# National Agency for Food & Drug Administration & Control (NAFDAC)

# Registration & Regulatory Affairs (R & R) Directorate

# SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

## 1. NAME OF THE MEDICINAL PRODUCT
Avro-SP Tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Avro-SP contains 500 mg sulfadoxine and 25 mg pyrimethamine.
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Avro-SP tablet is a white, flat tablet with beveled edges, inscribed "AVRO" on one side and "SP" on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indication

Avro-SP tablet is indicated for intermittent preventive treatment (IPT) of malaria in pregnancy in the second and third trimester. Avro-SP is effective against strains of Plasmodium falciparum resistant to chloroquine.

### 4.2 Posology and method of administration

Intermittent preventive treatment in pregnancy:
Adults: 3 Tablets taken as a single dose.

The dose may be repeated once every 2 to 4 weeks. The last dose should be given not later than one month before the expected date of delivery.

### 4.3 Contraindications
Avro-SP is contra indicated in the first trimester of pregnancy and the period close to delivery because of the risk of kernicterus in the neonate.

It should not be given to patients with a history of hypersensitivity to sulphonamides and Pyrimethamine.
Avro-SP should not be given to patients with serious haematological disorders.
Use with caution in patients with hepatic disorder or folate deficiency due either to innate disease or malnutrition.
It should be used cautiously and in reduced dosage in patients with impaired renal function because of the risk of crystalluria.

### 4.4 Special warnings and precautions for use
Long-acting sulfonamides have been reported to cause erythema multiforme. Avro-SP contains sulfadoxine, a long acting sulfonamide. Patients should be advised that sore throat, fever, cough, dyspnoea or purpura may be the first signs of serious side effects.
The intake of Avro-SP must be stopped immediately at the first signs of skin eruptions, a significant decrease of blood cells, or a bacterial or fungal superinfection.
Because of the long half-lives of sulfadoxine and pyrimethamine the possibility of accumulation should be borne in mind. Care should be exercised in patients with hepatic and particularly renal impairment and dosage adjustments made if necessary.
The renal clearance of sulfadoxine varies with pH. A decrease of urinary pH from 7.5 to 5.5 decreased renal clearance by a factor of 2.
Excessive exposure to the sun must be strictly avoided. Regular blood counts are indicated whenever Avro-SP is administered for more than three months.
During prolonged administration of high doses, urinalysis and complete blood cell counts (CBCs), including platelet counts, should be performed periodically. Signs of folic acid deficiency can be prevented by administration of folinic acid.
Pyrimethamine has been reported to cause aplastic anaemia if used between courses of antineoplastic agents. This should be borne in mind when using Avro-SP.

*Carcinogenicity*
Pyrimethamine was not carcinogenic in female mice or in male and female rats. The carcinogenic potential of pyrimethamine in male mice could not be assessed from the study because of markedly reduced life-span. Long term carcinogenicity studies have not been conducted with sulfadoxine alone, or with sulfadoxine/pyrimethamine combined.

*Mutagenicity/Genotoxicity*
Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test in Salmonella typhimurium. No genotoxicity studies have been conducted with sulfadoxine alone or with sulfadoxine/pyrimethamine combined.

**4.5 Interactions with other medicinal products and other forms of interaction**
Anticoagulants, Methotrexate, Phenytoin: sulfadoxine/pyrimethamine May potentiate their effects.
Sulphonyl Urea antidiabetics: sulfadoxine/pyrimethamine may enhance their hypoglycaemic effect.
The use of compounds which render the urine acidic may increase the risk of crystalluria.
Pyrimethamine by its mode of action, may further depress folate metabolism in patients receiving treatment with other folate inhibitors. Occasionally reports suggest that individuals taking pyrimethamine at doses in excess of 25mg weekly may develop megaloblastic anaemia should a trimethoprim / sulphomamide combination be prescribed concurrently.
The concurrent administration of lorazepam and Pyrimethamine may induce hepatotoxicity. Use of Pyrimethamine with other folate antagonists such as co-trimoxazole, trimethoprim, methotrexate or phenytoin may exacerbate bone marrow depression.
Pyrimethamine may prolong the half-life of zidovudine if used concurrently. In-vitro studies in animals suggest that zidovudine could reduce the effectiveness of Pyrimethamine in the treatment of toxoplasmic encephalitis.
Convulsions have occured after concurrent administratiion of methotrexate and pyrimethamine to children with central nervous system leukaemia and cases of fatal bone marrow aplasia have been associated with the administration of daunorubicin, cytosine arabinoside and pyrimethamine to individuals suffering from acute myeloid leukaemia.

