptable for Approval
Carton (7 X 60 mL unit-dose bottles)	April 9, 2004	2.1	A 3/2004	Acceptable for Approval
INSERT and Patient Information Insert	April 9, 2004	2.1	A 3/2004	Acceptable for Approval

- Revisions needed post-approval: None

BASIS OF APPROVAL:

- Was this approval based upon a petition? no
- 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 (page 3711, Red vol. 1.2)

Ingredient	Function
Mesalamine, USP*	Active
Edetate Disodium, USP	_____
Carbomer 934P, NF	_____
Xanthan Gum, NF	_____
Potassium Acetate, USP	_____
Sodium Benzoate, NF	_____
Potassium Metabisulfite, NF	preservative agent
Purified Water, USP	_____

- 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	

- 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). Packaged product stored at both accelerated condition (40°C/75% RH) and controlled room temperature conditions (25°C/60% RH) and also at 30° C/60% RH.
- DISPENSING STATEMENT COMPARISON
 - NDA: Dispense in original foil-wrapped package.
 - ANDA: Dispense in original foil-wrapped package.
- PACKAGE CONFIGURATION
 - NDA: 7 X 60 mL Unit-Dose Bottles
 - ANDA: 7 X 60 mL Unit-Dose Bottles
- CONTAINER/CLOSURE

Summary of packaging systems (page 3936, Red Vol. 1.2)

2 oz. _____ bottle, 20 mm Enema Nozzle screw-on, Enema Nozzle Cap, valve: _____ white petrolatum, _____ Absorbing Packet, Tray -7 Cavity Hips, and Foil Pouch 286 mm X 173 mm.
- FINISHED DOSAGE FORM



- NDA: FOIL POUCH HAS NO TEXT ON IT.
 - ANDA: 60 mL round bottles with screw cap applicator tip wrapped in a plain laminated foil pouch.
9. The Manufacturer of this drug product is:
TEVA Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960
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: April 27, 2004

Date of Submission: April 9, 2004

Primary Reviewer: Koung Lee *KL*

Date:

5/26/04

Team Leader: Lillie Golson *LG*

Date:

5/27/04

cc:

ANDA: 76-841
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76841.AP.Labeling
Review

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-841

CHEMISTRY REVIEW(S)



ANDA #76-841

Mesalamine Rectal Suspension, USP

TEVA PHARMACEUTICALS USA

Sema Basaran, Ph.D.

Office of Generic Drugs, Division of Chemistry II



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**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Review Data Sheet

- 1. ANDA # 76-841
- 2. REVIEW #: 1
- 3. REVIEW DATE: January 2, 2004
- 4. REVIEWER: Sema Basaran, Ph.D.
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Firm:
Original Submission

September 2, 2003

FDA:
Acknowledgement Letter

September 3, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

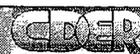
September 2, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA
Address: 650 Cathill Road
Sellersville, PA 18960
USA
Authorized U.S. Agent: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
Representative: Vincent Andolina



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone: 215-591-3000

**APPEARS THIS WAY
ON ORIGINAL**



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

Teva has submitted a Paragraph III Certification Statement for these patents. Teva Pharmaceuticals USA will not engage in the commercial distribution of Mesalamine Rectal Suspension USP, 4 g/60 mL prior to the expiration of these patents. There is no listed exclusivities for the RLD, Rowasa Rectal Suspension Enema, 4.0 grams/Unit(60 mL).

10. PHARMACOLOGICAL CATEGORY:

Treatment of active 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

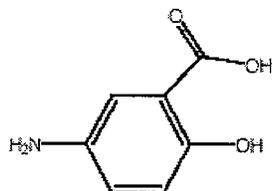
Not a SPOTS product

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			1	Adequate	1-13-04	Reviewed by S.Basaran
	III			4	NA		
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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



Chemistry Review Data Sheet

- 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)

**APPEARS THIS WAY
ON ORIGINAL**



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	Pending	1-02-2004	
Methods Validation	NA		
Labeling	deficient	1-16-04	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 # 76-841

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, minor.

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)

Drug Substance:

The Mesalamine is also known as 5-aminosalicylic acid. Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid. It is light tan to pink colored, needle shaped crystals. Color may darken on exposure to air. The active pharmaceutical ingredient, Mesalamine is a compendial product and it meets USP requirements.

Drug product:

The drug product is Mesalamine Rectal Suspension (Enema), packaged in one unit-dose container (4 g/60 mL). Each disposable unit contains: Mesalamine in a suspension containing Carbomer 934P, edetate sodium, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum.

The product is packaged as unit dose containers containing 4 g of Mesalamine in 60 mL suspension. Drug product should be shaken well before use and it will stored at controlled room temperature, between 20-25°C. The product should be dispensed in tight and light resistant container.

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, laboratory test, container and stability specifications. The minor amendment letter will issue. The Bioequivalence review and EER are pending.



III. Administrative

A. Reviewer's Signature

Sema Basaran, Ph.D.

B. Endorsement Block

HFD-645/SBasaran/1-13-04
HFD-645/BTArnwine/2-12-04
HFD-617/NPark/2-12-04

C. CC Block

ANDA 76-841
DIV FILE
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**APPEARS THIS WAY
ON ORIGINAL**

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # 1

Chemistry Assessment Section

4. 

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please note that Labeling and Bioequivalence reviews are pending.
2. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. The Establishment Evaluation Request is pending.
3. Please acknowledge that Mesalamine Rectal Suspension is an official monograph in the United States Pharmacopeia (USP). Therefore, in the event of a dispute, only the results obtained by the official method and procedures in the USP will be considered acceptable.
4. The dissolution specifications will be set by the Division of Bioequivalence.
5. Please submit updated room temperature stability data.

Sincerely yours,



Florence S. Fang
Director

Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

3/3/04



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-841
DIV FILE
Field Copy

Endorsements:

HFD-645/SBasaran/1-13-04

HFD-645/BTArnwine/2-12-04

HFD-617/NPark/2-12-04

S. Basaran 2/13/04
B. Arnwine 2/19/04
for CKend 2/13/04

F/T by: EW 2/13/04

V:\\FIRMSANZ\\TEVA\\LTRS&REV\\76841.RSB

TYPE OF LETTER: Not Approvable Minor

**APPEARS THIS WAY
ON ORIGINAL**

#2

ANDA #76-841

Mesalamine Rectal Suspension, USP

TEVA PHARMACEUTICALS USA

Sema Basaran, Ph.D.

