SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sulfasalazin medac 500 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg sulfasalazine

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gastro-resistant tablet
White, oval coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of active rheumatoid arthritis in adults.

Treatment of active juvenile idiopathic oligoarthritis in children from the age of 6, who responded insufficiently to non-steroidal antiinflammatory drugs (NSAIDs) and/or local glucocorticoid injections.

Treatment of active juvenile idiopathic polyarthritis and spondyloarthropathy with peripheral arthritis in children from the age of 6, who responded insufficiently to NSAIDs.

Sulfasalazin medac is not indicated for patients with systemic juvenile idiopathic arthritis or patients with juvenile spondyloarthropathy without peripheral arthritis.

4.2 Posology and method of administration

Posology

Active rheumatoid arthritis in adults
Unless prescribed otherwise by a physician Sulfasalazin medac should be given daily, starting with small initial doses and gradually (e.g. weekly) increasing to optimum amounts:

Week	1	2	3	4[1)]
morning	-	1 tablet (500 mg sulfasalazine)	1 tablet (500 mg sulfasalazine)	2 tablets (1,000 mg sulfasalazine)
evening	1 tablet (500 mg sulfasalazine)	1 tablet (500 mg sulfasalazine)	2 tablets (1,000 mg sulfasalazine)	2 tablets (1,000 mg sulfasalazine)

[1)] and each following week

In patients who, after 3 months, do not respond sufficiently to 2 x 2 tablets per day the daily dose may be increased to 3 x 2 tablets. A dose of 4,000 mg sulfasalazine should not be exceeded.

Paediatric population (age ≥ 6 years)

The recommended daily dose is 50 mg/kg body weight in two evenly divided doses. The maximum daily dose should not exceed 2 g. To reduce possible gastrointestinal intolerance, treatment should be commenced with a quarter to a third of the planned maintenance dose and increased weekly until reaching the maintenance dose after four weeks.

From experience clinical effectiveness sets in after 1 – 3 months. An additional therapy with analgesics or anti-inflammatory agents is advised, at least until Sulfasalazin medac starts being effective.

Therapy as well as additional therapy is carried out under medical supervision. In general, sulfasalazine is used for long-term treatment. It may be taken for years if it is efficacious and well-tolerated.

Method of administration

The tablets should be taken at least 1 hour before a meal with plenty of fluid and swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substance, its metabolites or to any of the excipients listed in section 6.1.
- Hypersensitivity to sulfonamides and salicylates
- Present or history of erythema exsudativum multiforme
- Porphyria
- Present blood count disorders such as leukopenia or thrombocytopenia
- Ileus
- Severe hepatic insufficiency
- Severe renal insufficiency
- In patients with glucose-6-phosphate dehydrogenase-deficiency (haemolytic anaemia can occur)
- Concomitant therapy with methenamine
- Use in children under the age of 6

4.4 Special warnings and precautions for use

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Sulfasalazin medac should only be administered under medical supervision.

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfasalazine.
Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is during the first weeks of treatment.
If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, sulfasalazine treatment should be discontinued.
The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect medicinal product. Early withdrawal is associated with a better prognosis.
If the patient has developed SJS or TEN with the use of sulfasalazine, sulfasalazine must not be re-started in this patient at any time.

Controls

Before and during treatment with Sulfasalazin medac the blood count including thrombocytes and differential blood count as well as liver function (AP, SGPT) and renal function (creatinine and urinalysis) should be checked regularly. During the first three months of therapy fortnightly checks are advised, monthly checks from 4^{th} to 6^{th} month, and every three months thereafter or when adverse reactions occur.

Clinical symptoms such as sore throat, fever, pallor, purpura or icterus during treatment may be due to myelosuppression, haemolysis or hepatotoxicity. Treatment with sulfasalazine should be discontinued until the results of blood tests are available. **Please see section 4.4 "Interference with laboratory testing".**

Like other sulfonamides, sulfasalazine can cause haemolysis in patients with glucose-6-phosphate dehydrogenase-deficiency (G6PD) (see section 4.3).

