SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SALAZOPYRIN® EN 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains sulphasalazine 500 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

SALAZOPYRIN EN 500 tablets are yellow-orange, elliptical, convex, film-coated tablets with 'KPh' on the one side and '102' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative colitis

For the treatment of acute ulcerative colitis. For maintenance of remission in ulcerative colitis.

Crohn's disease

For the treatment of acute Crohn's disease.

Rheumatoid arthritis

For the treatment and control of rheumatoid arthritis.

4.2 Posology and method of administration

Posology

The dosage should be adjusted according to the response to the treatment and the patient's tolerance to SALAZOPYRIN EN. The tablets should be taken at regular intervals during the day, preferably with meals. Night-time intervals between doses should not exceed eight hours.

Patients not previously treated with SALAZOPYRIN EN are advised to raise the dose gradually during the first few weeks. Patients experiencing gastrointestinal side effects to the uncoated SALAZOPYRIN are advised to use SALAZOPYRIN EN or a lower dose.

Ulcerative colitis/Crohn's disease

Adults

Acute attacks: Two to four tablets every six hours with a maximum of 24 tablets (12 g) per day.

Remission: The dose must be reduced to 4 tablets (2 g) per day.

Rheumatoid arthritis

Two enteric coated tablets twice a day, i.e. 2 g daily. The enteric coated tablets should not be crushed or broken. When starting therapy it is advisable to increase the daily dose according to the following schedule:

	1st week	2nd week	3rd week	4th week and after
Morning		1 tablet	1 tablet	2 tablets
Evening	1 tablet	1 tablet	2 tablets	2 tablets

If no response is obtained after two months' treatment, the dose may be increased to 3 g per day.

Paediatric population

SALAZOPYRIN EN tablets are not suitable for patients under 18 years of age.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to sulphasalazine, sulphonamides, salicylates or any of the excipients of SALAZOPYRIN EN (listed in section 6.1)
- Porphyria
- Haemorrhagic diathesis
- Severe renal or hepatic failure
- Gastric and duodenal ulcers
- Pregnancy and lactation (see section 4.6)
- Infants and children

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 SALAZOPYRIN EN should be monitored closely. Administration of SALAZOPYRIN EN should be discontinued if a patient develops a serious infection. Caution should be exercised when considering the use of SALAZOPYRIN EN in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections. There is no clinical experience or data on restarting SALAZOPYRIN after a serious infection and/or neutropenia have resolved.

SALAZOPYRIN EN should be administered under medical supervision before and during therapy. Complete blood counts, including differential white cell count and liver function tests should be performed

in all patients before starting therapy with SALAZOPYRIN EN and every second week during the first three months of therapy. During the second three months, the same tests should be done once monthly and thereafter once every three months and as clinically indicated. Assessment of renal function (including urinalysis) should be performed in all patients initially and at least monthly for the first three months of treatment. Thereafter, monitoring should be performed as clinically indicated. Discontinue SALAZOPYRIN EN treatment if the renal function continues to deteriorate. The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice during SALAZOPYRIN EN treatment may indicate myelosuppression, hemolysis, or hepatotoxicity. The patient should be advised to report any untoward symptoms immediately. Discontinue treatment with SALAZOPYRIN EN while awaiting the results of blood tests.

SALAZOPYRIN EN or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use nicotinamide adenine dinucleotide [NAD(H)] or nicotinamide adenine dinucleotide phosphate [NADP(H)]. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving SALAZOPYRIN EN (see section 4.5).

SALAZOPYRIN EN should not be given to patients with impaired hepatic or renal function or with blood dyscrasias. Reduction of dosage may be required in patients with renal impairment.

SALAZOPYRIN EN should be given with caution to patients with severe allergy or bronchial asthma.

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

Severe, life-threatening systemic hypersensitivity reactions such as Drug rash with eosinophilia and

systemic symptoms (DRESS) have been reported in patients taking various medicines including SALAZOPYRIN EN. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. SALAZOPYRIN EN should be discontinued if an alternative aetiology for the signs or symptoms cannot be established.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of SALAZOPYRIN EN. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. SALAZOPYRIN EN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Treatment should be discontinued immediately when a rash appears because of the danger of severe allergic reactions such as the Stevens-Johnson syndrome.

If serious toxic or hypersensitivity reactions occur, SALAZOPYRIN EN should be discontinued immediately. Some weeks after discontinuation, SALAZOPYRIN EN may be re-introduced beginning with a low dose followed by small increases in dosage regimen.

SALAZOPYRIN EN inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious haematological toxicity.

Patients, especially those with glucose-6-phosphate dehydrogenase deficiency, should be observed closely for signs of haemolytic anaemia.