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.....	9
A. Reviewer's Signature	9
B. Endorsement Block	9
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Chemistry Assessment	9



Chemistry Review Data Sheet

- 1. ANDA # 76-841
- 2. REVIEW #: 2
- 3. REVIEW DATE: May 24, 2004/Jun 10, 2004
- 4. REVIEWER: Sema Basaran, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Firm:	
Original Submission	September 2, 2003
Minor Amendment	May 14, 2004
Labeling Amendment	April 9, 2004
Telephone amendment	June 4, 2004
FDA:	
Acknowledgement Letter	September 3, 2003
Minor deficiency letter	March 3, 2004
Telephone conversation	May 26, 2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	May 14, 2004
Telephone Amendment	June 4, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Pharmaceuticals USA
Address: 1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Vincent Andolina
Telephone: 215-591-3000

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:

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

Teva has submitted a Paragraph III Certification Statement for these patents. Teva Pharmaceuticals USA will not engage in the commercial distribution of Mesalamine Rectal Suspension USP, 4 g/60 mL prior to the expiration of these patents. There is no listed exclusivities for the RLD, Rowasa Rectal Suspension Enema, 4.0 grams/Unit(60 mL).

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

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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):

SPOTS product – Form Completed

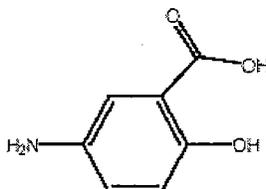
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Chemistry Review Data Sheet

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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	Adequate	1-13-04	Reviewed by S.Basaran
	III		_____	4	NA		
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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- 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)

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	7/26/04	
Methods Validation	NA		
Labeling	Acceptable	5/27/04	K.Lee
Bioequivalence	Acceptable	9/23/04	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 # 76-841

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The telephone amendment dated June 4, 2004 has addressed all the CMC deficiencies. The dissolution method will be revised based on the Division of Bioequivalence recommendation and the revised dissolution medium should be incorporated in their finished product and stability protocol methods. This application may be considered approvable based on the revised dissolution method, and acceptable EER, and bioequivalence status.

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)

Drug Substance:

The Mesalamine is also known as 5-aminosalicylic acid. Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid. It is light tan to pink colored, needle shaped crystals. Color may darken on exposure to air. The active pharmaceutical ingredient, Mesalamine is a compendial product and it meets USP requirements.

Drug product:

The drug product is Mesalamine Rectal Suspension (Enema), packaged in one unit-dose container (4 g/60 mL). Each disposable unit contains: Mesalamine in a suspension containing Carbomer 934P, edetate sodium, potassium acetate, potassium metabisulfite, purified water, sodium benzoate and xanthan gum.

Drug product should be shaken well before use and it will be stored at controlled room temperature, between 20-25°C. The product should be dispensed in a tight and light resistant container.

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

The Bioequivalence, Chemistry and EER status found acceptable for approval



CHEMISTRY REVIEW



Executive Summary Section

**APPEARS THIS WAY
ON ORIGINAL**



Executive Summary Section

III. Administrative

A. Reviewer's Signature

Sema Basaran, Ph.D.

B. Endorsement Block

HFD-645/SBasaran/5-26-04;6/16/04
HFD-645/BTArnwine/5-?-04;9/27/04
HFD-617/YKong/9/23/04

C. CC Block

ANDA 76-841
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ON ORIGINAL**

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CHEMISTRY REV. #2



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-841
DUP Jacket
Division File
Field Copy

Endorsements:

HFD-645 /S.Basaran/5-26-04/6-16-04

HFD-645 /B.Arnwine/9/27/04

HFD-617/9/23/04

S. Basaran 9/29/04

B. Arnwine 9/29/04

V:\\FIRMSANZ\\TEVA\\LTRS&REV\\76841N02.RSB

F/T by rad9/27/04

TYPE OF LETTER: Approvable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-841

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-841
Drug Product Name	Mesalamine Rectal Suspension, USP
Strength	4 gm/60 mL
Applicant Name	Teva Pharmaceuticals USA
Address	North Wales, PA
Submission Date(s)	September 2, 2003
Amendment Date(s)	No
Reviewer	Moheb H. Makary
First Generic	No
File Location	V:\FIRMSNZ\TEVA\LTRS&REV\76841N0903..doc

I. Executive Summary

This submission consisted of a bioequivalence (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=69).

Statistical analyses of the plasma concentration data for mesalamine demonstrate bioequivalence. Mesalamine results (point estimate, 90% CI) are: LAUC_t of 94, 82.96-106.4%, LAUC_i of 97.05, 82.7-113.87 and LC_{max} of 97.5, 88.5-107%.

The firm also conducted dissolution testing on its Mesalamine Rectal Suspension USP, 4 gm/60 mL.

Staff members from the Immediate Office of Generic Drugs and the Division of Bioequivalence met on August 12 to discuss this application. 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 certain criteria are met (see review). The formulations and particle size for Teva's mesalamine rectal suspension will be compared with the RLD. In the interim, the firm should provide additional dissolution data in buffers at different pHs. The application is incomplete.

II. Table of Contents

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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: <ul style="list-style-type: none"> A. Protocol #02-014 submitted 4/1/02 B. Control #02-230 submitted 4/29/01 C. ANDA #76-751 submitted 8/5/2003

The DBE recommends that ANDA sponsors for Mesalamine Rectal Suspension USP, 4 gm/60 mL conduct the following:

1. A single dose, two-way crossover bioequivalence study on Mesalamine Rectal Enema, 4 gm/60 mL under fasting conditions.
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 Drug Specific Issues (if any)

CDER 2000 BA/BE Guidance
Staff members from the Immediate Office of Generic Drugs and the Division of Bioequivalence met on August 12 to discuss this application. 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.

