500170
Rev May 2005

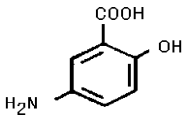
ROWASA®
(Mesalamine)
Rectal Suspension Enema
4.0 grams/unit (60 mL)

R_x only

DESCRIPTION

The active ingredient in ROWASA® (Mesalamine) Rectal Suspension Enema, a disposable (60 mL) unit, is mesalamine, also known as 5-aminosalicylic acid (5-ASA). Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid.

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



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

CLINICAL PHARMACOLOGY

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

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic 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 ROWASA® (Mesalamine) Rectal Suspension Enema is poorly absorbed from the colon and is excreted principally in the feces during subsequent bowel movements. The extent of absorption is dependent upon the retention time of the drug product, and there is considerable individual variation. At steady state, approximately 10 to 30% of the daily 4-gram dose can be recovered in cumulative 24-hour urine collections. Other than the kidney, the organ distribution and other bioavailability characteristics of absorbed mesalamine in man are not known. It is known that the compound undergoes acetylation but whether this process takes place at colonic or systemic sites has not been elucidated.

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

Efficacy

In a placebo-controlled, international, multicenter trial of 153 patients with active distal ulcerative colitis, proctosigmoiditis or proctitis, ROWASA® (Mesalamine) Rectal Suspension Enema reduced the overall disease activity index (DAI) and individual components as follows:

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

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

** Significant ROWASA®/placebo difference. $p<0.01$

*** Significant ROWASA®/placebo difference. $p<0.001$

Differences between ROWASA® (Mesalamine) Rectal Suspension Enema and placebo were also statistically different in subgroups of patients on concurrent sulfasalazine and in those having an upper disease boundary between 5 and 20 or 20 and 40 cm. Significant differences between ROWASA® (Mesalamine) Rectal Suspension Enema and placebo were not achieved in those subgroups of patients on concurrent prednisone or with an upper disease boundary between 40 and 50 cm.

INDICATIONS AND USAGE

ROWASA® (Mesalamine) Rectal Suspension Enema is indicated for the treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

CONTRAINDICATIONS

ROWASA® (Mesalamine) Rectal Suspension Enema is contraindicated for patients known to have hypersensitivity to the drug or any component of this medication.

WARNINGS

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

PRECAUTIONS

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

Although renal abnormalities were not noted in the clinical trials with ROWASA® (Mesalamine) Rectal Suspension Enema, the possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on ROWASA® (Mesalamine) Rectal Suspension Enema, especially those on concurrent oral products which liberate mesalamine and those with preexisting renal disease, should be carefully monitored with urinalysis, BUN (blood urea nitrogen), 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 ROWASA® (Mesalamine) Rectal Suspension Enema, some patients have developed pancolitis. However, extension of upper disease boundary and/or flare-ups occurred less often in the ROWASA® (Mesalamine) Rectal Suspension Enema treated group than in the placebo-treated group.

Worsening of colitis or symptoms of inflammatory bowel disease, including melena and hematochezia, may occur after commencing mesalamine.

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 ROWASA® (Mesalamine) Rectal Suspension Enema, 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 ROWASA® (Mesalamine) Rectal Suspension Enema should be investigated with this information in mind. Discontinuation of ROWASA® (Mesalamine) Rectal Suspension Enema may be warranted in some cases, but rechallenge with mesalamine can be performed under careful clinical observation should the continued therapeutic need for mesalamine be present.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mesalamine caused no increase in the incidence of neoplastic lesions over controls in a 2-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 has very rarely been reported among patients treated 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

ROWASA® (Mesalamine) Rectal Suspension Enema is usually well tolerated. Most adverse effects have been mild and transient.

