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, painting surfaces, marble, granite, vinyl, and enamel. Take care in choosing a suitable location for administration of this product.

1 Remove 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.

Each rectal suspension enema unit contains 4 grams of mesalamine. In addition to mesalamine the preparation contains the inactive ingredients carbomer 940M, 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. Khan in Lancet 2:910-915 (1977)]. The mesalamine component is poorly absorbed from the colon and is excreted principally of 2 µg/mL, about two-thirds of which is the N-acetyl metabolite. While the 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 [J. Kutz, Clin. Pharmacokinet. 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:

**EFFICACY IN TERMS OF SEVERITY OF DISEASE**

**DATA FROM U.S., CANADA TRIAL**

**COMBINED RESULTS OF EIGHT CENTERS**

<table>
<thead>
<tr>
<th>Activity Index, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall DAI</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Day 22</td>
</tr>
<tr>
<td>Change Baseline to End</td>
</tr>
</tbody>
</table>

**SEVERITY**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>ROWASA®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician's</td>
<td>1.82</td>
<td>1.57</td>
</tr>
<tr>
<td>Improvement</td>
<td>0.75</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**BIOLOGICAL ACTIVITY**

**Comparisons of ROWASA® (mesalamine) and Placebo**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ROWASA®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td>1.82</td>
<td>1.57</td>
</tr>
<tr>
<td>Frequency</td>
<td>1.23</td>
<td>1.01</td>
</tr>
<tr>
<td>Mucosal</td>
<td>0.81</td>
<td>1.23</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1.89</td>
<td>1.56</td>
</tr>
<tr>
<td>Physician's</td>
<td>1.98</td>
<td>1.76</td>
</tr>
<tr>
<td>Improvement</td>
<td>0.22</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**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 anaphylactic reactions including anaphylactoid 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 allergic nonasthmatic persons.

**PRECAUTIONS**

Medication 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 sulfite intolerance, if any, should be re-evaluated. It is recommended that a patient be re-challenged 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 4-gram dose can be recovered in cumulative 24-hour urine collections. Other than the kidney, the other organ distribution and the lack of ascites 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.

**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 other organ distribution and the lack of ascites 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.

**ADVERSE REACTIONS and PRECAUTIONS**

- the possible need to be considered.

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**ADVERSE REACTIONS and PRECAUTIONS**

- the possible need to be considered.
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 pericarditis. However, extension of upper digestive tract inflammation has also occurred in patients treated with mesalamine. Rare instances of pericarditis have been reported with mesalamine-containing products. In some of these cases, however, a second rechallenge with sulfasalazine was negative. Patients who experience chest pain or dyspnea while using mesalamine should stop the medication. At the earliest the patient should be referred to a physician for possible pericarditis.

The use of mesalamine in pregnancy has not been adequately evaluated. It is suggested that breastfeeding mothers avoid taking mesalamine.

It is unknown 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. 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.

Nursing Mothers

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A rare instance of pericarditis has been reported with mesalamine co-administered with sulfasalazine. Cases of pancreatitis and fibrosing adenolitis 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, thrombocytopenia, and infertility in men, Aplastic anemia, aplastic anemia, agranulocytosis, thrombocytopenia, eosinophilia, pancytopenia, neutropenia, thrombocytopenia, and infertility in men.

In the absence of adequate and well-controlled studies in pregnant women, the use of mesalamine during pregnancy should be avoided. However, studies available to date have not assessed if ROWASA® (mesalamine) Rectal Suspension Enema is for use only in women of reproductive age who are not attempting to become pregnant. ROWASA® (mesalamine) Rectal Suspension Enema should be used with caution in breastfeeding women.

Hair Loss

While using Rowasa® (mesalamine) Rectal Suspension Enema in some patients there have been positive rechallenges with mesalamine or mesalamine containing products. In some of these cases, however, a second rechallenge with sulfasalazine was negative. The patient should be instructed to discontinue the medication. At the earliest the patient should be referred to a physician for evaluation of possible hair loss.

There have been no reported reports of serious toxicity in man resulting from massive overdosing with mesalamine. ROWASA® (mesalamine) Rectal Suspension Enema should be used with caution in cases of severe toxicity in man resulting from massive overdosing with mesalamine.

OVERDOSAGE

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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 for a maximum of two weeks unless otherwise directed by your physician. The patient should be instructed to discontinue the medication. At the earliest the patient should be referred to a physician for evaluation of possible hair loss. ROWASA® (mesalamine) Rectal Suspension Enema for use only.

Patients should be instructed to discontinue the medication and see their physician if they experience any significant hair loss.

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 adenolitis and elevated liver enzymes. Cases of pancreatitis and fibrosing adenolitis 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, thrombocytopenia, and infertility in men, Aplastic anemia, aplastic anemia, agranulocytosis, thrombocytopenia, eosinophilia, pancytopenia, neutropenia, thrombocytopenia, and infertility in men.

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