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	

**APPEARS THIS WAY
ON ORIGINAL**

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Mesalamine
Internal Standard	4-aminosalicylic acid
Method description	HPLC/Fluorescence Detection
QC range	-----
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%
QC Intraday precision range (%)	1.9 to 4.6%
QC Intraday accuracy range (%)	99.1 to 111%
QC Interday precision range (%)	2.8 to 4.3%
QC 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)	76 at -20°C
Dilution integrity	2-fold, 101%
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chrom	Serial

APPEARS THIS WAY
ON ORIGINAL

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	10336014
Study Design	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	72
No. of subjects completing	69
No. of subjects analyzed	69, as per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: only completing subjects Female:
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		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	94.0	82.96-106.4
AUC _∞	97.05	82.7-113.87
C _{max}	97.46	88.51-107.32

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
Values above the quantifiable limit	38	1.31	Same	Same
Unacceptable chromatography.	7	0.24	Same	Same
Low IS	6	0.21	Same	Same
Laboratory accident	3	0.10	Same	Same
Peak in pre-dose with IS sample	3	0.10	Same	Same
High IS	2	0.07	Same	Same
No IS	1	0.035	Same	Same
The insert Leak	1	0.035	Same	Same
Peak in pre-dose without IS sample	1	0.035	Same	Same
Total	62	2.14	Same	Same

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

F. Formulation

Location in appendix	Section IV.B, Page 17
Are inactive ingredients within IIG limits?	Yes
If yes, list ingredients outside of limits	
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	Phosphate Buffer, pH 6.8
Volume (mL)	900
USP Apparatus type	USP 27 apparatus 2 (paddle)
Rotation (rpm)	50
Firm's proposed specifications	NLT —% (Q) in 15 minutes
FDA-recommended specifications	NLT —% (Q) in 15 minutes
Is method acceptable?	No
If not then why?	See below

H. Waiver Request(s)

N/A

I. Deficiency Comments

1. The particle size for Teva's mesalamine rectal suspension will be compared with the RLD. In the interim, 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.

J. Recommendations

1. The single-dose bioequivalence study conducted by Teva Pharmaceuticals USA, on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #1582-032, comparing it to Rowasa[®] (mesalamine) Rectal Suspension USP, 4 gm/60 mL, Lot #92599, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Teva's Mesalamine Rectal Suspension USP, 4 gm/60 mL, is bioequivalent to the reference product Rowasa[®] Rectal Suspension, 4 gm/60 mL, manufactured by Solvay Pharmaceuticals, Inc.

2. The dissolution testing conducted by Teva Pharmaceuticals USA, on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #1582-032, is incomplete for the reason given in deficiency comment.

The firm should be informed of the deficiency.

Moheb H. Makary

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

Kuldeep R. Dhariwal

8/18/2004

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

for

Dale P. Conner 8/19/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	10336014
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	Group 1: Period I: 6/7/2003 (Subjects 1-38) Period II 6/14/2003 Group 2: Period I: 6/21/2003 (Subjects 39-72) Period II 6/28/2003
Analytical Site	_____
Analytical Director	_____
Analysis Dates	July 11, 2003 and August 20, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	73 days

Treatment ID	Test	Reference
Test or Reference	Test	Reference
Product Name	Mesalamine Rectal Suspension, USP	Rowasa® (mesalamine) Rectal Suspension
Manufacturer	Teva Pharmaceuticals USA	Solvay Pharmaceuticals, Inc.
Batch/Lot No.	1582-032	92599
Manufacture Date	04/29/03	N/A
Expiration Date	N/A	10/04
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	102.0%	105.7%
Content Uniformity (mean, %CV)	102.1% (0.6%)	100.3% (0.5%)
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	2
Washout Period	7 days
Randomization Scheme	AB for subjects #1, 3, 5, 8, 10, 12, 13, 16, 18, 19, 21, 24, 26, 30, 32, 33, 35, 37, 38, 40, 41, 43, 45, 48, 50, 52, 54, 55, 58, 60, 61, 63, 65, 67, 69, 72 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 and 48 hours post-dose.
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Blood samples were centrifuged at high speed for about 15 minutes. The resulting plasma was transferred to appropriately labeled tubes and frozen at -20°C pending assay.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
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 36 hours post-dose.
Administration	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 53.3 gm (N=71) and Treatment B was 54.3 (N=70). 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.
Safety Monitoring	Blood pressure and heart rate were measured prior to dosing and were obtained prior to release from the clinical facility in both periods.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	48.61
Mean	30.4	Mean	75.1	18-40	83.3	Male	63.9	Afr. Amer.	45.8
SD	10.3	SD	11.1	41-64	16.7	Female	36.1	Hispanic	1.38
Range	18-62	Range	50-98	65-75	0			Asian	2.8
				>75	0			Others	1.38

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
16	Subject #16 was withdrawn from study participation by the investigator due to the subject inability to retain the enema until 8 hours post-dose.	I	No
43	Subject #43 was withdrawn from study participation by the investigator due to a positive drug screen.	II	No
56	Subject #56 was withdrawn from study participation by the investigator due to the subject inability to retain the enema until 8 hours post-dose.	I	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Tiredness	1	0
Nausea	1	0
Headache	1	1
Flatulence	0	1
Low back ache	1	0
Stomach cramps	1	1
Total:	5	3

Table 4 Protocol Deviations

No significant deviations from the protocol were reported.

Comments on Dropouts/Adverse Events/Protocol Deviations: The adverse events occurred approximately with similar frequency for both treatments.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent				Metabolite			
QC Conc. (ng/mL)	100	600	3000					
Inter day Precision (%CV)	11.5	8.3	6.8					
Inter day Accuracy (%)	103	104	103					
Cal. Standards Conc. (ng/mL)	40	80	200	500	1000	2000	3200	4000
Inter day Precision (%CV)	7.2	5.7	4.0	4.9	4.2	3.6	3.6	2.2
Inter day Accuracy (%)	97.8	101	102	102	98.8	98.1	102	99.3
Linearity Range (range of R² values)	0.999							

Comments on Study Assay Quality Control:

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: O.K.