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

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

In addition, the following adverse events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice: nephrotoxicity, pancreatitis, fibrosing alveolitis and elevated liver enzymes. Cases of pancreatitis and fibrosing alveolitis have been reported as manifestations of inflammatory bowel disease as well. Published case reports and/or spontaneous post marketing surveillance have described rare instances of aplastic anemia, agranulocytosis, thrombocytopenia, eosinophilia, pancytopenia, neutropenia, oligospermia, and infertility in men. 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 7 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 ROWASA® (Mesalamine) Rectal Suspension Enema in 60 mL units is one rectal instillation (4 grams) once a day, preferably at bedtime, and retained for approximately eight hours. While the effect of ROWASA® (Mesalamine) Rectal Suspension Enema may be seen within 3 to 21 days, the usual course of therapy would be from 3 to 6 weeks depending on symptoms and sigmoidoscopic findings. Studies available to date have not assessed if ROWASA® (Mesalamine) Rectal Suspension Enema will modify relapse rates after the 6-week short-term treatment. ROWASA® (Mesalamine) Rectal Suspension Enema is for rectal use only.

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

ROWASA® (Mesalamine) Rectal Suspension Enema for rectal administration is an off-white to tan colored suspension. Each disposable enema bottle contains 4.0 grams of mesalamine in 60 mL aqueous suspension. Enema bottles are supplied in boxed, foil-wrapped trays as follows:.

NDC 0032-1924-82..... Carton of 7 Bottles
NDC 0032-1924-28..... Carton of 28 Bottles

ROWASA® (Mesalamine) Rectal Suspension Enemas are for rectal use only.

Patient instructions are included.

Storage

Store at controlled room temperature 20° to 25°C (68° to 77°F). 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: ROWASA® (Mesalamine) Rectal Suspension Enema will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel. Take care in choosing a suitable location for administration of this product.

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U.S. Pat. Nos. 4657900 and RE33239

Solvay
Pharmaceuticals, Inc.
Marietta, GA 30062

PATIENT INSTRUCTIONS

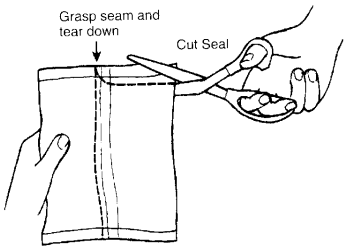
How to Use this Medication.

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

NOTE: ROWASA® (Mesalamine) Rectal Suspension Enema will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel. Take care in choosing a suitable location for administration of this product.

1 Remove the Bottles

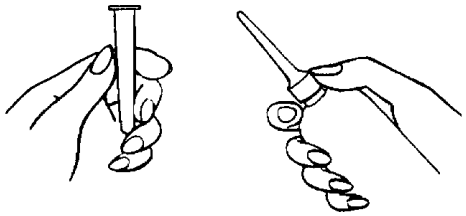
a. Remove the bottles from the protective foil pouch by tearing or by using scissors as shown, being careful not to squeeze or puncture bottles. ROWASA® (Mesalamine) Rectal Suspension Enema is an off-white to tan colored suspension. Once the foil-wrapped unit of seven bottles is opened, all enemas should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



2 Prepare the Medication for Administration

a. Shake the bottle well to make sure that the medication is thoroughly mixed.

b. Remove the protective sheath from the applicator tip. Hold the bottle at the neck so as not to cause any of the medication to be discharged.



3 Assume the Correct Body Position

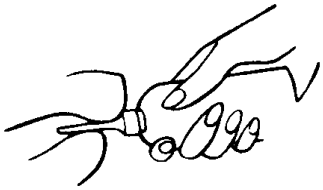
a. Best results are obtained by lying on the left side with the left leg extended and the right leg flexed forward for balance.

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

4 Administer the Medication

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

b. Grasp the bottle firmly, then tilt slightly so that the nozzle is aimed toward the back, squeeze slowly to instill the medication. Steady hand pressure will discharge most of the medication. After administering, withdraw and discard the bottle.



c. Remain in position for at least 30 minutes to allow thorough distribution of the medication internally. Retain the medication all night, if possible.

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