SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT
Salazopyrin Tablets, Salazopyrin EN Tablets enteric coated

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Ingredient: Sulfasalazine.

Each Salazopyrin uncoated tablet for oral administration contains 500 mg of sulfasalazine.

Each Salazopyrin EN coated gastro-resistant tablet for oral administration contains 500 mg of sulfasalazine.

For excipients, see Section 6.1

3. Pharmaceutical Form
Tablets: Yellow round tablets embossed “KPh” on one side and “101” and a score line on the other.

Enteric coated tablets: Yellow film-coated, ovoid gastro-resistant tablets embossed “Kph” on one side and “102” on the other.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications

Salazopyrin: Treatment of ulcerative colitis and Crohn’s disease.

Salazopyrin EN: For active rheumatoid arthritis which is not controlled by antiinflammatory drugs. Ulcerative colitis, Crohn’s disease and Pyoderma gangrenosum.

4.2. Posology and Method of Administration
The dosage of Salazopyrin should be individually adjusted according to the patient's tolerance and response to treatment.

EN-tabs must be swallowed intact, preferably after meals, and should not be crushed or broken.

Elderly Patients
No special precautions are necessary.

A) Ulcerative colitis
Adults
Severe Attacks
Salazopyrin 2-4 tablets four times a day may be given in conjunction with steroids as part of an intensive management regime. Rapid passage of the tablets may reduce effect of the drug.
Night-time interval between doses should not exceed 8 hours.

Moderate Attack
2-4 tablets four times a day may be given in conjunction with steroids.

For the EN tablets: Mild Attack: 2 tablets four times a day with or without steroids.

Maintenance Therapy
With induction of remission reduce the dose gradually to 4 tablets per day. This dosage should be continued indefinitely since discontinuance even several years after an acute attack is associated with a four fold increase in risk of relapse.
Children
The dose is reduced in proportion to body weight.
Acute Attack or relapse: 40- 60mg/kg per day
Maintenance Dosage: 20 - 30mg/kg per day

B) Crohn's Disease
In active Crohn's Disease, Salazopyrin should be administered as in attacks of ulcerative colitis (see above).

Systemic treatment of Rheumatoid Arthritis with sulfasalazine EN-tabs

Patients with rheumatoid arthritis, and those treated over a long period with NSAIDs, may have sensitive stomachs and for this reason enteric-coated Salazopyrin (EN-Tabs) are recommended for this disease, as follows:

Adults (Including Elderly):
The patient should start with one tablet daily, increasing his dosage by a tablet a day each week until one tablet four times a day, or two three times a day are reached, according to tolerance and response. Onset of effect is slow and a marked effect may not be seen for six weeks.
A reduction in ESR and C-reactive protein should accompany an improvement in joint mobility. NSAIDs may be taken concurrently with Salazopyrin.

Children (6 years or older):
30 to 75 mg/kg/day divided into 2 equal doses. Typically, the maximum dose is 2 g/day. To reduce possible gastrointestinal intolerance, begin with a quarter to a third of the planned maintenance dose and increase weekly until reaching the maintenance dose at one month (see Section 4.4 Special warnings and precautions for use).

4.3. Contraindications
i) Use in infants under the age of 2 years.
ii) Known hypersensitivity to sulfasalazine, its metabolites, or any other component of the product as well as sulfonamides, or salicylates.
iii) Porphyria.

4.4. Special warnings and special precautions for use
Complete blood counts, including differential white cell count, and liver function tests, should be performed before starting sulfasalazine 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. The patient should also be counselled to report immediately with the presence of clinical signs such as sore throat, fever, pallor, purpura, jaundice, malaise or unexpected non-specific illness during sulfasalazine treatment, this may indicate myelosuppression, hemolysis, or hepatotoxicity. Discontinue treatment with sulfasalazine while awaiting the results of blood tests.

Sulfasalazine should not be given to patients with impaired hepatic or renal function or with blood dyscrasias, unless the potential benefit outweighs the risk. Sulfasalazine should be given with caution to patients with severe allergy or bronchial asthma.

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

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.

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. 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). This can be normalised by administration of folic acid or folinic acid (leucovorin).

As with other sulfonamides, sulfasalazine may cause hemolysis in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

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

Sulfonamides bear certain chemical similarities to some oral hypoglycemic agents. Hypoglycemia has occurred in patients receiving sulfonamides. Patients receiving sulfasalazine and hypoglycemic agents should be closely monitored.

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

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**

Sulfasalazine and sulfapyridine are found in low levels in breast milk. 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 machinery**
The effect of sulfasalazine on the ability to drive and use machinery has not been systematically evaluated.