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

SOP No.	Date of SOP	SOP Title
L200.108	9/20/2001 (Initiation Date) 10/18/2002 (Revision Date) 6/10/2003 (Revision Date)	Samples Analysis Chromatographic

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC _{0-t}	hr-ng/mL	21543.6	72.8	22911.8	67.1	0.94
AUC _∞	hr-ng/mL	24458.9	68.1	26862.9	79.7	0.91
C _{max}	ng/mL	1451.7	49.5	1500.3	51.9	0.97
T _{max}	hr	6.9		6.8		
T _{1/2}	hr	10.4		10.3		
K _{el}	1/hr	0.133		0.22		

Table 9 Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC _{0-t}	16530.9	17592.0	93.97	82.9-106.4
AUC _∞	19003.0	19581.5	97.0	82.7-113.9
C _{max}	1274.4	1307.6	97.5	88.5-107.3

Table 10 Additional Study Information

Root mean square error, AUC _t	0.439
Root mean square error, C _{max}	0.339
Ke and AUC _i determined for how many subjects?	52 for the test product and 56 for the reference product
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C _{max}	None
Were the subjects dosed as more than one group?	Yes.

Comments on Pharmacokinetic Analysis:

Analyses of variance (ANOVA) were performed using the following model:

auc auci cmax lauc lauci lmax = grp seq subj(seq*grp) per(grp) trt grp*trt;

As the trt*grp interaction was not statistically significant at the 5% level, the grp term was dropped from the model. GRP term is always kept in the model. The thing we drop is GRP*TRT.

Summary and Conclusions, Single-Dose Bioequivalence Study:

The single-dose bioequivalence study is acceptable.

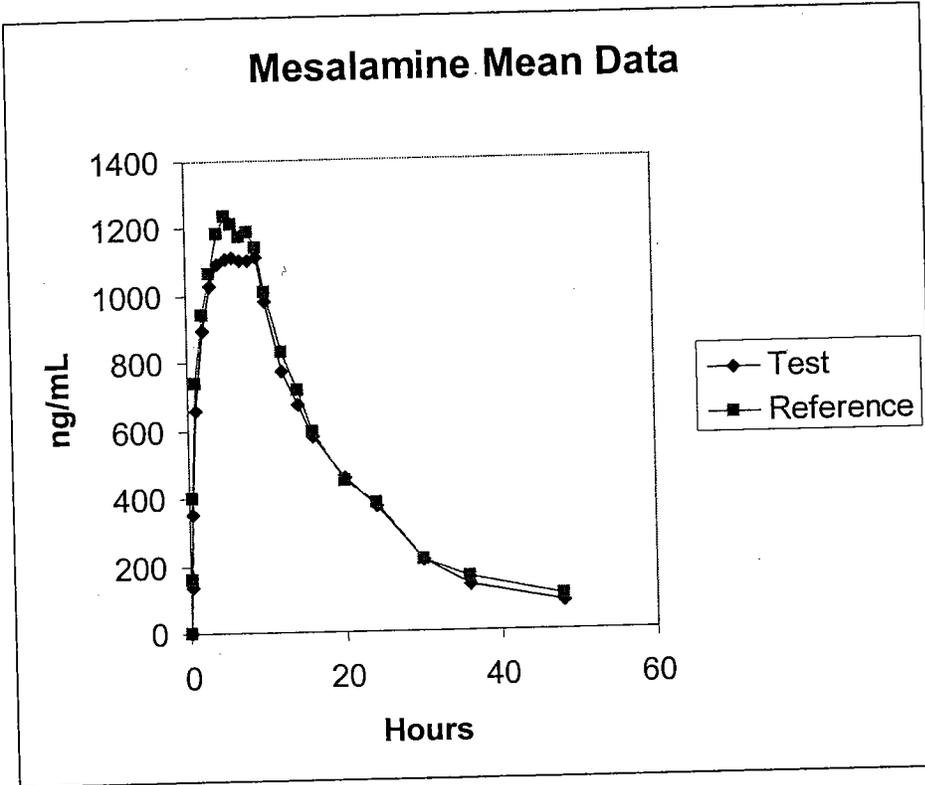
**APPEARS THIS WAY
ON ORIGINAL**

Table 11 Mean Mesalamine Plasma Concentrations (ng/mL), Single-Dose Bioequivalence Study

Time (hr)	Test (n=69)		Reference (n=69)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0	.	0	.	.
0.25	137.32	62.57	160.79	65.39	0.85
0.5	353.25	57.10	400.16	59.17	0.88
1	658.29	58.16	741.88	57.53	0.89
2	895.14	56.07	942.03	56.37	0.95
3	1026.36	54.53	1063.10	60.61	0.97
4	1091.62	52.25	1183.99	54.34	0.92
5	1107.22	50.71	1233.01	58.89	0.90
6	1110.33	49.72	1211.59	57.81	0.92
7	1104.13	49.90	1173.01	58.44	0.94
8	1104.71	53.12	1185.83	56.02	0.93
9	1110.84	60.69	1140.35	69.46	0.97
10	979.92	73.80	1006.64	77.54	0.97
12	771.13	88.34	829.31	84.93	0.93
14	672.57	99.60	716.65	87.65	0.94
16	577.77	113.11	594.89	88.67	0.97
20	457.92	109.35	448.05	92.74	1.02
24	372.24	116.87	381.90	112.73	0.97
30	212.18	134.55	212.68	137.02	1.00
36	135.55	209.77	159.73	186.51	0.85
48	84.88	308.30	104.03	241.76	0.82

**APPEARS THIS WAY
ON ORIGINAL**

Figure 1 Mean Mesalamine Plasma Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study



APPEARS THIS WAY
ON ORIGINAL

B. Formulation Data

Teva

Ingredient	Function	%w/w (ANDA executed batch)	4 g/60 mL
Mesalamine, USP	Active	_____	4.0800g
Xanthan Gum, NF	_____	_____	_____
Potassium Acetate, USP	_____	_____	_____
Sodium Benzoate, NF	_____	_____	_____
Potassium Metabisulfite, NF	_____	_____	_____
Carbomer 934P, NF	_____	_____	_____
Edetate Disodium, USP	_____	_____	_____
Purified Water, USP	_____	_____	_____
Total		100%	61.8600g (60 mL)

RLD's Formulation* (Solvay Pharmaceuticals)**INGREDIENT**

Mesalamine, USP
Sodium Benzoate, NF
Carbomer 934P, NF
Edetate Disodium, USP
Potassium Metabisulfite, NF
Potassium Acetate, USP
Xanthum Gum, NF
Purified Water, USP q.s.

grams/unit % w/w
4.080

*(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.