Adequate fluid intake (1 200 mL to 1 500 mL daily) is necessary to reduce the risk of crystalluria. If this

cannot be accomplished, sodium bicarbonate may be given.

Oligospermia and infertility in men treated with SALAZOPYRIN EN has been reported.

SALAZOPYRIN EN may cause yellow staining of soft contact lenses.

Patients with HIV may have an increased incidence of adverse effects especially rash, fever and leukopenia.

Patients with slow acetylator phenotype are more likely to show adverse effects due to sulphapyridine.

SALAZOPYRIN EN may cause an orange colouring of the urine.

4.5 Interaction with other medicines and other forms of interaction

Reduced absorption of folate and digoxin have been reported when used concomitantly with SALAZOPYRIN EN.

Due to inhibition of thiopurine methyltransferase (TPMT) by SALAZOPYRIN EN, bone marrow suppression and leukopenia have been reported when thiopurine 6-mercaptopurine or its prodrug, azathioprine, and oral SALAZOPYRIN EN were used concomitantly.

Sulphonamides as in SALAZOPYRIN EN may potentiate the effects of oral coagulants, methotrexate and phenytoin. Coadministration of SALAZOPYRIN EN and methotrexate to rheumatoid arthritis patients did not alter the pharmacokinetic disposition of the medicines. However, an increased incidence of gastrointestinal adverse events, especially nausea, was reported.

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 SALAZOPYRIN EN or its metabolite, mesalamine/mesalazine.

SALAZOPYRIN EN 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 alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), ammonia, thyroxine, or glucose. 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 SALAZOPYRIN EN. Results should be interpreted in conjunction with clinical findings (see section 4.4).

The hypoglycaemic effect of sulphonylureas may be enhanced. Interactions with warfarin, methotrexate, probenecid, sulfinpyrazone, spironolactone, furosemide and rifampicin may occur.

Potentiation of undesirable glucocorticoid effects on the stomach may occur.

SALAZOPYRIN EN chelates iron and interferes with its absorption.

The action of SALAZOPYRIN EN may be antagonised by para-aminobenzoic acid and medicines derived from it, particularly the procaine group of local anaesthetics.

Paraldehyde has been reported to increase the acetylation of sulphonamides with subsequent increased risk of crystalluria with concomitant use with SALAZOPYRIN EN.

Concomitant antibiotic therapy may possibly alter the patient's response to SALAZOPYRIN EN.

4.6 Fertility, pregnancy and lactation

SALAZOPYRIN EN is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

SALAZOPYRIN EN inhibits the absorption and metabolism of folic acid which may lead to teratogenicity. SALAZOPYRIN EN should therefore not be used during pregnancy and lactation.

Breastfeeding

Sulphasalazine as in SALAZOPYRIN EN is found in breast milk. There have been reports of bloody stools or diarrhoea in infants who were breastfeeding from mothers on SALAZOPYRIN EN.

4.7 Effects on ability to drive and use machines

SALAZOPYRIN EN may affect your ability to drive and use machinery (see section 4.8).

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse events have been reported in association with SALAZOPYRIN EN therapy. In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency: 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 adverse reactions may also be associated with the underlying disease and/or concomitant medicines.

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Pseudomembranous colitis (as a result of alteration of the intestinal

		bacterial flora), parotitis
	Not known	Aseptic meningitis
Blood and lymphatic system disorders	Common	Leukopenia (following bone marrow depression), red cell abnormalities
	Uncommon	Thrombocytopenia, eosinophilia, methaemoglobinaemia, hypoprothrombinaemia
	Not known	Pancytopenia, agranulocytosis, aplastic anaemia, macrocytosis, megaloblastic anaemia, haemolytic anaemia
Immune system disorders	Not known	Serum sickness
Endocrine disorders	Uncommon	Hypothyroidism
Metabolism and nutrition disorders	Common	Loss of appetite
	Uncommon	Hypoglycaemic effect (with high doses)
Psychiatric disorders	Uncommon	Depression, insomnia, hallucinations
Nervous system disorders	Common	Dizziness, headache, taste disorders
	Uncommon	Peripheral neuropathy, ataxia, peripheral neuritis, convulsions, multiple sclerosis, chorea
	Not known	Encephalopathy, smell disorders

