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2 15E Rev 5/2003



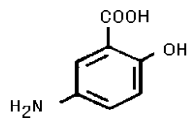
ROWASA®
(Mesalamine)
Rectal Suspension Enema
4.0 grams/unit (60 mL)

R_x only

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4 **DESCRIPTION**

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

8
9 The empirical formula is C₇H₇NO₃, representing a molecular weight of 153.14. The
10 structural formula is:



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

25
26 **CLINICAL PHARMACOLOGY**

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

34
35 The mechanism of action of mesalamine (and sulfasalazine) is unknown, but
36 appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA)
37 metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through
38 the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids
39 (HETEs) is increased in patients with chronic inflammatory bowel disease, and it is
40 possible that mesalamine diminishes inflammation by blocking cyclooxygenase and
41 inhibiting prostaglandin (PG) production in the colon.

42

43 **Preclinical Toxicology**

44 Preclinical studies have shown the kidney to be the major target organ for mesalamine
45 toxicity. Adverse renal function changes were observed in rats after a single 600 mg/kg
46 oral dose, but not after a 200 mg/kg dose. Gross kidney lesions, including papillary
47 necrosis, were observed after a single oral >900 mg/kg dose, and after i.v. doses of
48 >214 mg/kg. Mice responded similarly. In a 13-week oral (gavage) dose study in rats,
49 the high dose of 640 mg/kg/day mesalamine caused deaths, probably due to renal
50 failure, and dose-related renal lesions (papillary necrosis and/or multifocal tubular
51 injury) were seen in most rats given the high dose (males and females) as well as in
52 males receiving lower doses 160 mg/kg/day. Renal lesions were not observed in the
53 160 mg/kg/day female rats. Minimal tubular epithelial damage was seen in the 40
54 mg/kg/day males and was reversible. In a six-month oral study in dogs, the no-
55 observable dose level of mesalamine was 40 mg/kg/day and doses of 80 mg/kg/day
56 and higher caused renal pathology similar to that described for the rat. In a combined
57 52-week toxicity and 127-week carcinogenicity study in rats, degeneration in kidneys
58 was observed at doses of 100 mg/kg/day and above admixed with diet for 52 weeks,
59 and at 127 weeks increased incidence of kidney degeneration and hyalinization of
60 basement membranes and Bowman's capsule were seen at 100 mg/kg/day and above.
61 In the 12 month eye toxicity study in dogs, Keratoconjunctivitis Sicca (KCS) occurred at
62 oral doses of 40 mg/kg/day and above. The oral preclinical studies were done with a
63 highly bioavailable suspension where absorption throughout the gastrointestinal tract
64 occurred. The human dose of 4 grams represents approximately 80 mg/kg but when
65 mesalamine is given rectally as a suspension, absorption is poor and limited to the
66 distal colon (see **Pharmacokinetics**). Overt renal toxicity has not been observed (see
67 **ADVERSE REACTIONS** and **PRECAUTIONS**), but the potential must be considered.

68

69 **Pharmacokinetics**

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

79

80 Whatever the metabolic site, most of the absorbed mesalamine is excreted in the
81 urine as the N-acetyl-5-ASA metabolite. The poor colonic absorption of rectally
82 administered mesalamine is substantiated by the low serum concentration of 5-ASA
83 and N-acetyl-5-ASA seen in ulcerative colitis patients after dosage with mesalamine.
84 Under clinical conditions patients demonstrated plasma levels 10 to 12 hours post
85 mesalamine administration of 2 µg/mL, about two-thirds of which was the N-acetyl
86 metabolite. While the elimination half-life of mesalamine is short (0.5 to 1.5 h), the

87 acetylated metabolite exhibits a half-life of 5 to 10 hours [U. Klotz, **Clin. Pharmacokin.**
 88 10:285-302 (1985)]. In addition, steady state plasma levels demonstrated a lack of
 89 accumulation of either free or metabolized drug during repeated daily administrations.
 90

91 **Efficacy**

92 In a placebo-controlled, international, multicenter trial of 153 patients with active distal
 93 ulcerative colitis, proctosigmoiditis or proctitis, ROWASA® (Mesalamine) Rectal
 94 Suspension Enema reduced the overall disease activity index (DAI) and individual
 95 components as follows:
 96

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

		N	Baseline	Day 22	EndPoint	Change Baseline to Endpoint †
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

101 Each parameter has a 4-point scale with a numerical rating:
 102 0=normal, 1=mild, 2=moderate, 3=severe. The four parameters are added together to
 103 produce a maximum overall DAI of 12.
 104

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

107 * Significant ROWASA®/placebo difference. p<0.05

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

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

110 Differences between ROWASA® and placebo were also statistically different in
 111 subgroups of patients on concurrent sulfasalazine and in those having an upper
 112 disease boundary between 5 and 20 or 20 and 40 cm. Significant differences between
 113 ROWASA® and placebo were not achieved in those subgroups of patients on
 114 concurrent prednisone or with an upper disease boundary between 40 and 50 cm.