C. Dissolution Data

Table 1

Sampling Time (min)	Test Product, Mesalamine Rectal Suspension USP Strength 4 gm/60 mL Lot No. 1582-032			Reference Product, Rowasa ^R (Mesalamine) Rectal Suspension Enema Strength 4 gm/60 mL Lot No. 92599		
	Mean	%CV	Range	Mean	%CV	Range
5	86	9.2	/	102	4.8	/
10	94	3.8		101	4.0	
15	93	5.1		101	1.1	
30	92	5.8		101	1.4	

APPEARS THIS WAY
ON ORIGINAL

D. SAS Output

Study	Data	Sas Code	SAS Output
BE Study	 mesalamine.prn	 mesalaminesascode.dbt	 mesalaminesasoutput.txt

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

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-841

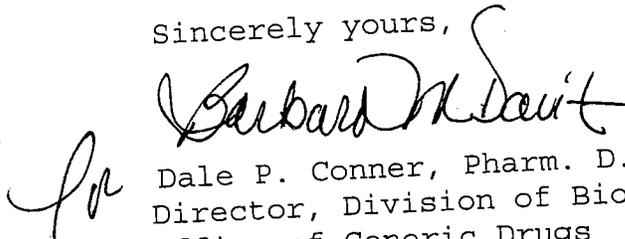
APPLICANT: Teva
Pharmaceuticals USA

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:

The dissolution testing you submitted is not acceptable. Please 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. 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

CC: ANDA #76-841
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

HFD-658/ Bio team Leader K. Dhariwal

HFD-650/ D. Conner

MHM 8/18/04

MD

DCD 8/18/04

Ch

BIOEQUIVALENCE - DEFICIENCIES

1. Fasting Study

Clinical: _____

Analytical: _____

Submission Date: 9/2/2003

Strength: 4 gm/60 mL

Outcome: IC

APPEARS THIS WAY
ON ORIGINAL

Mesalamine Rectal Suspension, USP
4 gm/60 mL
ANDA #76-841
Reviewer: Moheb H. Makary
W 76841A0904.doc

Teva Pharmaceuticals USA
North Wales, PA
Submission Date:
September 20, 2004
September 8, 2004

Review of Two Amendments

Executive Summary

These amendments are responses to the Division of Bioequivalence (DBE) deficiency letter of August 30, 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. On September 20, 2004, 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

In the September 8, 2004 amendment, the firm submitted comparative dissolution results using the above recommended dissolution media and rotation

speeds. Five mL of the suspension was used in the dissolution testing. On September 16, 2004, Teva was requested to use one dosage unit (60 mL) per vessel in the dissolution testing. In the September 20, 2004 amendment, the firm submitted the requested information. The firm emptied the contents of one rectal suspension container (60 mL) 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 Teva's Mesalamine Rectal Suspension, USP and Solvay's Rowasa[®] (mesalamine) Rectal Suspension Enema in various pH media and rotation speeds are comparable.

The firm indicated that the reference lot, (Solvay Pharmaceuticals, Inc.'s Rowasa^R Rectal Suspension Enema, 4 gm/unit (60 mL), lot #92599, Expiration Date: 10/2004) used in the biostudy is no longer available for testing. Therefore, the firm has tested Rowasa^R Lot #93056, Expiration Date: 02/2006. In addition, samples from its bio-lot #1582-032 are no longer available; therefore lot #22051D was used in the dissolution testing.

The firm's reply to the comment is acceptable.

Recommendation:

1. The single-dose bioequivalence study conducted by Teva Pharmaceuticals USA, on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #1582-032, comparing it to Rowasa[®] (mesalamine) Rectal Suspension USP, 4 gm/60 mL, Lot #92599, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Teva's 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 Teva Pharmaceuticals USA, on its Mesalamine Rectal Suspension USP, 4 gm/60 mL, Lot #22051D, is acceptable.

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

Not less than \leftarrow % (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 acceptable.

The firm should be informed of the above recommendations.

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

Mohariwal. 9/22/04
Kuldeep Dhariwal, Ph.D.
Team Leader Review Branch IV
Division of Bioequivalence

for Barbara D. Dawts 9/22/04
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-841

APPLICANT: Teva Pharmaceuticals USA

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 —% (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 #76-841
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 9/21/04

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary *MHM*
HFD-658/ Bio team Leader K. Dhariwal *MD 9/22/04*
HFD-650/ D. Conner *DC 9/22/04*

for

BIOEQUIVALENCE - ACCEPTABLE

Submission date: 9-20-04

- ✓ 1. STUDY AMENDMENT (STA)
September 20, 2004
Outcome: AC
Strengths: 4 gm/60 mL
- ✓ 2. STUDY AMENDMENT (STA)
September 8, 2004
Outcome: IC
Strengths: 4 gm/60 mL
- ✗ 3. New Correspondence (NC)
September 21, 2004
Strengths: 4 gm/60 mL

Outcome Decisions: AC – ACCEPTABLE

Table I

Table 1: 900 mL 0.1N HCl, 25 rpm

Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # 22051D

% Mesalamine Dissolved (900 mL 0.1 N HCl, Paddles, 25 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5															
10															
15															
30															

Table 2: 900 mL 0.1N HCl, 25 rpm

Rowasa® (Mesalamine) Rectal Suspension Enema, 4 g/60 mL, Lot # 93056

% Mesalamine Dissolved (900 mL 0.1 N HCl, Paddles, 25 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5															
10															
15															
30															

Table 3: 900 mL 0.1N HCl, 50 rpm

Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # 22051D

% Mesalamine Dissolved (900 mL 0.1 N HCl, Paddles, 50 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5															
10															
15															
30															

Table 4: 900 mL 0.1N HCl, 50 rpm

Rowasa® (Mesalamine) Rectal Suspension Enema, 4 g/60 mL, Lot # 93056

% Mesalamine Dissolved (900 mL 0.1 N HCl, Paddles, 50 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5															
10															
15															
30															

Table 5: 900 mL pH 4.5 Acetate Buffer, 25 rpm

Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # 22051D

% Mesalamine Dissolved (900 mL pH 4.5 Acetate Buffer, Paddles, 25 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Table 6: 900 mL pH 4.5 Acetate Buffer, 25 rpm

Rowasa® (Mesalamine) Rectal Suspension Enema, 4 g/60 mL, Lot # 93056

% Mesalamine Dissolved (900 mL pH 4.5 Acetate Buffer, Paddles, 25 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # 22051D

