Salazopyrin EN

Sulfasalazine

500 mg gastro-resistant tablets

Reference market :Sweden

AfME markets using the same LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Salazopyrin EN 500 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gastro-resistant tablet contains 500 mg sulfasalazine

Excipient with known effect
One gastro-resistant tablet Salazopyrin EN 500 mg contains 5 mg propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Active rheumatoid arthritis that cannot be controlled with anti-inflammatory drugs. Ulcerative Colitis. Crohn's disease. Pyoderma gangrenosum.

4.2 Posology and method of administration

Inflammatory bowel disease
The dose should be adjusted to the severity of the disease and the tolerance.
It is recommended that patients who have not previously been treated with Salazopyrin EN gradually increase their dose over a period of a few weeks. The tablets should preferably be taken with meals and distributed evenly throughout the day. Salazopyrin EN is a gastro-resistant tablet specially developed for patients with active rheumatoid arthritis and for patients who suffer from gastrointestinal adverse effects from Salazopyrin tablets. The gastro-resistant tablets must be swallowed whole.

Acute attacks
Adults: Severe attacks: 2-4 tablets 3-4 times daily.
Moderate and mild attacks: 2 tablets 3-4 times daily.
Children: 40-60 mg/kg of body weight per day, divided into 3-6 doses.

Prophylactic treatment
Adults: When the disease is in remission, a maintenance dose is prescribed to keep the patient asymptomatic, normally 2 tablets 2 (-3) times daily. Treatment with this dose should be administered continually, as lifelong treatment, unless undesirable effects occur. If the disease worsens, the dose should be increased to 2 (-4) tablets 3-4 times daily.
Children: 20-30 mg/kg of body weight per day, divided into 3-6 doses.

Active rheumatoid arthritis
When treating rheumatoid arthritis, only Salazopyrin EN must be used. The tablets should preferably be taken with meals.
Adults: The dose should be adapted individually. The effective dose varies between 1 and 3 grammes per day. The most common dose is 2 gastro-resistant tablets twice daily. When initiating treatment, the dose should be increased as shown in the following table:

	Day 1-4	Day 5-8	Day 9 and later
Morning	1 gastro-resistant tablet	1 gastro-resistant tablet	2 gastro-resistant tablets

Evening	1 gastro-resistant tablet	2 gastro-resistant tablets	2 gastro-resistant tablets

If the patient has not responded to treatment within 2-3 months, the dose may be increased to 3 g per day. Patients who suffer adverse effects from the gastrointestinal tract may temporarily reduce their dose.
Children: No recommendation may currently be given for the treatment of juvenile chronic arthritis.

Treatment monitoring:
It is recommended that blood picture and liver function tests are performed initially and every two weeks during the first three months of treatment. Tests are then carried out every four weeks in the following three-month period. Blood picture and liver function tests are then performed every three months. Renal function tests are recommended initially and at regular intervals during treatment. Blood picture changes that may be related to folic acid deficiency may be normalised through the administration of folinic acid (leucovorin).

4.3 Contraindications

Hypersensitivity to the active substance or to any other excipient listed in section 6.1. Acute intermittent porphyria.

4.4 Special warnings and precautions for use

Serious infections associated with myelosuppression, including sepsis and pneumonia, have been reported. Patients who develop a new infection while undergoing treatment with sulfasalazine should be monitored closely. Administration of sulfasalazine should be discontinued if a patient develops a serious infection. Caution should be exercised when considering the use of sulfasalazine in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.

It is recommended that complete blood counts (including differential white cell counts) and liver function tests are performed initially and every two weeks during the first three months of treatment. Tests are then carried out every four weeks in the following three-month period. Blood counts and liver function tests are then performed every three months or when it is clinically indicated. It is recommended that the renal function (including urine analyses) is tested initially and every four weeks during the first three months of treatment. The renal function is then tested when it is clinically indicated. If clinical symptoms such as sore throat, fever, pallor, purpura or jaundice occur during sulfasalazine treatment, this may indicate bone marrow suppression, haemolysis or hepatotoxicity. Treatment with sulfasalazine should be discontinued while awaiting the results of blood tests, see also section 4.4 “Interference with laboratory testing”. Blood picture changes that may be related to folic acid deficiency may be normalised through the administration of folinic acid (leucovorin).

