1. NAME OF THE MEDICINAL PRODUCT
Salazopyrin EN-Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each coated gastro-resistant tablet for oral administration contains 500 mg of sulfasalazine.

3. PHARMACEUTICAL FORM
Oral: gastro-resistant tablets.

4. CLINICAL PARTICULARS

DESCRIPTION
Salazopyrin is used for the treatment of inflammatory bowel diseases and rheumatoid arthritis. The use of enteric coated tablets will reduce the incidence of gastrointestinal side effects. For rheumatoid arthritis only Salazopyrin EN-tabs should be used. In the colon, sulfasalazine is split by intestinal bacteria into sulfapyridine and 5-aminosalicylic acid. Sulfasalazine and its metabolites have anti-inflammatory, immunosuppressive and antibacterial effects.

4.1 Therapeutic indications
Tablets and enteric coated tablets
Ulcerative colitis
In the treatment of mild to moderate ulcerative colitis and as adjunctive therapy in severe ulcerative colitis. For maintenance of remission in ulcerative colitis.

Crohn's disease
In the treatment of active Crohn's disease, especially in patients with colonic involvement.

Enteric coated tablets
Ulcerative colitis and Crohn's disease.
Rheumatoid Arthritis.

Suppositories
Ulcerative proctitis

4.2 Posology and method of administration
Tablets and enteric coated tablets
The dosage should be adjusted according to the patient's response to treatment and tolerance to the drug. The tablets should be taken at regular intervals during the day, preferably in connection with meals. Patients not previously treated with Salazopyrin/Salazopyrin EN-tabs are recommended to increase the dose gradually during the first few weeks. The use of enteric coated tablets will reduce the incidence of gastrointestinal side effects. The enteric coated tablets must be swallowed intact, preferably after meals, and should not be crushed or broken.

Inflammatory bowel diseases
Acute attacks:
Adults
Severe attacks: 2-4 tablets 3-4 times a day may be given in conjunction with steroids as part of an intensive management regime.

Moderate and mild attacks: 2 tablets 3-4 times a day.

Children
40-60 mg/kg body weight and day, divided into 3-6 doses.

Prophylaxis against relapses:
Adults
In ulcerative colitis in a state of remission a maintenance dose is recommended for keeping the patient free from symptoms, as a rule 2 tablets 2(-3) times a day. Treatment with this dosage should continue indefinitely, unless adverse effects are observed. In case of deterioration, the dosage is raised to 2(-4) tablets 3-4 times a day.

Children
20-30 mg/kg body weight and day, divided into 3-6 doses.

Enteric coated tablets
Rheumatoid Arthritis
Experience has shown that the clinical effect appears within 1-2 months' treatment.

Concurrent treatment with analgesics and/or non-steroidal anti-inflammatory agents is recommended at least until the disease-modifying effect of Salazopyrin EN-tabs is apparent. Salazopyrin EN-tabs has been shown effective and well tolerated in long-term treatment.

Adults
Two enteric coated tablets twice a day, i.e., 2 g a day. 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:

(Salazopyrin EN-tabs)

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

If no response has been seen after 2 months' treatment, the dose may be increased to 3 g per day.

Children
At present no recommendation regarding treatment with Salazopyrin EN-tabs in juvenile chronic arthritis can be given.

Suppositories
Individual. 1-2 suppositories in the morning after defaecation and in the evening. After 4-5 weeks, the dosage can be reduced by half. The local treatment can be combined with oral therapy with Salazopyrin/Salazopyrin EN tabs.

4.3 Contraindications
- Known hypersensitivity to sulfasalazine, its metabolites, or any other component of the product as well as sulfonamides, or salicylates.
- 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.

Patients treated with Salazopyrin/Salazopyrin EN-tabs should be under medical supervision. Bone marrow depression and leukopenia have been reported, usually within the first 3 months of starting treatment. In the vast majority of patients, this has been reversible on stopping the drug.

Complete blood counts, including differential white blood cell count, and liver function tests should be carried out before starting sulfasalazine and every second week during the first 3 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, patients should be screened if their condition changes or if they present with symptoms of infection, however mild clinically. A falling trend in the blood count is a better indication than a single value. Red cell and platelet counts should be carried out before and periodically during therapy.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice during sulfasalazine treatment may indicate myelosuppression, hemolysis, or hepatotoxicity. Discontinue treatment with sulfasalazine while awaiting the results of blood tests.

