1 NAME OF THE MEDICINAL PRODUCT

Rafassal 500 mg Suppositories

Rafassal 1 gram Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rafassal 500 mg Suppositories: Each suppository contains mesalazine (5-aminosalicylic acid) 500 mg.

Rafassal 1 gram Suppositories: Each suppository contains mesalazine (5-aminosalicylic acid) 1000 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal suppositories.

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 Suppositories are contraindicated in patients with:
Hypersensitivity to the active substance, salicylates or to any of the excipients listed in section 6.1
Severe impairment of hepatic or renal 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, these tests should be performed immediately. Caution is recommended in patients with impaired hepatic function.

Rafassal Suppositories should not be used in patients with impaired renal function.
Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

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).

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

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.

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 Rafassal Suppositories. Should the suppositories cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

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 Rafassal in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on 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 of mesalazine (2-4g/day, 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 Suppositories 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 during lactation in women is available to date. Hypersensitivity reactions such as diarrhoea in the infant cannot be excluded. Therefore, Rafassal Suppositories should only be used during breastfeeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

Rafassal Suppositories have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies involving 248 participants, approximately 3% experienced adverse reactions while receiving 1g mesalazine Suppositories. The most commonly reported ADRs were headache, in approximately 0.8%, and gastrointestinal side effects (constipation in approximately 0.8%; nausea, vomiting and abdominal pain in 0.4% each).

The following side effects have been reported with the use of mesalazine:

System Organ Class	Frequency According to MedDRA convention		
	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	
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	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 parameters of cholestasis), 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).

Photosensitivity
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.

Clinical efficacy and safety of mesalazine 1 g suppositories was evaluated in a multicentre phase III study, which included 403 patients with endoscopically and histologically confirmed mild to moderately active ulcerative proctitis. The mean disease activity index (DAI) at base line was 6.2 ± 1.5 (range: 3 – 10). Patients were randomised to treatment with one mesalazine 1 g suppository (1 g OD group) or 3 suppositories containing 0.5 g mesalazine (0.5 g TID group per day for 6 weeks. The primary efficacy variable was clinical remission defined as DAI < 4 at the final visit or withdrawal. At the final per protocol analysis, 87.9% of the patients in the 1 g OD group and 90.7% of the 0.5 g TID group were in clinical remission (Intention-to-treat analysis: 1 g OD group: 84.0%; 0.5 g TID group: 84.7%). The mean change in DAI from baseline was -4.7 in both treatment groups. No drug-related serious AEs occurred.

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.

Mesalazine 1g suppositories specific:
Distribution:
Scintigraphic studies with a similar medicinal product, technetium-labelled mesalazine 500mg suppositories showed peak spread of the suppository that

had melted due to body temperature after 2 – 3 hours. The spread was limited primarily to the rectum and rectosigmoid junction. It is assumed that mesalazine 1g suppositories act very similar and thus are particularly suitable for treating proctitis (ulcerative colitis of the rectum).
Absorption:
In healthy subjects mean peak plasma concentrations of 5-ASA after a single rectal dose of 1g mesalazine (mesalazine 1 g Suppository) were 192 ± 125 ng/ml (range 19 –557 ng/ml), those of the main metabolite N-Ac-5-ASA were 402 ± 211 ng/ml (range 57 – 1070 ng/ml). Time to reach the peak plasma concentration of 5-ASA was 7.1 ±4.9 h (range 0.3 – 24 h).
Elimination:
In healthy subjects, after a single rectal dose of 1g mesalazine (mesalazine 1g Suppository) approx. 14 % of the administered 5-ASA dose were recovered in the urine during 48 hours.

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 mesalazine Suppositories.

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

Hard Fat W-45

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

Rafassal 500 mg Suppositories: Cartons of 30 suppositories in PVC/PE strips.

Rafassal 1gram Suppositories: Cartons of 15 or 30 suppositories in PVC/PE strips.

Not all pack sizes may be marketed.

6.6. Instruction for Use/Handling

None

7 MANUFACTURER AND REGISTRATION HOLDER

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

Registration number:

Rafassal 500 mg Suppositories: 051-12-26439

Rafassal 1 gram Suppositories: 069-50-28345

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