115

116 **INDICATIONS AND USAGE**

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

119

120 **CONTRAINDICATIONS**

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

123

124 **WARNINGS**

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

136

137 **PRECAUTIONS**

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

148

149 Although renal abnormalities were not noted in the clinical trials with ROWASA®
150 (Mesalamine) Rectal Suspension Enema, the possibility of increased absorption of
151 mesalamine and concomitant renal tubular damage as noted in the preclinical studies
152 must be kept in mind. Patients on ROWASA® (Mesalamine) Rectal Suspension Enema,
153 especially those on concurrent oral products which liberate mesalamine and those with
154 preexisting renal disease, should be carefully monitored with urinalysis, BUN and
155 creatinine studies.

156

157 In a clinical trial most patients who were hypersensitive to sulfasalazine were able to
158 take mesalamine enemas without evidence of any allergic reaction. Nevertheless, caution
159 should be exercised when mesalamine is initially used in patients known to be allergic to

160 sulfasalazine. These patients should be instructed to discontinue therapy if signs of rash
161 or fever become apparent.

162
163 While using ROWASA® (Mesalamine) Rectal Suspension Enema some patients have
164 developed pancolitis. However, extension of upper disease boundary and/or flare-ups
165 occurred less often in the ROWASA® (Mesalamine) Rectal Suspension Enema treated
166 group than in the placebo-treated group.

167
168 Rare instances of pericarditis have been reported with mesalamine containing
169 products including sulfasalazine. Cases of pericarditis have also been reported as
170 manifestations of inflammatory bowel disease. In the cases reported with ROWASA®
171 (Mesalamine) Rectal Suspension Enema there have been positive rechallenges with
172 mesalamine or mesalamine containing products. In one of these cases, however, a
173 second rechallenge with sulfasalazine was negative throughout a 2 month follow-up.
174 Chest pain or dyspnea in patients treated with ROWASA® (Mesalamine) Rectal
175 Suspension Enema should be investigated with this information in mind. Discontinuation
176 of ROWASA® (Mesalamine) Rectal Suspension Enema may be warranted in some
177 cases, but rechallenge with mesalamine can be performed under careful clinical
178 observation should the continued therapeutic need for mesalamine be present.

179
180 **Carcinogenesis, Mutagenesis, Impairment of Fertility**
181 Mesalamine caused no increase in the incidence of neoplastic lesions over controls in a
182 two-year study of Wistar rats fed up to 320 mg/kg/day of mesalamine admixed with diet.
183 Mesalamine is not mutagenic to Salmonella typhimurium tester strains TA98, TA100,
184 TA1535, TA1537, TA1538. There were no reverse mutations in an assay using E. coli
185 strain WP2UVRA. There were no effects in an *in vivo* mouse micronucleus assay at 600
186 mg/kg and in an *in vivo* sister chromatid exchange at doses up to 610 mg/kg. No effects
187 on fertility were observed in rats receiving up to 320 mg/kg/day. The oligospermia and
188 infertility in men associated with sulfasalazine have not been reported with mesalamine.

189
190 **Pregnancy (Category B)**
191 Teratologic studies have been performed in rats and rabbits at oral doses up to five and
192 eight times respectively, the maximum recommended human dose, and have revealed no
193 evidence of harm to the embryo or the fetus. There are, however, no adequate and well
194 controlled studies in pregnant women for either sulfasalazine or 5-ASA. Because animal
195 reproduction studies are not always predictive of human response, 5-ASA should be used
196 during pregnancy only if clearly needed.

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

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203 **Pediatric Use**
204 Safety and effectiveness in pediatric patients have not been established.

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206 **ADVERSE REACTIONS**

207 **Clinical Adverse Experience**

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

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

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SYMPTOM	ROWASA® 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	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

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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.

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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 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 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 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.

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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

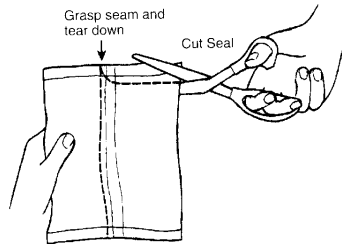
PATIENT INSTRUCTIONS
How to Use this Medication.

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.

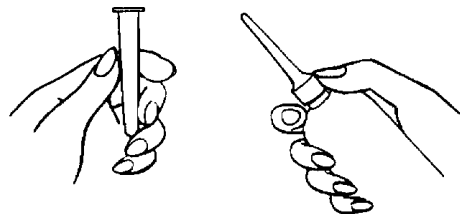
1 Remove the Bottles

- 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.



335 **3 Assume the Correct Body Position**

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

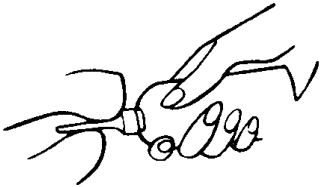


- b. An alternative to lying on the left side is the "knee-chest" position as shown here.



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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