Oral sulfasalazine inhibits absorption and metabolism of folic acid and can cause folic acid deficiency, which may result in serious blood disorders such as macrocytosis and pancytopenia (see section 4.5).

Fluid intake should be adequate during treatment, since sulfasalazine can cause crystalluria and kidney stones.

Yellow skin colouration and secretions have been reported, including discolouration of soft contact lenses (see section 4.8).

Male fertility

Therapy with sulfasalazine may cause oligospermia in men with reversible impaired fertility. At an average, sperm production returns to normal within 2 – 3 months after discontinuation of therapy. No cases of teratogenicity resulted from the reversible impaired fertility.

Sulfasalazin medac should be administered with caution to patients with a tendency to hypersensitivity (allergic disposition) or bronchial asthma. Patients with known hypersensitivity to sulfonyl ureas should also be treated with caution.

Sulfasalazine should not be used in patients with impaired hepatic or renal function or blood dyscrasia unless the potential benefits of treatment outweigh the risk.

N-acetyltransferase 2 (NAT2) Polymorphism
Sulfasalazine is metabolised in the colon to 5-aminosalicylate (5-ASA) and sulfapyridine (SP) by bacterial azoreductase. SP which is highly associated with adverse drug reactions (ADRs), is mostly absorbed from the colon, acetylated by N-acetyltransferase 2 (NAT2) in the liver, and then eliminated renally (see section 5.2).
NAT2 is a polymorph enzyme and the slow acetylator type is more common in the Asian population that might be more susceptible to ADRs.

Such NAT2 acetylator status may influence the occurrence of ADRs during sulfasalazine treatment. Studies indicated that NAT2 slow acetylators were associated with an increased risk of mostly dose related ADRs (see section 4.8) which appear to be more severe. This may lead to a higher incidence of discontinuation of sulfasalazine treatment, compared with rapid and intermediate acetylators. Dose adaption should be considered in case of the occurrence of severe ADRs due to NAT2 slow acetylator status.

. Determination of the acetylator type is also reasonable in cases where several concomitantly administered substances are to be acetylated and where rheumatoid arthritis is combined with Sjögren's syndrome and/or other overlap syndromes (age, body weight, accompanying illness).

Paediatric population

Therapy should only be initiated and monitored by specific physicians who are sufficiently experienced in diagnosis and therapy of rheumatic disease in children (JIA).

Sulfasalazine is not recommended for use in children with manifest systemic juvenile rheumatoid arthritis, since it can result in serum sickness-like reactions (see section 4.1).

Interference with laboratory testing

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include urea, ammonia, LDH, α-HBDH and glucose. It is possible that alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), or thyroxine may also show interference when sulfasalazine treatment is given at high doses. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings.

4.5 Interaction with other medicinal products and other forms of interaction

Sulfasalazine may interact with other medicinal products on its own or via its major metabolites. Most clinical relevant pharmacokinetic interactions are with antibiotics, iron and calcium, folic acid and highly protein-bound medicinal products.

Folic acid absorption

During therapy with sulfasalazine, folic acid levels might decrease presumably due to inhibition of absorption. This may lead to a folic acid deficiency or intensify a folic acid deficiency already caused by the underlying disease or pregnancy.

Iron

Sulfasalazine and iron form chelates. This leads to malabsorption for sulfasalazine but not for sulfapyridine.

Calcium

Concomitant sulfasalazine and calcium gluconate therapy have been reported to result in a delayed absorption of sulfasalazine.

Digoxin

It has been reported in single cases that the administration of sulfasalazine inhibits the uptake of digoxin.

Antibiotics

Concomitant administration of antibiotics (proved for ampicillin, neomycin, rifamycin, ethambutol) may reduce efficacy of sulfasalazine by inhibiting the partial bacterial decomposition due to impairment of the bowel flora.

Anion-exchange resins

Anion-exchange resins such as colestipol or cholestyramine bind both sulfasalazine and its metabolites in the bowel.

Anticoagulants

Hepatic metabolism of oral anticoagulants such as phenprocoumon or dicoumarol may be impaired. If used concurrently, extra caution and frequent monitoring of the coagulation status are necessary.

