1 ASAMAX® 500

Mesalazine (5-aminosalicylic acid) 500 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Asamax 500 gastro-resistant tablet 500 mg: yellow ochre coloured biconvex tablets containing 500 mg mesalazine (5-aminosalicylic acid). Length approx. 17 mm, average, weight approx. 750 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of:

i) Crohn's disease localised to the colon
ii) mild to moderate ulcerative colitis.

4.2 Dose and method of administration

Ulcerative colitis
Treatment of active disease:
Adults: Individual dosage, up to 2–4 g daily in divided doses.
Children: Individual dosage, starting with 20–30 mg/kg bodyweight daily in divided doses.

Maintenance treatment:
Adults: Individual dosage, starting with 1.5–2 g daily in divided doses.
Children: Individual dosage, starting with 20–30 mg/kg bodyweight daily in divided doses.

Crohn's disease
Treatment of active disease:
Adults: Individual dosage, up to 4 g daily in divided doses.
Children: Individual dosage, starting with 20–30 mg/kg bodyweight daily in divided doses.

Maintenance treatment:
Adults: Individual dosage, up to 4 g daily in divided doses.
Children: Individual dosage, starting with 20–30 mg/kg bodyweight daily in divided doses.

Asamax tablets must be taken whole and must not be divided. Asamax tablets should be taken after meals with some liquid. The tablets must not be chewed.
Different oral formulations of mesalazine should not be regarded as interchangeable.

4.3 Contraindications

Hypersensitivity to mesalazine, any other component of the product, or salicylates.
Severe liver and/or renal impairment.
Increased tendency to bleeding.
Active ulcers of the stomach and/or duodenum.

4.4 Special warnings and precautions for use

Most patients who are intolerant or hypersensitive to sulfasalazine are able to take Asamax without risk of similar reactions. However, caution is recommended when treating patients allergic to sulfasalazine (risk of allergy to salicylates) Including keeping patients under close medical surveillance and should mesalazine cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Caution is recommended in patients with impaired liver function. Differential blood count and liver function parameters like alanine aminotransferase (ALT) or aspartate transaminase (AST) should be assessed 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.

The medicine is not recommended for use in patients with renal impairment. Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. The renal function should be regularly monitored (e.g. serum creatinine), especially during the initial phase of treatment. The concurrent use of other known nephrotoxic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine, may increase the risk of renal reactions.

Mesalazine-induced cardiac hypersensitivity reactions (pleuropericarditis) and serious blood dyscrasias have rarely been reported with mesalazine. Concomitant treatment with mesalazine can increase the risk of dyscrasia in patients receiving azathioprine or 6-mercaptopurine. Treatment should be discontinued on suspicion or evidence of these adverse reactions.

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

As with all salicylic acid derivatives, special caution is recommended in patients with Chronic Non Specific Lung Disease (CNSLD) due to the potential for hypersensitivity reactions. Patients with pulmonary disease, in particular asthma, should be very carefully monitored
during a course of treatment with mesalazine.

Asamax is not recommended for use in infants and toddlers under 2 years of age due to a lack of data on safety and/or efficacy.

4.5 Interaction with other medicines and other forms of interaction

The blood sugar level lowering effect of sulfonylureum-derivatives and coumarin-induced gastro-intestinal bleeding may be enhanced by mesalazine as well as the toxicity of methotrexate.
The uricosurical effect of probenecid and sulfinpyrazone and the diuretic effect of furosemide and spironolactone may be decreased by mesalazine. The anti-tuberculosis effect of rifampicin may be weakened. Mesalazine can induce the unwanted effects of glucocorticoids on the stomach.

Theoretically, caution should be practiced in the case of concomitantly administered anti-coagulants.

4.6 Fertility, pregnancy, and lactation

Mesalazine is a Pregnancy Category C medication (drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful but reversible effects on the human fetus or neonate without causing malformations).

Asamax should be used with caution during pregnancy and lactation, and only if the prescriber judges the potential benefits outweigh the possible risks.

Mesalazine is known to cross the placental barrier, but the limited data available on the use of this compound in pregnant women do not allow the assessment of possible noxious effects. In one single case after long-term use of a high dose of 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.