Sulfasalazine should be administered with caution to patients with impaired renal or hepatic function and to patients with a severe allergy or asthma. As sulfasalazine may cause haemolytic anaemia, it should be administered with caution in the treatment of patients with G-6-PD deficiency.

Desensitisation may be considered in individual patients who report milder hypersensitivity reactions. The drug must be discontinued in patients who report more severe reactions.

Severe hypersensitivity reactions may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome, hematological abnormalities (including hematophagic histiocytosis), and/or pneumonitis including eosinophilic infiltration.

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 within 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, Salazopyrin EN treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Salazopyrin EN, Salazopyrin EN must not be re-started in this patient at any time.

Severe, life-threatening systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking sulfasalazine. It is important to note that early signs of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not visible. The patient should be examined immediately if these symptoms occur. Sulfasalazine treatment should be discontinued if another cause for the symptoms cannot be identified.

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.

Because sulfasalazine causes crystalluria and kidney stone formation, adequate fluid intake must be maintained.

Excipient information
Salazopyrin EN 500 mg tablets contain propylene glycol (see section 2).

Examples of propylene glycol exposure based on daily dose (see section 4.2) are as follows:

- 16 Salazopyrin EN 500 mg tablets administered to an adult weighing 70 kg would result in a propylene glycol exposure of 1.14 mg/kg/day.
- 2 Salazopyrin EN 500 mg tablets administered to a 6 year-old child weighing 20 kg would result in a propylene glycol exposure of 0.50 mg/kg/day.

4.5 Interaction with other medicinal products and other forms of interaction

Reduced absorption of digoxin has been reported during concomitant treatment with sulfasalazine.
Folic acid deficiency may occur as sulfasalazine inhibits the absorption of folic acid.
Rifampicin reduces the concentration of sulfapyridine in plasma during sulfasalazine treatment, probably due to an enzyme-inducing effect. The clinical significance is unclear.
Bone marrow suppression and leukopenia have been reported when mercaptopurine or azathioprine and oral sulfasalazine have been administered concomitantly. *In vitro* studies show that sulfasalazine inhibits thiopurine methyltransferase (TPMT), which is involved in the metabolism of mercaptopurine.

4.6 Fertility, pregnancy and lactation

Fertility
There is no available data on fertility.

Pregnancy
Reproduction studies on rats and rabbits indicate no risk of harm to the foetus.
Sulfasalazine passes via the placenta in such quantities that the foetus may be expected to have the same plasma concentrations as the mother, which may also put the foetus at risk of undesirable effects.

As oral sulfasalazine inhibits the absorption and metabolism of folic acid, this may cause folic acid deficiency (see section 4.4). There have been reports of children with neural tube defects whose mothers were exposed to sulfasalazine during pregnancy, although the importance of sulfasalazine for these defects has not been proven.

As risks associated with use during pregnancy cannot be completely ruled out, treatment should only be given after careful consideration.

Lactation
Low levels of sulfasalazine and sulfapyridine pass into breast milk. Caution should be used particularly when breast-feeding premature infants with G-6-PD deficiency. Bloody stools and diarrhoea have been reported in infants being breast-fed by women who had been treated with sulfasalazine. In cases where this was reported, the bloody stools or diarrhoea in the infant ceased when the nursing woman discontinued treatment with sulfasalazine.

4.7 Effects on ability to drive and use machines

No effects have been observed.

4.8 Undesirable effects

Undesirable effects, normally from the gastrointestinal tract or in the form of headaches, are seen in approximately one third of the patients being treated with sulfasalazine. Some undesirable effects are dose-dependent. Approximately 75% of the undesirable effects occur within the first three months of starting therapy.