% Mesalamine Dissolved (900 mL pH 4.5 Acetate Buffer, Paddles, 50 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Table 8: 900 mL pH 4.5 Acetate Buffer, 50 rpm

Rowasa® (Mesalamine) Rectal Suspension Enema, 4 g/60 mL, Lot # 93056

% Mesalamine Dissolved (900 mL pH 4.5 Acetate Buffer, Paddles, 50 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Table 9: 900 mL pH 6.8 Phosphate Buffer, 25 rpm

Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # 22051D

% Mesalamine Dissolved (900 mL pH 6.8 Phosphate Buffer, Paddles, 25 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Table 10: 900 mL pH 6.8 Phosphate Buffer, 25 rpm

Rowasa® (Mesalamine) Rectal Suspension Enema, 4 g/60 mL, Lot # 93056

% Mesalamine Dissolved (900 mL pH 6.8 Phosphate Buffer, Paddles, 25 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Table 11: 900 mL pH 6.8 Phosphate Buffer, 50 rpm

Mesalamine Rectal Suspension USP, 4 g/60 mL, Lot # 22051D

% Mesalamine Dissolved (900 mL pH 6.8 Phosphate Buffer, Paddles, 50 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

Table 12: 900 mL pH 6.8 Phosphate Buffer, 50 rpm

Rowasa® (Mesalamine) Rectal Suspension Enema, 4 g/60 mL, Lot # 93056

% Mesalamine Dissolved (900 mL pH 6.8 Phosphate Buffer, Paddles, 50 rpm)														Avg. (%)	RSD (%)
Time (Minutes)	1	2	3	4	5	6	7	8	9	10	11	12			
5	[]														
10															
15															
30															

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-841

SPONSOR : Teva Pharmaceuticals USA

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 : MM

DATE : 9/22/04

TEAM LEADER : Kuldeep Dhariwal, Ph.D

BRANCH : IV

INITIAL : MD

DATE : 9/22/04

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

INITIAL : Barbara M. Dewitt

DATE : 9/23/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-841

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

<p>-We called the firm to tighten _____ for finished product and stability protocol.</p> <p>-Particle size and sedimentation rate should be included as well.</p> <p>-They haven't responded to 4b completely- the firm needs to provide _____</p> <p>****Revised finished product and stability protocols and sedimentation rate analysis should be provided.</p>	DATE: 5-26-2004
	ANDA NUMBER: 76-841
	PRODUCT NAME: Mesalamine Rectal Suspension
	Firm Name: Teva
	FIRM REPRESENTATIVE: Vincent Andolina
	PHONE NUMBER: 215-591-3000
	FDA REPRESENTATIVES: Nicole Lee Sema Basaran
SIGNATURES:	

CC: ANDA
Telecon Binder

V:firmsnz/teva/tcon/76841.5-26-2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-841

CORRESPONDENCE



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Direct Dial: (215) 591 8642
Direct FAX: (215) 591 8812
vincent.andolina@tevausa.com

September 2, 2003

*505 (16) (1) O.K.
Morton
15 October 2003*

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

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Mesalamine Rectal Suspension USP, 4 g/60 mL.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 23 volumes; 11 for the archival copy and 12 for the review copy.

The application contains a full report of a pharmacokinetic study. This study compares Mesalamine Rectal Suspension USP, 4 g/60 mL manufactured by TEVA Pharmaceuticals USA to the reference listed drug, Rowasa® Rectal Suspension Enema, 4.0 grams/unit (60 mL).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please contact me by phone at (215) 591-8642 or by facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/st
Enclosures

RECEIVED

SEP 03 2003

OGD/CDER

ANDA 76-841

TEVA Pharmaceuticals USA
Attention: Vincent Andolina
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

OCT 17 2003

Dear Sir:

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

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

DATE OF APPLICATION: September 2, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 3, 2003

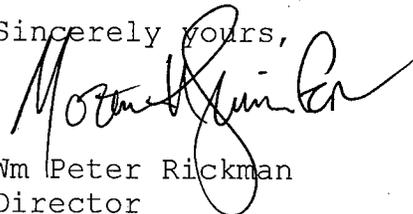
We will correspond with you further after we have had the opportunity to review the application.

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 76-841

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement:

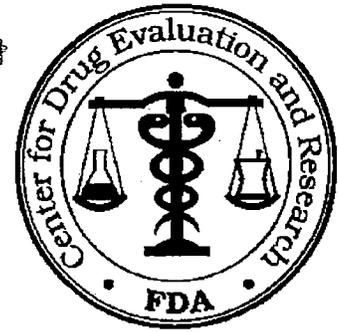
HFD-615/MShimer, Chief, RSB Martin Shimer date 15 Oct 2003
HFD-615/CBina, CSO Cheryl Bina date 10/15/03
Word File
V:\FIRMSNZ\TEVA\ltrs&rev\76841.ack
F/T
ANDA Acknowledgment Letter!

MINOR AMENDMENT

ANDA 76-841

MAR 03 2004

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)



APPLICANT: TEVA Pharmaceuticals USA

TEL: 215-591-3141

ATTN: Philip Erickson

FAX: 215-591-8812

FROM: Nicole Lee

PROJECT MANAGER: (301) 827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated September 2, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Mesalamine Rectal Suspension USP, 4 g/ 60 mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 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:

Chemistry and labeling comments attached

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.

CL 3/3/04

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

3/3/2004 FDA FAX



Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
FAX: (215) 591 8812

ORIG AMENDMENT

NIAF

April 9, 2004

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

LABELING AMENDMENT

ANDA# 76-841
MESLAMINE RECTAL SUSPENSION USP, 4 g/60 mL
LABELING AMENDMENT – RESPONSE TO MARCH 3, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Labeling Amendment to the above-referenced pending ANDA in response to a March 3, 2004 review letter from the Division of Labeling and Program Support. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments are addressed in the order in which they were presented.

Labeling Deficiencies:

1. CONTAINER: (60 mL unit-dose)

We have revised our container labeling storage temperature recommendations to include, "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".

Please find twelve final print copies of our container labels and a comparison to our previous revision in **Attachment 2**. These changes will be implemented at the time of next printing.