Mesalazine is excreted in breast milk. The concentration is much lower than in maternal blood, whereas the metabolite — acetyl-mesalazine — appears in similar concentrations. There is limited experience of the use of oral mesalazine in lactating women.

Reversible oligospermia have been very rarely reported with the use of mesalazine. There is no evidence that mesalazine adversely affects female fertility.

4.7 Effects on ability to drive and use machines

Treatment with Asamax is unlikely to affect the ability to drive and/or use machines. When driving or operating machinery, the potential occurrence of dizziness or headache should be borne in mind.

4.8 Undesirable effects

The most frequent adverse reactions seen in clinical trials are diarrhoea (3%), nausea (3%), abdominal pain (3%), headache (3%), vomiting (1%) and rash (1%). Hypersensitivity reactions and drug fever may occasionally occur.

System Organ Class	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10,000, <1/1000	Very rare <1/10,000
Blood and the lymphatic system disorders				Eosinophilia (as part of an allergic reaction), aplastic anaemia, pancytopenia, leucopenia (including granulocytopenia and neutropenia), thrombocytopenia, agranulocytosis, bone marrow depression, increased methaemoglobin levels

System Organ Class	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10,000, <1/1000	Very rare <1/10,000
Immune system disorders				Pancolitis, systemic lupus erythematosus, hypersensitivity reaction
Nervous system disorders	Dizziness			Peripheral neuropathy
Cardiac disorders			Myocarditis, pericarditis	Pleuropericarditis*
Respiratory, thoracic and mediastinal disorders				Allergic and fibrotic lung reactions (including dyspnoea, coughing, bronchospasm, allergic alveolitis, eosinophilic pneumonia, interstitial lung disease, pulmonary infiltration, pneumonitis, pleuritis)
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, abdominal pain		Flatulence	Pancreatitis acute,*
Hepato-biliary disorders				Changes in liver function parameters (transaminases increased and cholestasis parameters), hepatitis,* cholestatic hepatitis, cirrhosis, hepatic failure
Skin and subcutaneous tissue disorders			Allergic dermatitis, Alopecia	
Musculoskeletal and connective tissue disorders				Myalgia, arthralgia
Reproductive system disorders				Oligospermia (reversible)
Psychiatric disorders	Mood swings			
Renal and urinary disorders				Nephritis interstitial,* nephrotic syndrome, renal failure
General disorders and administration site conditions	Headache		Fever	
Investigations				Blood methaemoglobin present

*The mechanism of pleuropericarditis, pancreatitis, hepatitis, or interstitial nephritis caused by Asamax is unknown, but it could be of an allergic origin.

It is important to note that several of these disorders also can be attributed to the inflammatory bowel disease itself.

Post marketing data

Cases of Nephrolithiasis have been reported, (refer section 4.4 Special warnings and precautions for use), however, the frequency cannot be estimated from the available data.

4.9 Overdose

Acute experience in animals
Single oral doses of mesalazine up to 5 g/kg in pigs or a single intravenous dose of mesalazine at 920 mg/kg in rats were not lethal.

Human experience
No cases of overdose have been reported.

Management of overdose in humans
Symptomatic treatment at hospital. Close monitoring of renal function.

Contact the National Poisons Centre on 0800 POISON or 0800 764 766 for advice on management of an overdose.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Intestinal anti-inflammatory agents (A07 EC02).

5.1 Pharmacodynamic properties

It has been established that mesalazine is the active component of sulfasalazine, which is used for the treatment of ulcerative colitis and Crohn's disease.

Based on clinical results, the therapeutic value of mesalazine after oral or rectal administration appears to be due to local effect on the inflamed intestinal tissue, rather than to systemic effect.

Increased leucocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B4, and increased free radical formation in the inflamed intestinal tissue are all present in patients with inflammatory bowel disease. Mesalazine has *in vitro* and *in vivo* pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leukotriene production, and scavenge for free radicals. It is currently unknown which, if any, of these mechanisms play a predominant role in the clinical efficacy of mesalazine.