Sulfasalazine 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 sulfasalazine (see Section **4.5 Interaction with other medicinal products and other forms of interaction**).

Salazopyrin/Salazopyrin EN-tabs should be used with caution in patients with reduced kidney or liver function. Liver function tests and urinalysis should be carried out before and periodically during therapy. If serious toxic or hypersensitivity reactions occur, the drug should be discontinued immediately.

Sulfasalazine 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), hematological abnormalities (including hematophagic 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 drugs including sulfasalazine. 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.

Sulfasalazine should be discontinued if an alternative etiology 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 sulfasalazine. 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. Sulfasalazine should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Use in children with systemic onset juvenile rheumatoid arthritis may result in a serum sickness-like reaction; therefore, sulfasalazine is not recommended in these patients.

Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency (see Section **4.6 Fertility, pregnancy and lactation**), potentially resulting in serious blood disorders (e.g., macrocytosis and pancytopenia). Patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should be closely observed for signs of hemolytic anemia.

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

Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.

4.5 Interaction with other medicinal products and other forms of interaction

Reduced absorption of digoxin, resulting in non-therapeutic serum levels, has been reported when used concomitantly with oral sulfasalazine.

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

Coadministration of oral sulfasalazine and methotrexate to rheumatoid arthritis patients did not alter the pharmacokinetic disposition of the drugs. 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 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 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 sulfasalazine. Results should be interpreted in conjunction with clinical findings (see Section **4.4 Special warnings and precautions for use**).

Folate deficiency may occur as sulfasalazine inhibits the absorption of folate.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in rats and rabbits have revealed no evidence of harm to the fetus. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency (see Section **4.4 Special warnings and precautions for use**). There have been reports of babies with neural tube defects born to mothers who were exposed to sulfasalazine during pregnancy, although the role of sulfasalazine in these defects has not been established. Because the possibility of harm cannot be completely ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Lactation

The amount of sulfasalazine that passes into the milk is negligible.

The concentration of sulfapyridine in the mother's milk is about 40% of that in serum.

However, the risk of kernicterus in healthy suckling children has been assessed as low at therapeutic doses, since sulfapyridine has been shown to have a poor bilirubin displacing capacity.

Caution should be used, particularly if breastfeeding premature infants or those deficient in G-6-PD. There have been reports of bloody stools or diarrhea in infants who were breastfeeding from mothers on sulfasalazine. In cases where the outcome was reported, bloody stools or diarrhea resolved in the infant after discontinuation of sulfasalazine in the mother.

4.7 Effects on ability to drive and use machines

The effect of sulfasalazine on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

The following events have been reported in patients receiving sulfasalazine:

MedDRA System Organ Class	Frequency	Adverse Drug Reaction
Infections and Infestations	Not known	aseptic meningitis, pseudomembranous colitis
Blood and lymphatic system disorders	Common	leukopenia
	Uncommon	thrombocytopenia†
	Not known	pancytopenia, agranulocytosis, aplastic anemia, pseudomononucleosis*†, hemolytic anemia, macrocytosis, megaloblastic anemia
Immune system disorders	Not known	anaphylaxis*, serum sickness
Metabolism and nutrition system disorders	Common	loss of appetite
	Not known	folate deficiency*†
Psychiatric disorders	Uncommon	depression