Protein-bound medicinal products

Concurrent use of methotrexate, phenylbutazone, sulfinpyrazone or other protein-bound medicinal products may potentiate the effect of these medicinal products.

Myelotoxic medicinal products

Leukopenia, anaemia and / or thrombopenia may be more frequent and intense, therefore close observation should be performed.

Cyclosporine

The combination can lead to a reduced cyclosporine level, probably due to cytochrome P450 induction. Dose control and adaptation may be necessary.

Live typhoid vaccine

Decreased immunological response to live typhoid vaccine is possible. An interval of at least 24 hours between the administration of sulfasalazine and the live typhoid vaccine is recommendable.

Hepatotoxic agents

If a combination of sulfasalazine with hepatotoxic agents is not avoidable monitor liver function carefully.

Azathioprine

Sulfasalazine is an inhibitor of thiopurine methyltransferase (TPMT) which metabolises azathioprine. In order to avoid increased myelotoxicity careful monitoring of blood counts is recommended.

Methenamine

Due to an increased risk of crystalluria sulfasalazine and methenamine should not be administered concomitantly (see section 4.3).

Sulfonyl ureas

Sulfasalazine may potentiate the hypoglycaemic effect of sulfonyl ureas.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of sulfasalazine on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. Limited animal studies do not indicate harmful effects with respect to pregnancy and embryo/foetal development (see section 5.3).
Caution should be exercised when prescribing Sulfasalazin medac to pregnant women, particularly if belonging to the slow acetylator phenotype.

Sulfasalazine therapy may lead to folic acid deficiency or intensify folic acid deficiency caused by the underlying disease or pregnancy (see section 4.5). Since folic acid deficiency at conception or during the first trimester of pregnancy has been associated with an increased risk of neural tube defects (e.g. spina bifida), folic acid supplementation is recommended during sulfasalazine therapy in women of child-bearing potential and in the first trimester of pregnancy.

Breastfeeding

Sulfasalazine and its metabolites pass the placenta and are excreted in human milk. The plasma levels of sulfasalazine in the foetus and the new-born are approximately the same as the plasma concentration of the mother. The concentration of sulfapyridine in human milk amounts to about 40 % of the maternal blood level. While normally this may not be associated with a risk of kernicterus or other adverse effects in the infant, problems may arise in mother-child-pairs with decreased metabolic activity (slow acetylators, premature babies, new-borns with jaundice, glucose-6-phosphate dehydrogenase deficiency). Therefore, caution should be exercised when prescribing Sulfasalazin medac to breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Ability to react might be impaired in some patients. Patients who experience dizziness or other central nervous system disturbances while taking sulfasalazine should not drive, use machines or engage in other activities that may be hazardous because of decreased alertness.

4.8 Undesirable effects

Singular adverse reactions cannot be easily distinguished from symptoms or complications of the disease.
Many adverse reactions are dose-dependent and may be diminished by decreasing the dose.
In patients who are slow acetylators the concentration of the medicinal product may be increased. If adverse reactions occur the assessment of the acetylator phenotype is recommended.

Adverse reactions can be broadly divided into 2 groups.

The first is dose-related, dependent on acetylator phenotype, and largely predictable; this group includes nausea and vomiting, headache, haemolytic anaemia and methaemoglobinaemia (See section 4.4).

The second group are the hypersensitivity reactions which are essentially unpredictable and usually occur at the start of treatment; this group includes skin rash, aplastic anaemia, hepatic and pulmonary dysfunction and auto-immune haemolysis.

Adverse reaction frequencies have been categorised as follows:

Very common (≥ 1/10)
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).