5.2 Pharmacokinetic properties

General characteristics of the active substance

Disposition and local availability
The therapeutic activity of mesalazine most likely depends on local contact of the medicine with the diseased area of the intestinal mucosa.

Asamax tablets consist of a compressed mesalazine tablet core coated with a gastro-resistant coating. Following administration, tablet disintegration occurs in the last part of the small intestine and in the ascending colon interstitial fluid, releasing mesalazine for local action.

The transit and release of mesalazine after oral administration is independent of food co-administration, whereas the systemic absorption will be reduced.

Absorption
5–20% of the ingested dose will be absorbed following oral administration, predominantly from the large intestine.

Following oral administration of Asamax tablets, mesalazine is detectable in plasma approximately 5 hours following administration. Maximum plasma concentrations are seen 8.5 hours post-dose.

Distribution
Mesalazine and acetyl-mesalazine do not cross the blood-brain barrier. Protein binding of mesalazine is approximately 50%, and of acetyl-mesalazine about 80%.

After a gradual decrease, mesalazine will no longer be detectable 12 hours post-dose. The plasma concentration curve for acetyl-mesalazine follows the same pattern, but the concentrations are generally higher and the elimination is slower.

The metabolic ratio of acetyl-mesalazine to mesalazine in plasma after oral administration ranges from 3.5 to 1.3 after three x 500 mg and three x 2 g dosages, respectively, implying a saturable dose-dependent acetylation.

Mean steady-state plasma concentrations of mesalazine are approximately 2 µmol/L, 8 µmol/L, and 12 µmol/L after 1.5g, 4g, and 6g daily dosages, respectively. For acetyl-mesalazine the corresponding concentrations are 6 µmol/L, 13 µmol/L, and 16 µmol/L.

Biotransformation
Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to *N*-acetyl-mesalazine (acetyl-mesalazine). Some acetylation also occurs through the action of colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient.

Acetyl-mesalazine is thought to be clinically as well as toxicologically inactive, but this still needs final confirmation.

Elimination
The plasma half-life of pure mesalazine is approximately 1 hour and for acetyl-mesalazine several hours. Both substances are excreted with the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine.

Characteristics in patients
For use in patients with impaired liver and kidney functions, the resultant decrease in the rate of elimination and increased systemic concentration of mesalazine may constitute an increased risk of nephrotoxic adverse reactions.

5.3 Preclinical safety data

Definitive toxic effect on the kidney was demonstrated in all species. In general, the toxic doses exceed those used in humans by a factor of 5-10.

No significant toxicity associated with the gastrointestinal tract, liver, or haematopoietic system in animals has been observed.

In vitro test systems and *in vivo* studies showed no evidence of mutagenic effects. Studies of the tumourigenic potential carried out in rats showed no evidence of any substance-related increase in the incidence of tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, povidone, colloidal silicon dioxide, crospovidone, magnesium stearate, hypromellose, polyethylene glycol, methacrylic acid copolymer, triethyl citrate, talc, titanium dioxide, and yellow iron oxide. Ethanol is used during the manufacturing process and trace amounts could be present in the final product.

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years in original packaging.

6.4 Special precautions for storage

Store in a dry place at room temperature (at or below 25°C) in original packaging. Keep out of reach of children.

6.5 Nature and contents of container

Asamax 500 gastro-resistant tablets 500 mg– PVC/PVDC-Aluminium blister strip-packaging in cardboard boxes containing 100 tablets.

6.6 Special precautions for disposal

None.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

New Zealand distributor:
Seqirus (NZ) Ltd
PO Box 62 590
Greenlane
Auckland 1546
NEW ZEALAND
Telephone: 0800 502 757

9 DATE OF FIRST APPROVAL

9 October 2008

10 DATE OF REVISION OF THE TEXT

2 June 2020

Asamax® is a registered trademark of Astellas Pharma Europe B.V.

SUMMARY TABLE OF CHANGES

Section affected	Summary of new information
Section 4.4, 4.6, 4.8	Updated safety information regarding Nephrolithiasis, Oligospermia (reversable), and various undesirable effects.