Organ system class	***Common*** *(≥1/100, <1/10)*	***Uncommon*** *(≥1/1,000, <1/100)*	***Rare*** *(≥1/10,000, <1/1,000)*	***Unknown frequency*** *(Cannot be estimated from the available data)*
Infections and infestations				pseudomembranous colitis
Blood and lymphatic system disorders	leukopenia	thrombocytopenia†	megaloblastic anaemia, aplastic anaemia.	pancytopenia, haemolytic anaemia, macrocytosis, agranulocytosis, mononucleosis-like syndrome*†
Immune system disorders		facial oedema		anaphylactic reactions, including isolated cases of anaphylactic shock*. angioedema, including oedema of the larynx/pharynx. serum sickness
Metabolism and nutrition disorders	loss of appetite			folate deficiency*†

Psychiatric disorders		depression		
Central and peripheral nervous system disorders	headache, dizziness, taste alterations			peripheral neuropathy, aseptic meningitis, encephalopathy, smell alterations
Ear and labyrinth disorders	tinnitus			
Cardiac disorders				pericarditis, cyanosis, myocarditis *†
Respiratory, thoracic and mediastinal disorders	cough	dyspnoea		interstitial lung disease*, fibrosing alveolitis, eosinophilic infiltration of the lungs, oropharyngeal pain*†
Vascular disorders				pallor*†
Gastrointestinal disorders	abdominal pain, nausea, bloatedness, diarrhoea, vomiting			pancreatitis, worsening of ulcerous colitis
Hepatobiliary disorders			jaundice†	hepatitis†, hepatic failure*, fulminant hepatitis*, cholestasis*
Skin and subcutaneous tissue disorders	urticaria, itching, purpura†	alopecia	epidermal necrolysis (Lyell's syndrome) †, Stevens-Johnson syndrome (SJS)†, nail alterations	drug rash with eosinophilia and systemic symptoms (DRESS)*†, exanthema, erythema, exfoliative dermatitis, photosensitivity
Musculo-skeletal and connective tissue disorders	arthralgia			SLE syndrome
Renal and urinary disorders	proteinuria		nephritis.	nephrotic syndrome, haematuria, crystalluria†, interstitial nephritis, nephrolithiasis*

Reproductive system and breast disorders	reversible oligospermia†			
General symptoms and/or administration site symptoms	fever†			yellow discolouration of skin and bodily fluids have been reported and also yellow discolouration of soft contact lenses
Investigations	transient elevation of liver enzymes			induction of autoantibodies

* undesirable effects identified after introduction into the market
† see section 4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions (SCARS); Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

It may sometimes be difficult to distinguish between an undesirable effect of the drug and complications from the underlying diseases, particularly if they manifest in other organ systems. Cases of aseptic meningitis have only been reported in patients with a rheumatic disease.

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 according to their local country requirements.
To Report side effects

- Saudi Arabia

National Pharmacovigilance Centre (NPC)
- SFDACall center : 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa

Other GCC States

- *Please contact the relevant competent authority.*

4.9 Overdose

25 g sulfasalazine in an adult resulted in mild intoxication following early gastric lavage.

The following applies to sulfonamides in general:

Toxicity: Individual instances of patients ingesting high amounts have resulted in severe poisoning in rare cases.
43 g in a 24-hour period in an adult resulted in lethal intoxication (sulfhaemoglobinaemia and methaemoglobinaemia). Note: allergic symptoms may occur. Risk of kernicterus in newborns.

Symptoms: Nausea, vomiting. Crystalluria, haematuria, oliguria and anuria. Hypoglycaemia, in individual cases methaemoglobinaemia, cyanosis, liver damage, sulfhaemoglobinaemia. CNS damage. Hypersensitivity reactions, such as blood picture changes (lethal agranulocytosis), urticaria, polyneuritis, cerebral symptoms.