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

a. We have revised our container labeling storage temperature recommendations to include, "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".

b. As recommended by the Agency, we have added the statement, "Patient Instructions Enclosed".

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APR 12 2004

DGD/C

Please find twelve final print copies of our carton labeling and a comparison to our previous revision in **Attachment 3**. These changes will be implemented at the time of next printing.

3. INSERT:

a. CLINICAL PHARMACOLOGY

We have changed "noobservable" to "no-observable" in the Preclinical Toxicology subsection.

b. DOSAGE AND ADMINISTRATION

We have changed '——' to "USP".

HOW SUPPLIED

- a. We have deleted the statement, " _____ ."
- b. We have removed the terminal zero, "4 g" instead of "4.0g".
- c. We have revised our container labeling storage temperature recommendations to include, "Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature)".

Please find twelve final print copies of our package insert and a comparison to our previous revision in **Attachment 4**.

4. PATIENT INSTRUCTIONS

Our Patient Instructions is provided at the end of our Professional Insert, which is separated by a perforation.

The information presented herein represents, in our opinion, a complete response to the March 3, 2004 review letter from the Division of Labeling and Program Support. We look forward to your approval of ANDA # 76-841. Should you have any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Nincent Andolina

VA/st
Enclosures



ORIGINAL

21

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Direct Dial: (215) 591 8642
Direct FAX: (215) 591 8812
vincent.andolina@tevausa.com

May 14, 2004

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

MINOR AMENDMENT

ORIG AMENDMENT

N/A M

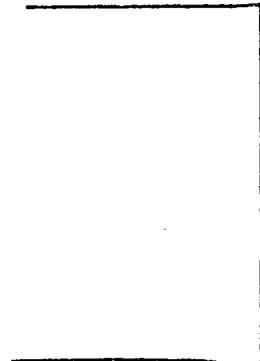
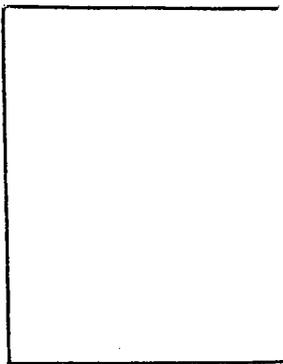
ANDA# 76-841
MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL
MINOR AMENDMENT – RESPONSE TO MARCH 3, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Minor Amendment to the above-referenced pending ANDA in response to a review letter from the Office of Generic Drugs dated March 3, 2004. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments are addressed in the order in which they were presented.

A. DEFICIENCIES:

1.



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MAY 17 2004

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information from

TEVA 5/14/2004 LETTER

ANDA# 76-841

MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL

MINOR AMENDMENT – RESPONSE TO MARCH 3, 2004 REVIEW LETTER

Page 5 of 5

The information presented herein represents, in our opinion, a complete response to the March 3, 2004 review letter from the Office of Generic Drugs. We look forward to your approval of ANDA # 76-841. Should you have any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/st

Enclosures



Administrative Offices:
 TEVA PHARMACEUTICALS USA
 1090 Horsham Road, PO Box 1090
 North Wales, PA 19454-1090

Vincent Andolina, RAC
 Director, Regulatory Affairs
 Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
 FAX: (215) 591 8812

ORIG AMENDMENT

N/AM

June 4, 2004

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

TELEPHONE AMENDMENT

ANDA# 76-841
 MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL
 TELEPHONE AMENDMENT – RESPONSE TO MAY 26, 2004 TELEPHONE CONTACT

Dear Mr. Buehler:

We submit herewith a Telephone Amendment to the above-referenced pending ANDA in response to a May 26, 2004 telephone contact from Sema Basaran, Ph.D., review chemist and Nicole Lee, Pharm.D., project manager of the Office of Generic Drugs, Division of Chemistry II, Team 7. Comments are addressed in the order in which they were presented.

DEFICIENCIES:

- As requested by the Agency, we have tightened our _____ specifications. Below we have provided a table summarizing our current and proposed specifications:

_____ Test	Current Specification	Proposed Specification
Release	_____	_____
Stability	_____	_____
In-Process	_____	_____

In support of our revised specifications, we have provided in **Attachment 1** a table of _____ results from various lots including Teva bulk, finished product, and stability samples, as well as innovator samples.

- We have incorporated Particle Size and Sedimentation Rate testing in our finished product and stability specifications. Please note that our Particle Size test _____ Comparative data with the innovator product for both the Particle Size and Sedimentation Rate tests are provided in **Attachment 2**

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JUN 20 7 2004

OGD/CDER

Below we have provided a table summarizing the proposed Particle Size and Sedimentation Rate specifications:

Testing	Particle Size Specification	Sedimentation Rate Specification
Release	/	/
Stability	/	/

- 3) We have provided in **Attachment 3** a table showing comparison of the innovator's Rowasa® and Teva's Mesalamine Rectal Suspension USP, 4 g/60 mL, results for color, viscosity and specific gravity. Please refer to **Attachment 2** for similar comparison data for sedimentation rate and particle size tests. In addition, we have provided in **Attachment 4** a revised Finished Product Procedure Manual to include tighter limits and the addition of particle size and sedimentation rate tests for release and stability testing.

Please refer to **Attachment 5** for copies of our updated Stability Protocol and Finished Product Certificate of Analysis, which have been revised in accordance with the aforementioned changes. In addition, all future release and stability testing will be performed and comply with the revised specifications proposed herein.

The information presented herein represents, in our opinion, a complete response to the May 26, 2004 telephone contact from the Office of Generic Drugs. We look forward to your approval of ANDA # 76-841. Should you have any questions regarding the information contained herein, please contact me at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Vincent Andolina

VA/st
Enclosures

BIOEQUIVALENCY AMENDMENT

ANDA 76-841

AUG 30 2004

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)



APPLICANT: TEVA Pharmaceuticals USA

TEL: 215-591-8642

ATTN: Vincent Andolina

FAX: 215-591-8812

FROM: Beth Fabian-Fritsch *BFF*

PROJECT MANAGER: (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on September 2, 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 30 2004

21

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-841

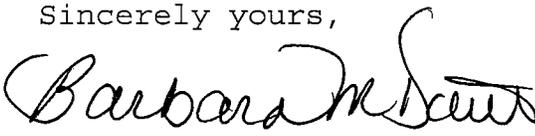
APPLICANT: Teva
Pharmaceuticals USA

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:

The dissolution testing you submitted is not acceptable. Please 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. 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,

for 

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



ORIGINAL

31

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
FAX: (215) 591 8812

September 8, 2004

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

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AB

ANDA# 76-841
MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL
BIOEQUIVALENCY AMENDMENT – RESPONSE TO AN AUGUST 30, 2004 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a Bioequivalency Amendment to the above-referenced pending ANDA in response to an August 30, 2004 review letter from the Division of Bioequivalence. For ease of review, a copy of the letter is provided in **Attachment 1**. Comments are addressed in the order in which they were presented.

