1. Name of the medicinal product

RAFASSAL 500 MG CAPLETS

RAFASSAL 1 GRAM CAPLETS

2. Qualitative and quantitative composition

Rafassal 500 mg Caplets: Each gastro-resistant caplet contains 500mg mesalazine (5 - Aminosalicylic acid).

Rafassal 1 gram Caplets: Each gastro-resistant caplet contains 1000mg mesalazine (5 - Aminosalicylic acid).For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Gastro-resistant caplets

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 Caplets 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 three months. If additional symptoms occur, these tests should be performed immediately.

Caution is recommended in patients with impaired hepatic function.

Rafassal Caplets 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 Caplets.

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 Caplets.

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

Note:

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

Rafassal 500 mg caplet contains about 50 mg sodium, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Rafassal 1 gram caplet contains about 100 mg sodium, equivalent to 5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 on the use of Rafassal Caplets 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 Caplets should only be used during pregnancy if the potential benefit outweighs the possible risk.

Breast-feeding

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 Caplets 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

Rafassal Caplets have 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 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to <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)	
Immune system disorders				Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
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, dyspepsia, flatulence, nausea, vomiting, acute pancreatitis			
Hepatobiliary disorders			Cholestatic hepatitis	Hepatitis	
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			Arthralgia	Myalgia	
Renal and urinary disorders				Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	Nephrolithiasis*
Reproductive system and breast disorders				Oligospermia (reversible)	
General disorders			Asthenia, fatigue		
Investigations		Changes in liver function parameters (increase in transaminases and parameters of cholestasis), changes in pancreatic enzymes (lipase and amylase increased), eosinophil count increased			

* 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 overdose (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: Intestinal anti-inflammatory 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 Caplets are coated with Eudragit L; they are thus gastro-resistant and release of mesalazine is pH-dependent.

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 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.

Caplets/Tablets specific

Distribution

A combined pharmacoscintigraphic/pharmacokinetic study showed that 500mg tablets (Salofalk®), 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

Release of mesalazine from 500mg tablets (Salofalk®), begins after a lag-phase of approximately 3‑4 hours. Peak plasma concentrations are reached after approximately 5 hours (ileocoecal region) and, at 3 x 500 mg mesalazine/ day under steady-state conditions, are 3.0 ± 1.6 mcg/ml for mesalazine and 3.4 ± 1.6 mcg/ml for the metabolite, N-Ac-5-ASA.

Release of mesalazine from 1g tablets(Salofalk®) begins after a lag-phase of approximately 4 hours. Peak plasma concentrations of mesalazine are reached after 8 hours and are 2.5 ± 3.4 mcg/ml for mesalazine and 2.5 ± 2.4 mcg/ml for the metabolite, N-Ac-5-ASA, after single dose administration.

Elimination

The total renal elimination rate for mesalazine and N-Ac-5-ASA over 24 hours during multiple intake (3 x 1 500 mg 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%.

5.3 Preclinical safety data

Preclinical data 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

Sodium carbonate, Glycine, Povidone K25, Cellulose microcrystalline, Carboxymethyl cellulose sodium Silicon dioxide, Calcium stearate, Hydroxypropyl methyl cellulose, Methacrilic acid copolymer (Eudragit L), Talc, Titanium dioxide, Ferric oxide brown, Polyethylene glycol 6000, Simethicone, Sodium hydroxide.

6.2 Incompatibilities

Not applicable.

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

Blister foil

Package sizes:

Rafassal 500 mg Caplets: Blister packs with 60 caplets.

Rafassal 1 gram Caplets: Blister packs with 30 caplets.

6.6 Special precautions for disposal and other handling

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 500 mg Caplets: 0511126440

Rafassal 1 gram Caplets: 0678028346

Revised in May 2023 according to MOHs guidelines.