The following adverse reactions may occur:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Very rare: Myelodysplastic syndrome

Blood and lymphatic system disorders

Common: Folic acid deficiency anaemia (megaloblastosis, macrocytemia), leukopenia
Uncommon: Agranulocytosis, pancytopenia, haemolytic anaemia, methaemoglobinaemia, thrombocytopenia, pseudomononucleosis
Rare: Bone-marrow depression, aplastic anaemia, plasmocytosis

Immune system disorders

Uncommon: Serum sickness-like disorder, hypogammaglobulinaemia, induction of autoantibodies
Rare: DRESS syndrome (skin reaction with eosinophilia and systemic symptoms), reactions are partly similar to mononucleosis infectiosa or serum sickness; anaphylaxis

Metabolism and nutrition disorders

Very common: Anorexia
Rare: Acute attacks of porphyria

Psychiatric disorders

Uncommon: Depressions
Very rare: Psychosis

Nervous system disorders

Very common: Headache
Common: Drowsiness, dizziness, impaired concentration, insomnia
Uncommon: Paraesthesia, peripheral neuropathy, disturbances of smell and taste
Rare: Metallic taste
Very rare: Aseptic meningitis, encephalopathy, transverse myelitis

Eye disorders

Uncommon: Allergic conjunctivitis
Rare: Contact lens discolouration (one singular case of a yellow tint of soft contact lenses)

Ear and labyrinth disorders

Uncommon: Tinnitus

Cardiac disorders

Uncommon: Palpitations, tachycardia
Very rare: Myocarditis, pericarditis

Vascular disorders

Uncommon: Increased blood pressure
Very rare: Raynaud's syndrome

Respiratory, thoracic and mediastinal disorders

Uncommon: Eosinophilic pneumonitis, cough, asthma, dyspnoea
Rare: Fibrosing alveolitis
Very rare: Bronchiolitis obliterans
Not known: Interstitial lung disease

Gastrointestinal disorders

Very common: Nausea and vomiting, abdominal pain
Uncommon: Meteorism, diarrhoea, pancreatitis
Rare: Stomatitis
Very rare: Exacerbation of remittent ulcerative colitis

Hepatobiliary disorders

Common: Increased hepatic enzymes
Uncommon: Hepatic dysfunction
Rare: Hepatitis
Very rare: Fulminant hepatitis (with potentially lethal outcome)

Skin and subcutaneous tissue disorders

Very common: Pruritus, skin eruption
Common: Urticaria, photosensitivity
Uncommon: Cyanosis of the skin, Quincke's oedema
Rare: Alopecia, exfoliative dermatitis, yellow-orange discolouration of the skin
Very rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; Lyell's syndrome), see section 4.4
Not known: Lichen planus

Musculoskeletal and connective tissue disorders

Uncommon: Lupus erythematosus syndrome, myasthenia, arthralgia
Rare: Myalgia

Renal and urinary disorders

Rare: Haematuria, crystalluria, yellow-orange discolouration of urine
Very rare: Acute interstitial nephritis, nephrotic syndrome, proteinuria

Reproductive system and breast disorders

Very common: Oligospermia in men, reversible impaired fertility

General disorders and administration site conditions

Very common: Fatigue, asthenia
Common: Fever
Uncommon: Enanthema

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of intoxication

There is evidence that the incidence and severity of toxicity following overdose is directly related to the total serum sulfapyridine concentration. Symptoms of overdose may include nausea, vomiting, gastric distress and abdominal pains. In more advanced cases central nervous system symptoms such as drowsiness, convulsions, etc. may be observed. Serum sulfapyridine concentrations may be used to monitor the progress of recovery from overdose.

Therapy of intoxication

Symptomatic treatment is indicated, possibly gastric lavage and activated charcoal.
In cases of overdose gastric lavage up until 2.5 hours after taking the tablets is advised.
Agents that accelerate intestinal passage may decrease resorption if the tablets have been taken before that.
Administration of copious intravenous fluids to encourage diuresis and alkalinisation of the urine with intravenous sodium bicarbonate.
Patients should be monitored for oliguria, anuria and development of methaemoglobinaemia or sulfahaemoglobinaemia.

Sulfasalazine and its metabolites are dialyzable. Dialysis should be performed in the event of anuria.
In cases of severe toxic or hypersensitivity reactions administration of Sulfasalazin medac should be stopped immediately. In the case of dose-dependent adverse reactions Sulfasalazin medac may be administered once more after a one-week discontinuation in small doses which are to be increased slowly, preferably under clinical supervision.

