**Doctor leaflet**

**Rafassal Caplets, Suppositories, Enemas**

**Composition**

**Rafassal Caplets:**
- **Active ingredient:**
  - Rafassal 500 mg Caplets: Each caplet contains mesalazine (5-aminosalicylic acid) 500 mg.
  - Rafassal 1 gram Caplets: Each caplet contains mesalazine (5-aminosalicylic acid) 1000 mg.
- **Inactive ingredients:**
  - Sodium carbonate anhydrous, Glycine, Povidone K25, Cellulose microcrystalline, Sodium carboxymethyl cellulose, Silicon dioxide colloidal 200, Calcium stearate, Hydroxypropyl methyl cellulose, Methacrylic acid copolymer (Eudragit L), Talc (micronized), Titanium dioxide, Ferric oxide brown, Polyethylene glycol 6000, Simethicone emulsion, Sodium hydroxide.

**Rafassal Suppositories:**
- **Active ingredient:**
  - 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.
- **Inactive ingredients:**
  - Hard Fat W-45.

**Rafassal Enemas:**
- **Active ingredient:**
  - Rafassal 1 gram Enema: Each enema (60 gram bottle) contains mesalazine (5-aminosalicylic acid) 1 gram.
  - Rafassal Enema 4 gram: Each enema (60 gram bottle) contains mesalazine (5-aminosalicylic acid) 4 gram.
- **Inactive ingredients:**
  - Sodium benzoate, Carbomer 934P, Disodium edetate, Potassium metabisulfite, Potassium acetate, Xanthan gum, Purified water.

**Action**

**Pharmacotherapeutic group:** Intestinal antiinflammatory agents; aminosalicylic acid and similar agents.

**ATC code:** A07EC02

**Mechanism of action**
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.

**Pharmacodynamic effects**
Mesalazine, orally administered, acts predominantly locally at the gut mucosa and in the submucous tissue from the luminal side of the intestine. It is important, therefore, that mesalazine is available at the regions of inflammation. Systemic bioavailability / plasma concentrations of mesalazine therefore are of no relevance for therapeutic efficacy, but rather a factor for safety. In order to fulfil these criteria, Rafassal are coated with Eudragit L; they are thus gastro-resistant and release of mesalazine is pH-dependent.

**Rectally administered mesalazine:**
On reaching the intestinal lumen, rectally administered mesalazine has largely local effects on the intestinal mucosa and submucosal tissue.

**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 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.

**Orally administered mesalazine:**

**Distribution:**
Tablets reach the ileocoecal region after approximately 3–4 hours in fasting subjects and reach the ascending colon within approximately 4–5 hours. The total transit time in the colon is approximately 17 hours.

**Absorption:**
The release of mesalazine from caplets begins after a lag-phase of approximately 3–4 hours. Peak plasma concentrations are reached after approximately 5 hours (ileocecal region) and, at 3 x 500 mg mesalazine/ day under steady-state conditions, are 3.0±1.6 µg/ml for mesalazine and 3.4±1.6 µg/ml for the metabolite, N-Ac-5-ASA.

**Elimination:**
The total renal elimination rate for mesalazine and N-Ac-5-ASA over 24 hours during multiple intake (3 x 500mg tablets, for 2 days; 1 tablet on the third day=examination day) was approximately 60%. The non-metabolised mesalazine fraction after oral administration was approximately 10%.

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

**Contraindications**
Hypersensitivity to the active substance, salicylates or any of the excipients.
Severe impairment of liver and kidney function.

**Warnings and Precautions**
Mesalazine has occasionally been implicated in an acute intolerance syndrome. This syndrome is characterized by abdominal cramps, acute abdominal pain and bloody diarrhea, fever, severe headache and a rash. In such cases, prompt withdrawal is required. It is important to be aware of this syndrome in patients who have already displayed intolerance to sulfasalazine. 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.

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 liver function.

Mesalazine is not recommended for use in patients with renal impairment. The renal function should be monitored regularly (e.g. serum creatinine), especially during the initial phase of
treatment. Mesalazine induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. Caution should be exercised in patients with elevated blood urea or proteinuria.

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

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have rarely been reported. Serious blood dyscrasias have very rarely been reported with mesalazine. Haematological investigations should be performed if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat.