Nervous system disorders	Common	dizziness, headache, taste disorders
	Not known	encephalopathy, peripheral neuropathy, smell disorders
Ear and labyrinth disorders	Common	tinnitus
Cardiac disorders	Not known	myocarditis*†, pericarditis, cyanosis
Vascular disorders	Not known	pallor*†
Respiratory, thoracic and mediastinal disorders	Common	cough
	Uncommon	dyspnea
	Not known	interstitial lung disease*, eosinophilic infiltration, fibrosing alveolitis, oropharyngeal pain*†
Gastrointestinal disorders	Very common	gastric distress, nausea
	Common	abdominal pain, diarrhea*, vomiting*
	Not known	aggravation of ulcerative colitis*, pancreatitis
Hepatobiliary disorders	Uncommon	jaundice*†
	Not known	hepatic failure*, hepatitis fulminant*, hepatitis†, hepatitis cholestatic*, cholestasis*
Skin and subcutaneous tissue disorders	Common	purpura*†, pruritus
	Uncommon	alopecia, urticaria
	Not known	drug rash with eosinophilia and systemic symptoms (DRESS)*†, epidermal necrolysis (Lyell's syndrome)†, Stevens-Johnson syndrome†, exanthema, exfoliative dermatitis†, angioedema*, toxic pustuloderma, lichen planus, photosensitivity, erythema
Musculoskeletal and connective tissue disorders	Common	arthralgia
	Not known	system lupus erythematosus, Sjogren's syndrome
Renal and urinary disorders	Common	proteinuria
	Not known	nephrotic syndrome, interstitial nephritis, nephrolithiasis*, hematuria, crystalluria†
Reproductive system and breast disorders	Not known	reversible oligospermia†
General disorders and administration site conditions	Common	fever†
	Uncommon	facial edema
	Not known	yellow discoloration of skin and body fluids*
Investigations	Uncommon	elevation of liver enzymes
	Not known	induction of autoantibodies

Frequency categories: Very common ≥1/10; Common ≥1/100 to <1/10; Uncommon ≥1/1000 to <1/100; Rare ≥1/10,000 to <1/1000; Very rare <1/10,000; Not known (cannot be estimated from available data).
*ADR identified post-marketing.
†see Section **4.4 Special warnings and precautions for use.**

4.9 Overdose

The most common symptoms of overdose, similar to other sulfonamides, are nausea and vomiting. Patients with impaired renal function are at increased risk of serious toxicity. Treatment is symptomatic and should be supportive, including alkalinization of urine. Patients should be observed for development of methemoglobinemia or sulfahemoglobinemia. If these occur, treat appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic effects

The mode of action of sulfasalazine (SSZ) or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), may be related to the anti-inflammatory

and/or immunomodulatory properties that have been observed in animal and *in vitro* models, to its affinity for connective tissue, and/or to the relatively high concentration it reaches in serous fluids, the liver and intestinal walls, as demonstrated in autoradiographic studies in animals. In ulcerative colitis, clinical studies utilizing 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

In vivo studies have indicated that the absolute bioavailability of orally administered SSZ is less than 15% for parent drug. In the intestine, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Of the two species, SP is relatively well absorbed from the intestine and highly metabolized, while 5-ASA is much less well absorbed.

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: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine 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 metabolized to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized 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 feces. The calculated clearance of SSZ following intravenous administration was 1 L/hr. Renal clearance was estimated to account for 37% of total clearance.

5.3 Preclinical safety data

Two-year oral carcinogenicity studies were conducted in male and female F344/N rats and B6C3F1 mice. Sulfasalazine was tested at 84 (496 mg/m^2), 168 (991 mg/m^2) and 337.5 (1991 mg/m^2) mg/kg/day doses in rats. A statistically significant increase in the incidence of urinary bladder transitional cell papillomas was observed in male rats. In female rats, two (4%) of the 337.5 mg/kg rats had transitional cell papilloma of the kidney. The increased incidence of neoplasms in the urinary bladder and kidney of rats was also associated with an increase in the renal calculi formation and hyperplasia of transitional cell epithelium. For the mouse study, sulfasalazine was tested at 675 (2025 mg/m^2), 1350 (4050 mg/m^2) and 2700 (8100 mg/m^2) mg/kg/day. The incidence of hepatocellular adenoma or carcinoma in male and female mice was significantly greater than the control at all doses tested.

Sulfasalazine did not show mutagenicity in the bacterial reverse mutation assay (Ames test) or in the L51784 mouse lymphoma cell assay at the HGPRT gene. However, sulfasalazine showed equivocal mutagenic response in the micronucleus assay of mouse and rat bone marrow and mouse peripheral RBC and in the sister chromatid exchange, chromosomal aberration, and micronucleus assays in lymphocytes obtained from humans.

Impairment of male fertility was observed in reproductive studies performed in rats at a dose of 800 mg/kg/day (4800 mg/m^2). Oligospermia and infertility have been described in men treated with sulfasalazine. Withdrawal of the drug appears to reverse these effects.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

Refer to Outer Carton for shelf life.

6.2 Special precautions for storage

Store below 30°C.

6.3 Nature and contents of container

Bottle of 100's.

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017, US

SAL-SIN-0519/0
Date of Last Revision: May 2019