A methaemoglobinaemia is counteracted by administering toluidine blue 2 – 4 mg/kg body weight IV or methylene blue 1 – 2 mg/kg body weight IV.
Plasmapheresis may be indicated for severe sulfhaemoglobinaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: intestinal anti-inflammatory agent, ATC code: A07EC01

Mechanism of action

The clinical effect of sulfasalazine in rheumatoid arthritis may be discussed especially in connection with the reported antibacterial effect, the anti-inflammatory effect and the immunosuppressive effect. Moreover, it has a wide variety of effects in other biological systems. However, it is difficult to assess the significance of each single pharmacological effect as the aetiology of active rheumatoid arthritis is widely unknown.

5.2 Pharmacokinetic properties

Absorption

After oral administration sulfasalazine is absorbed in the small intestine by approx. 20 %.

Distribution

The highest serum concentration is reached after 3 – 6 hours. The medium half-life after single dose is 5.7 hours, after repeated doses 7.6 hours. Protein bond is more than 95 %.

Metabolism and elimination

A smaller part of the absorbed substance is excreted with the urine, the rest returns via the bile into the small intestine (enterohepatic cycle). Within 2 days after taking the tablets the serum levels drop down to negligible concentrations. The largest part of the given dose of sulfasalazine reaches the large intestine and is split into its metabolites sulfapyridine and 5-aminosalicylic acid by colon bacteria. Sulfapyridine is absorbed, partly acetylated and hydroxylated and glucuronidated. The biggest part of sulfapyridine is then excreted with the urine. Non-acetylated sulfapyridine is bound to serum albumin and reaches its highest levels after 12 hours. After 3 days the sulfapyridine is not detectable anymore in the serum. All in all, within 3 days after a single dose of 2 g sulfasalazine approximately 80 % (70 – 90 %) of the given dose is detectable as molecule as a whole and sulfapyridine metabolites in the urine. Slow acetylators, according to their genetic disposition, develop higher serum concentrations in free sulfapyridine and are therefore more likely to show adverse reactions.

The absorbed part of 5-aminosalicylic acid is excreted quickly in the urine, primarily as acetyl-5-aminosalicylic acid. A larger part is excreted with the faeces.

5.3 Preclinical safety data

Acute toxicity

The acute toxicity of sulfasalazine is low. LD_{50} values for mice and rats are higher than 8 – 12 g/kg body weight.

Chronic toxicity

Studies over 6 months with dogs (250 mg and 500 mg/kg body weight) showed a slight enlargement of thyroid. A small effect on the testicle epithelium was only observed in the high dose of 500 mg/kg body weight. Similar results were obtained in 6-month studies with rats.

Reproduction toxicology

Studies with rats showed reversible impairment of male fertility. After daily administration of 500 mg/kg body weight for a certain period of time administration of the medicinal product was interrupted for 10 days (new spermatogenic cycle). Fertility and general fecundity were back to normal after that.
Teratological studies with rats showed no undesirable effects after oral administration of 500 mg/kg body weight per day. The respective innocuous dose in tests on the effect on peri- and postnatal development was 200 mg/kg body weight.

Mutagenic and tumorigenic potential

Results of the *in vitro* and *in vivo* mutagenicity studies available for sulfasalazine to date are equivocal.
In two-year oral carcinogenicity studies an increased incidence of urinary bladder and kidney transitional cell papilloma and of hepatocellular adenoma/carcinoma was observed in rats and mice, respectively, treated with sulfasalazine. To date, the available epidemiological data do not indicate a tumorigenic potential of sulfasalazine in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: crospovidone, stearic acid, povidone, anhydrous colloidal silicon dioxide, purified water, magnesium stearate

Tablet coating: titanium dioxide, talc, sodium carmellose, sodium citrate, macrogol, propylene glycol, methacrylic acid-ethyl-acrylate copolymer (1:1) (dispersion 30 per cent)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Polyethylene bottle with polypropylene screw cap

Available pack sizes:
100 tablets
300 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

06/2022