**4.8. Undesirable effects**
Overall, about 75% of ADRs occur within 3 months of starting therapy, and over 90% by 6 months. Some undesirable effects are dose-dependent and symptoms can often be alleviated by reduction of the dose.

**General**
Sulfasalazine is split by intestinal bacteria to sulfapyridine and 5-amino salicylate so ADRs to either sulfonamide or salicylate are possible. Patients with slow acetylator status are more likely to experience ADRs related to sulfapyridine. The most commonly encountered ADRs are nausea, headache, rash, loss of appetite and raised temperature.

**Specific**
The adverse reactions observed during clinical studies conducted with Sulfasalazine have been provided in a single list below by class and frequency (very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 to < 1/100). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in the list below.
<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Not known</td>
<td>Aseptic meningitis, Pseudomembranous colitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Common</td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Pancytopenia, Agranulocytosis, Aplastic anemia, Hemolytic anemia, Macrocytosis,</td>
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<tr>
<td></td>
<td></td>
<td>Megaloblastic anemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy,</td>
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<tr>
<td></td>
<td></td>
<td>methaemoglobinemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Anaphylaxis*, Serum sickness, polyarteritis nodosa,</td>
</tr>
<tr>
<td>Metabolism and nutrition system disorders</td>
<td>Not known</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dizziness, Headache, Taste disorders</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Aseptic meningitis, ataxia, Encephalopathy, Peripheral neuropathy, Smell disorders</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Common</td>
<td>Tinnitus</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Eye Disorders:</td>
<td>Common</td>
<td>Conjunctival and scleral injection</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Allergic myocarditis, Pericarditis, Cyanosis</td>
</tr>
<tr>
<td>Vascular Disorders:</td>
<td>Uncommon</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td>Common</td>
<td>Cough</td>
</tr>
<tr>
<td>disorders</td>
<td>Uncommon</td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Interstitial lung disease*, Eosinophilic infiltration, Fibrosing alveolitis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Gastric distress, Nausea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Abdominal pain, Diarrhea*, Vomiting* stomatitis</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Aggravation of ulcerative colitis* Pancreatitis parotitis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Hepatic failure*, Hepatitis fulminant*, Hepatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Alopecia, Urticaria</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Drug rash with eosinophilia and systemic symptoms (DRESS)* **, Epidermal necrolysis</td>
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<tr>
<td></td>
<td></td>
<td>(Lyell’s syndrome) <strong>, Stevens-Johnson syndrome</strong> <em>, Exantheama, Exfoliative dermatitis</em></td>
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<tr>
<td></td>
<td></td>
<td>Toxic pustuloderma, Lichen planus, Photosensitivity, Erythema, peri orbital oedema</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>Common</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>disorders</td>
<td>Not known</td>
<td>System lupus erythematosus, Sjogren’s</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Common</td>
<td>Proteinuria</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Nephrotic syndrome, Interstitial nephritis, Hematuria, Crystalluria**</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Not known</td>
<td>Reversible oligosperma**</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Common</td>
<td>Fever</td>
</tr>
<tr>
<td>conditions</td>
<td>Uncommon</td>
<td>Facial edema</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Yellow discoloration of skin and body fluids*</td>
</tr>
</tbody>
</table>
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), is still under investigation, but 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/m²), 168 (991 mg/m²) and 337.5 (1991 mg/m²) mg/kg/day doses in rats. In male rats, there was a statistically significant increase in the incidence of transitional cell papillomas in the urinary bladder. 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. In the mouse study, sulfasalazine was tested at 675 (2025 mg/m²), 1350 (4050 mg/m²) and 2700 (8100 mg/m²) mg/kg/day. There was a significant increase in the incidence of hepatocellular adenoma or carcinoma in male and female mice.

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 positive or equivocal mutagenic responses in the micronucleus assays 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/m²). 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. List of Excipients

- **Salazopyrin tablets:** Povidone, starch pregelatinized, magnesium stearate, silica colloidal anhydrous.
- **Salazopyrin EN tablets:** Povidone; starch pregelatinized; magnesium stearate; silica colloidal anhydrous; cellulose acetate phthalate; propylene glycol; beeswax white, carnauba wax, glycerol monostearate, talc, macrogol.

#### 6.2. Incompatibilities

Certain types of extended wear soft contact lenses may be permanently stained during therapy.

#### 6.3. Special Precautions for Storage

Store at room temperature, below 25°C. Bottles: Use within 6 months of first opening.

#### 6.4. Instruction for Use/Handling

Take with water

**Manufacturer:** KEMWELL AB, SWEDEN

**Authorization holder:** PFIZER PHARMACEUTICALS ISRAEL LTD, 9 SHENKAR ST, HERZELIYA