DEFICIENCIES:

- 1) Please note that the innovator's reference lot as used in the biostudy, Solvay Pharmaceuticals, Inc.'s Rowasa[®] Rectal Suspension Enema, 4 grams/unit (60 mL), Lot #92599, Expiration Date: 10/2004, is no longer available for testing. Therefore, we have tested Rowasa[®] Lot No. 92872, Expiration Date: 06/2005. A Certificate of Analysis for this lot and our ANDA lot 1582-032 are provided in **Attachment 2**.
- 2) As request by the Agency, we have provided in **Attachment 3** Comparative Dissolution Studies in the following media:

- (900 mL): 0.1 N HCl and USP Buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 rpm and 25 rpm.

The lots of test and reference products compared in these studies are:

- Mesalamine Rectal Suspension USP, 4 g/60 mL (Lot No. 1582-032)
- Rowasa[®] Rectal Suspension Enema, 4 grams/unit (60 mL) (Lot No. 92872), Expiration Date: 06/2005

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SEP 09 2004

OGD/CDER

These studies were performed by:
Teva Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960
USA

The dissolution data provided in Attachment 3 demonstrate that the dissolution profiles performed at 50 rpm are comparable over the entire pH range. However, the data at the 25 rpm speed are highly variable due to insufficient mixing within the vessel. At 25 rpm, the samples tend to pool and lie at the bottom of the vessel, resulting in high relative standard deviations (RSD) for both test and reference products. In addition, the 25 rpm data appears to vary with sample introduction technique.

Due to the slow mixing at 25 rpm, variable rates of sample addition will lead to variable mixing from vessel to vessel, resulting in higher data variability. It is our opinion that the 25 rpm dissolution profiles have no physiological relevance, as the PK study submitted with our original ANDA has already demonstrated the bioequivalence of the Teva and Solvay mesalamine rectal suspension products.

Please note that our dissolution method distinguishes mesalamine dissolved in dissolution media from drug particles by filtering the media through a 0.45 µm filter during sample preparation.

In addition, we have provided in **Attachment 4** a diskette containing the dissolution data as supplied in the report in Attachment 3.

The information presented herein represents, in our opinion, a complete response to the August 30, 2004 review letter from the Division of Bioequivalence. We look forward to your prompt approval of ANDA # 76-841. Should you have any questions regarding the information contained herein, please contact the undersigned at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,



VA/st
Enclosures



4.1

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Vincent Andolina, RAC
Director, Regulatory Affairs
Liquids, Semisolids and Specialty Projects

Phone: (215) 591 8642
FAX: (215) 591 8812

September 20, 2004

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

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT

NLAB

ANDA# 76-841
MESALAMINE RECTAL SUSPENSION USP, 4 g/60 mL
BIOEQUIVALENCY AMENDMENT – RESPONSE TO SEPTEMBER 10 & 16, 2004
TELEPHONE CONTACTS

Dear Mr. Buehler:

We submit herewith a Bioequivalency Amendment to the above-referenced pending ANDA in response to telephone contacts on September 10 & 16, 2004 from Barbara M. Davit, Ph.D., Deputy Director, Kuldeep Dhariwal, Ph.D., Moheb Makary, Ph.D., Beth Fritsch, Project Manager, and Nhan L. Tran, Ph.D., Dissolution Expert, all from the Division of Bioequivalence of the Office of Generic Drugs. Specifically, the Division of Bioequivalence requested the additional dissolution profiles performed at 25 rpm and 50 rpm utilizing the Agency's recommended technique so that the data variability is lower. In addition, the Agency requested the methodology used to perform the dissolution profiles be provided.

DEFICIENCIES:

- 1) Please note that the innovator's reference lot as used in the biostudy, Solvay Pharmaceuticals, Inc.'s Rowasa[®] Rectal Suspension Enema, 4 grams/unit (60 mL), Lot #92599, Expiration Date: 10/2004, is no longer available for testing. Therefore, we have tested Rowasa[®] Lot No. 93056, Expiration Date: 02/2006. In addition, samples from our ANDA Lot No. 1582-032 are no longer available; as such we have tested Lot No. 22051D. Certificates of Analysis for Rowasa[®] Lot No. 93056 and our Lot No. 22051D are provided in **Attachment 1**.

RECEIVED

SEP 21 2004

OGD/QUER

2) We have provided in **Attachment 2** the dissolution method from our Finished Product Procedure Manual (Version 4.0, Release Date: 6/2/04). In addition, we have provided in **Attachment 2** an Addendum to our dissolution method. This Addendum describes a revision to the sample preparation, as well as the addition of the sample to the vessel. Please note that this Addendum supercedes the current procedure in Method Number 6888F Version 4.0.

3) As request by the Agency, we have provided in **Attachment 3** Comparative Dissolution Studies in the following media:

- (900 mL): 0.1 N HCl and USP Buffers at pH 4.5, pH 6.8 and pH 7.2 using apparatus 2 (paddle) at 50 rpm and 25 rpm.

These studies were performed by:

Teva Pharmaceuticals USA
650 Cathill Road
Sellersville, PA 18960
USA

In addition, we have provided in **Attachment 4** a diskette containing the dissolution data as supplied in the report in Attachment 3.

The information presented herein represents, in our opinion, a complete response to the telephone contacts on September 10 & 16, 2004 from the Division of Bioequivalence. We look forward to your prompt approval of ANDA # 76-841. Should you have any questions regarding the information contained herein, please contact the undersigned at (215) 591-8642 or via facsimile at (215) 591-8812.

Sincerely,

Nincent Andolina

VA/st
Enclosures