In rare cases, in patients who have undergone bowel resection/bowel surgery in the ileocoecal region with removal of the ileocoecal valve, it has been observed that tablets contain mesalasine were excreted undissolved in the stool, due to an excessively rapid intestinal passage.

**Rafassal Enemas** contain sodium benzoate, which may be mildly irritant to the skin, eyes and mucous membranes.

**Use in Pregnancy**
There are no adequate and well-controlled studies 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 mesalazine (2-4 g, 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. Therefore mesalazine should only be used during pregnancy if the potential benefit outweighs the possible risk.

**Use in 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 mesalazine should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, the breast-feeding should be discontinued.

**Use in Pediatrics**
Infants and young children should not be treated with mesalazine unless it is strictly indicated, or when alternative treatment is ineffective or unavailable.

**Interference with Laboratory Tests**
Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, Nacetylaminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

**Drug Interactions**
The concurrent use of mesalazine with other known nephrotoxic agents may increase the risk of renal reaction.

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.
**Effects on ability to drive and use machines**
No or negligible effects on the ability to drive and use machines have been observed.

**Adverse Reactions**
Mesalazine may be associated with an exacerbation of the symptoms of colitis in those patients who have previously had such problems with sulphasalazine.

Undesirable effects are as follows:

**Common**
- **Gastrointestinal disorders:**
  - Nausea, vomiting, diarrhoea, abdominal pain

- **Skin disorders:**
  - Rash (including urticaria and erythematous rash)

- **General:**
  - Headache

**Rare**
- **Blood and lymphatic system disorders:**
  - Altered blood counts (aplastic anaemia, agranulocytosis, granulocytopenia, neutropenia, leukopenia, thrombocytopenia)

- **Nervous system disorders:**
  - Peripheral neuropathy, dizziness

- **Cardiac disorders:**
  - Myocarditis, pericarditis

- **Respiratory, thoracic and mediastinal disorders:**
  - Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, pulmonary infiltration, pneumonitis)

- **Gastrointestinal disorders:**
  - Pancreatitis, increased amylase, flatulence

- **Liver:**
  - Abnormalities of hepatic function and hepatotoxicity (including, hepatitis, cirrhosis, hepatic failure)

- **Renal and urinary disorders:**
  - Impairment of renal function (including acute and chronic interstitial nephritis, renal insufficiency, nephrotic syndrome), urine discolouration (*see additional text*)

- **Collagen disorders:**
  - Lupus erythematosus syndrome

**Very rare**
- **Blood disorders:**
  - Anaemia, eosinophilia (as part of an systemic allergic reaction)
and pancytopenia

*Hepatobiliary disorders:*

Increased bilirubin.
Changes in liver function parameters (increase in transaminases and parameters of cholestasis), cholestatic hepatitis

*Skin and subcutaneous tissue disorders:*

Alopecia, bullous skin reactions including erythema multiforme and Stevens-Johnson syndrome

*Musculoskeletal and connective tissue disorders:*

Myalgia, arthralgia

*Immune system disorders:*

Hypersensitivity reactions such as allergic exanthema anaphylactic reaction, angioedema, drug fever, pancolitis.

*Reproductive system and breast disorders:*

Oligospermia (reversible)

*Renal failure has been reported. Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.*

The mechanism of mesalazine-induced myocarditis, pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin.

Hypersensitivity reactions (which are not dose-related) such as allergic skin eruptions, hyperpyrexia, bronchospasm and lupus erythematosus-like syndrome, cannot be excluded. Theoretically, elevated methemoglobin levels may occur. Mesalazine may be associated with the exacerbation of the symptoms of colitis in patients who have previously had such problems when treated with sulfasalazine. Following rectal administration local reactions such as pruritus, rectal discomfort and urge may occur.

**Dosage and Administration**

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. 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.

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.

Storage condition: Store below 25°C.

Presentations and Registration Numbers:
Rafassal Caplets 500 mg: 0511126440
Rafassal Caplets 1 g: 0678028346
Rafassal 500 mg Suppositories: 0511226439
Rafassal Suppositories 1 g: 0695028345
Rafassal Enema 1 g: 1203926001
Rafassal Enema 4 g: 0295825321

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

The format and content of this document have been approved by the Ministry of Health in May 2015.