UMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

RAFASSAL® 1 GRAM ENEMA
RAFASSAL® 4 GRAM ENEMA

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rafassal 1 gram Enema: Each enema contains mesalazine (5-aminosalicylic acid) 1 gram.

Rafassal 4 gram Enema: Each enema contains mesalazine (5-aminosalicylic acid) 4 gram.

Each enema contains 60 gram suspension.

Excipients with known effect:

Rafassal Enemas contain potassium metabisulphite (281 mg per bottle).
Rafassal Enemas contain sodium benzoate (60 mg per bottle).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enema for rectal use.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Treatment and prevention of ulcerative colitis and Crohn's disease.

4.2 Posology and method of administration

Posology (oral and rectal)

During the acute inflammatory stage and in long-term maintenance therapy, Rafassal must be taken reliably and consistently by the patient. This is essential in order to attain the desired therapeutic success.

Rafassal Caplets

For acute inflammatory symptoms:

Individual dosage up to 4 gram/day, divided into 2 or 3 doses.

Rafassal Caplets should be taken with an ample amount of fluid 1 hour before meals.

As soon as remission occurs, the dose should be reduced (to 2 g divided into 2 or 3 doses, to avoid recurrence.

Children

There is only limited documentation for an effect in children (age 6-18 years).

Children 6 years of age and older

Active disease: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum

dose: 75 mg/kg/day. The total dose should not exceed the maximum adult dose (4 grams).

Maintenance treatment (ulcerative colitis): To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed the recommended adult dose (2 grams).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

Rafassal Suppositories

For acute inflammatory symptoms: 1 suppository of 500 mg 3 times daily. The suppositories should be inserted deeply.

As soon as remission occurs, the dose should be reduced.

Rafassal Enemas

Dosage should be adjusted to the individual response to each patient.

Higher daily doses are recommended for acute disease episodes, with dose strength tapering as disease remits.

Rectal suspensions of 5-aminosalicylic acid are best retained if administered at bedtime. Optimal results are expected for those individuals retaining the medication during the entire rest period.

Initiate therapy with bedtime administration of a 4 gram enema.

Response to therapy and adjustment of dosage should be determined by periodic examination, including endoscopy and assessment of symptomatology, i.e. frequency of bowel movements and rectal bleeding. The daily dosage should be tapered when a significant response (improvement) or remission is attained. Abrupt withdrawal of therapy without tapering to lower daily doses is not recommended.

Maintenance therapy is indicated to assure continued remission. The dosing schedule may be every other day, every third day, or as required. The optimum maintenance dose should be determined for each patient. If symptoms recur, dosage should be increased to the previously effective level.

The 1 gram enema provides flexibility in dosing.

4.3 Contraindications

Rafassal is contraindicated in cases of:

- Hypersensitivity to the active substance, salicylates or any of the excipients listed in section 6.1.
- Severe impairment of renal or hepatic function.

4.4 Special warnings and precautions for use

Blood tests (differential blood count; liver function parameters such as ALT or AST; serum creatinine) and urinary status (dip-sticks) should be determined prior to and during treatment, at the discretion of the treating physician. As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks.

If the findings are normal, follow-up tests should be carried out every 3 months. If additional symptoms occur, tests should be performed immediately.

Caution is recommended in patients with impaired hepatic function.

Mesalazine should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment. If this is the case, Rafassal enemas should be discontinued immediately.

Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g., in toilets cleaned with sodium hypochlorite contained in certain bleaches).

Serious blood dyscrasias have been reported very rarely with mesalazine. Hematological investigations should be performed if patients suffer from unexplained haemorrhages, bruises, purpura, anaemia, fever or pharyngolaryngeal pain. Rafassal enemas should be discontinued in case of suspected or confirmed blood dyscrasia.