Treatment: If required, gastric lavage at an early stage, charcoal. Substantial intravenous fluid administration to keep diuresis at a high level, alkalinisation with sodium bicarbonate intravenously. The risk of oliguria and anuria must be monitored. Dialysis in the event of anuria. In the event of marked methaemoglobinaemia (cyanosis), methylthionine 1-2 mg/kg slowly intravenously. Symptomatic treatment otherwise. In severe cases of sulfhaemoglobinaemia, an exchange transfusion may be performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal antiinflammatory agents, *ATC code:* A07E C01

Sulfasalazine has an anti-inflammatory, immunosuppressive and antibacterial effect and is used to inhibit inflammatory conditions, particularly those localised in the intestinal mucosa. The primary effect of sulfasalazine administration is considered to be the anti-inflammatory effect of locally formed mesalazine. An immunosuppressive effect has also been shown by inhibiting lymphocyte and granulocyte metabolism and by inhibiting different enzyme systems through all three of the components (sulfasalazine, sulfapyridine, mesalazine). The bacteriostatic activity of sulfapyridine formed locally in the colon may have a clinical effect. Both the aerobic and the anaerobic bacterial flora are affected.

5.2 Pharmacokinetic properties

Following oral administration, part of the dose (approximately 20% of an administered dose) is absorbed in the small intestine that is subsequently excreted through enterohepatic circulation. Maximum serum concentration is reached after 3-6 hours, with protein binding at approximately 99%. There are significant individual differences in serum concentration. There is a moderate tendency to accumulation; the serum concentration is insignificant 24 hours after a single dose of sulfasalazine. A few percent of the dose is excreted in the urine.

Sulfasalazine is split by intestinal bacteria in the colonic lumen into two main metabolites, sulfapyridine and mesalazine (5-aminosalicylic acid). Sulfapyridine is absorbed rapidly; it is partly metabolised in the liver into inactive acetyl sulfapyridine and is primarily excreted as this in the urine. Non-acetylated sulfapyridine is partly bound to serum proteins and the maximum serum concentration is reached after 12 hours. Sulfapyridine shows a certain tendency for accumulation; the serum concentration only disappears completely 3 days after discontinuation.
The degree of acetylation of sulfapyridine is genetically determined. Patients with slow acetylation have higher serum concentrations of free sulfapyridine and they are therefore more likely to develop adverse effects. Mesalazine (5-aminosalicylic acid) is absorbed to a lesser extent; the serum concentration is approximately 1 µg/ml. 15% of the dose is excreted in the urine. The majority, 75%, remains in the colonic lumen and is excreted as 5-aminosalicylic acid in the faeces.

5.3 Preclinical safety data

-

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone 16 mg
Maize starch, pregelatinized 90.80 mg
Magnesium stearate 10.90 mg
Colloidal anhydrous Silica 3.27 mg
Cellulose acetate phthalate 20 mg
Propylene glycol 5 mg
White beeswax 3 mcg
Carnauba wax 6 mcg
Glyceryl monostearate 5 mcg
Macrogol 8 mcg
Talc 13 mcg

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use Salazopyrin EN after the expiry date which is stated on the carton after EXP:. The expiry date refers to the last day of that month.

Shelf life: 48 Months.

6.4 Special precautions for storage

Store below 25C.

6.5 Nature and contents of container

Yellow, orange, elliptical, convex, enteric-coated tablets, with the letters “KPh” on one face, and the product code “102” on the other.

Container with a screw top lid made of HD polyethylene and/or polypropylene.

The lid has a notch so that it can be opened easily with a pen, for example.

Pack size: 100 tablets.

6.6 Special precautions for disposal and Storage

Keep out of the sight and reach of children.

7 FURTHER INFORMATION

8 MARKETING AUTHORISATION HOLDER

Pfizer AB
191 90 Sollentuna, Sweden

MANUFACTURER

Recipharm Uppsala AB (formerly Kemwell AB), 75182 Uppsala, Sweden

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01-Jan-1990

10. DATE OF REVISION OF THE TEXT

October 2021