Eye disorders	Uncommon	Yellow staining of soft contact lenses, optic neuropathy, transient myopia, periorbital oedema
Ear and labyrinth disorders	Common	Tinnitus
	Uncommon	Vertigo
Cardiac disorders	Uncommon	Cyanosis
	Not known	Pericarditis
Vascular disorders	Uncommon	Vasculitis including polyarteritis nodosa
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Fibrosing alveolitis, dyspnoea
	Not known	Eosinophilic infiltration
Gastrointestinal disorders	Very common	Gastric distress, nausea
	Common	Abdominal pain
	Uncommon	Stomatitis
	Not known	Pancreatitis
Hepato-biliary disorders	Uncommon	Hepatitis
	Not known	Hepatotoxic reactions
Skin and subcutaneous tissue disorders	Common	Pruritus, exanthema, erythema, urticaria
	Uncommon	Alopecia, skin rashes, photosensitivity, contact dermatitis, exfoliative dermatitis, toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome,

		erythema nodosum
	Not known	Toxic pustuloderma, Lichen planus
Musculoskeletal and connective tissue disorders	Common	Arthralgia
	Not known	Systemic lupus erythematosus, Sjogren's syndrome
Renal and urinary disorders	Common	Proteinuria, urine may be coloured orange
	Uncommon	Nephrotoxic syndrome, haematuria
	Not known	Interstitial nephritis, crystalluria
Reproductive system and breast disorders	Common	Oligospermia
General disorders and administration site conditions	Common	Fever
	Uncommon	Fatigue, facial oedema, manifestations of a generalised hypersensitivity reaction to sulphonamides includes a syndrome resembling pulmonary eosinophilia
Investigations	Uncommon	Elevation of liver enzymes
	Not known	Induction of autoantibodies

Post-marketing:

System organ class	**Adverse reaction**
Blood and lymphatic system disorders	Pseudomononucleosis
Immune system	Anaphylaxis

disorders	
Metabolism and nutrition disorders	Folate deficiency
Cardiac disorders	Myocarditis
Vascular disorders	Pallor
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease, oropharyngeal pain
Gastrointestinal disorders	Diarrhoea, vomiting, aggravation of ulcerative colitis
Hepato-biliary disorders	Jaundice, hepatic failure, fulminant hepatitis, cholestatic hepatitis, cholestasis
Skin and subcutaneous tissue disorders	Yellow discoloration of skin and body fluids, purpura, drug rash with eosinophilia and systemic symptoms (DRESS), angioedema
Renal and urinary disorders	Nephrolithiasis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit / risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

Symptoms of overdosage include those of salicylism and overdosage with sulphonamides. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.1 Sulphonamides

The mode of action of sulphasalazine (SSZ) or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP) is thought to be related to anti-inflammatory and/or immunomodulatory properties. Clinical studies utilising rectal administration of SSZ, SP and 5-ASA have indicated that the major therapeutic action may reside in the 5-ASA moiety. The relative contribution of the parent drug and the major metabolites in rheumatoid arthritis is unknown.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of 1 g of SSZ to 9 healthy males, less than 15 % of a dose of SSZ is absorbed as parent drug. Detectable serum concentrations of SSZ have been found in healthy subjects within 90 minutes after the ingestion. Maximum concentrations of SSZ occur between 3- and 12-hours post-ingestion, with the mean peak concentration (6 µg/mL) occurring at 6 hours. In comparison, peak plasma levels of both SP and 5-ASA occur approximately 10 hours after dosing. This longer time to peak is indicative of gastrointestinal transit to the lower intestine, where bacteria-mediated metabolism occurs. SP apparently is well absorbed from the colon, with an estimated bioavailability of 60 %. In this same study, 5-ASA is much less well absorbed from the gastrointestinal tract, with an estimated bioavailability of from 10 % to 30 %.

Distribution

Following intravenous injection, the calculated volume of distribution (Vdss) for SSZ was 7,5 ± 1,6 L. SSZ is highly bound to albumin (> 99,3 %), while SP is only about 70 % bound to albumin. Acetylsulfapyridine (AcSP), the principal metabolite of SP, is approximately 90 % bound to plasma proteins.

Metabolism

SSZ is metabolised by intestinal bacteria to SP and 5-ASA. Approximately 15 % of a dose of SSZ is absorbed as parent and is metabolised to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulphasalazine is 7,6 ± 3,4 hrs. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10,4 hrs, while in slow acetylators it is 14,8 hrs. SP can also be metabolised to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolised in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a non-acetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible.

Excretion

Absorbed SP and 5-ASA and their metabolites are primarily eliminated in the urine either as free metabolites or as glucuronide conjugates. The majority of 5-ASA stays within the colonic lumen and is excreted as 5-ASA and acetyl-5-ASA with the faeces. The calculated clearance of SSZ following intravenous administration was 1 L/hr. Renal clearance was estimated to account for 37 % of total clearance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch

Magnesium stearate

Colloidal silicon dioxide

Coating

Cellulose acetate phthalate

Propylene glycol

Acetone

Ethanol

Polish

White beeswax

Carnauba wax

Self-emulsifying glycerol monostearate

Polyethylene glycol 20 000

Ethanol

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture.

6.5 Nature and contents of container

Securitainers of 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

E /20.2.1/910

9. DATE OF FIRST AUTHORISATION

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BOTSWANA: S2

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