Cardiac hypersensitivity reactions (myocarditis, and pericarditis) induced by mesalazine have been rarely reported. Rafassal enemas should then be discontinued immediately.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with Rafassal Enemas.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

Patients with a history of adverse drug reactions to preparations containing sulphasalazine should be kept under close medical surveillance on commencement of a course of treatment with mesalazine. Should the enema cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Each bottle of enema contains sodium benzoate (60 mg per bottle), which may cause local irritation.

Each bottle of enema contains potassium metabisulfite, which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed.

In patients who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, 6-mercaptopurine or thioguanine should be taken into account.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of mesalazine in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiologic data are available. In one single case after long-term use of a high dose mesalazine (2-4g, orally) during pregnancy, renal failure in a neonate was reported.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.

Rafassal Enemas should only be used during pregnancy if the potential benefit outweighs the possible risk.

Lactation (breastfeeding)

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. Only limited experience with mesalazine during lactation in women is available to date.
Hypersensitivity reactions such as diarrhoea in the infant cannot be excluded. Therefore, Rafassal Enemas should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Mesalazine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects have been observed after administration of mesalazine:

System Organ Class	Frequency According to MedDRA Convention			
	Common (≥ 1/100; <1/10)	Rare (≥ 1/10,000; <1/1,000)	Very rare (< 1/ 10,000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)	
Nervous system disorders		Headache, dizziness	peripheral neuropathy	Idiopathic intracranial hypertension (see section 4.4)
Cardiac disorders		Myocarditis, Pericarditis		

Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)	
Gastrointestinal disorders		Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation	Acute pancreatitis	
Renal and urinary disorders			Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	Nephrolithiasis*
Skin and subcutaneous tissue disorders	Rash, pruritus	Photosensitivity	Alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders			Myalgia, arthralgia	
Immune system disorders			Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Hepatobiliary disorders			Changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis	
Reproductive system disorders			Oligospermia (reversible)	

* see section 4.4 for further information

Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS),Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

<u>Photosensitivity</u>

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

There are rare data on overdosage (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminosalicylic acid and similar agents
ATC code: A07EC02
The mechanism of the anti-inflammatory action is unknown. The results of *in vitro* studies indicate that inhibition of lipoxygenase may play a role.
Effects on prostaglandin concentrations in the intestinal mucosa have also been demonstrated. Mesalazine (5-Aminosalicylic acid / 5-ASA) may also function as a radical scavenger of reactive oxygen compounds.
On reaching the intestinal lumen, rectally administered mesalazine has largely local effects on the intestinal mucosa and submucosal tissue.

5.2 Pharmacokinetic properties

General considerations of mesalazine:

Absorption:
Mesalazine absorption is highest in proximal gut regions and lowest in distal gut areas.

Biotransformation:
Mesalazine is metabolised both pre-systemically by the intestinal mucosa and in the liver to the pharmacologically inactive N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Protein binding of mesalazine and N-Ac-5-ASA is 43% and 78%, respectively.

Elimination:
Mesalazine and its metabolite N-Ac-5-ASA are eliminated via the faeces (major part), renally (varies between 20 and 50 %, dependent on kind of application, pharmaceutical preparation and route of mesalazine release, respectively), and biliary (minor part). Renal excretion predominantly occurs as N-Ac-5-ASA. About 1 % of total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

5.3 Preclinical safety data

With the exception of a local tolerance study in dogs, which demonstrated good rectal tolerance, no preclinical studies have been performed with rectal preparations.

Preclinical data on mesalazine reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity (rat) or toxicity to reproduction.

Kidney toxicity (renal papillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine. The clinical relevance of this finding is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium metabisulfite, potassium acetate, xanthan gum, sodium benzoate, disodium edetate, carbomer 934P, purified water

6.2. Incompatibilities

None known.

6.3. Shelf Life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Storage condition: Store below 25ºC.

6.5. Nature and Contents of Container

Opaque squeeze bottles packed in cartons containing seven bottles of 60 gram each.

6.6 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER AND REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301

Registration number:

Rafassal® 1 g Enema:1203926001

Rafassal® 4 g Enema:0295825321

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