The hypoglycaemic effect of some sulfonylureas is enhanced by sulfonamides. Long acting sulfonamides may displace protein bound drugs, such as phenytoin, coumarin derivatives etc., and thus, enhance their toxicity. The urinary excretion of sulfonamides is pH dependent and can significantly influence their plasma half-life. Drugs containing the para-aminobenzoic acid nucleus (e.g. some local anaesthetics) competitively antagonise the effects of sulfonamides. Pyrimethamine may displace quinine from its protein binding site in the plasma. It can also potentiate the effects of folic acid antagonists e.g. methotrexate. Concomitant administration of sulfadoxine/pyrimethamine and trimethoprim or trimethoprim-sulfonamide combinations may intensify the impairment of folic acid metabolism and the related haematological side effects, and should therefore be avoided. There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with sulfadoxine/pyrimethamine as compared with the use of sulfadoxine/pyrimethamine alone.

**4.6 Pregnancy and lactation**

*Pregnancy*
Sulphadoxine/Pyrimethamine has been shown to be teratogenic in rats when given in weekly doses approximately 12 times weekly human prophylactic dose. A teratology study in rats showed the minimum oral teratogenic dose to be approximately 18/0.9 mg/kg/day sulfadoxine/pyrimethamine. In rabbits, no teratogenic effects were noted at oral doses as high as 400/20 mg/kg/day sulfdoxine/pyrimethamine. The use of antimalarials in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus. Prophylaxis in high risk situations is also justified. In pregnant women, limited prophylactic and therapeutic use of Sulphadoxine/Pyrimethamine did not indicate a risk of foetal damage. Nevertheless, Sulphadoxine/Pyrimethamine should be used in pregnancy only if it is absolutely essential, and only after the expected benefit has been weighed against the potential risk to the foetus. However, women of child bearing potential who are travelling to areas where malaria is endemic should be advised against becoming pregnant. In addition, they should be advised to practice contraception during treatment with Sulphadoxine/Pyrimethamine and for three months after the last dose.

Pyrimethamine may interfere with folic acid metabolism and if pyrimethamine is given during pregnancy, folic acid supplementation may be required. Sulfadoxine may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulfadoxine should therefore be avoided during the last month of pregnancy.

*Breastfeeding*
Sulfadoxine and pyrimethamine is excreted in breast milk. Sulfonamides may cause jaundice and haemolytic anaemia in the newborn. Avro-SP should not be given to pregnant women at term or breast feeding mothers. If Avro-SPe administration is considered essential, alternate arrangements should be made for feeding the infant.

*Fertility*
Fertility of male rats and the ability of male or female rats to mate were not adversely affected at doses of up to 210 mg/kg/day of sulfadoxine/pyrimethamine. The pregnancy rate of rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at doses of 31.5 mg/kg/day or higher, a dose approximately 30 times the weekly human prophylactic dose or higher. A 3-month gavage study rats showed delayed sperm maturation with 100/5 mg/kg/day of sulfadoxine/pyrimethamine and 15 mg/kg/day of pyrimethamine alone

**4.7 Effects on ability to drive and use machines**
Side effects of Sulfadoxine/pyrimethamine are not expected to affect attention or reduce co-ordination but care should be taken if the patient feels dizzy or balance is affected.

**4.8 Undesirable effects**
Mild adverse events associated with pyrimethamine/sulfadoxine involve the skin and mucous membranes. Serious cutaneous toxicity (Steven–Johnson syndrome) and hepatotoxicity may occur rarely.
The adverse events listed below are not based on adequately sized studies, but on literature data generally published after approval and for the use of each of these antimalarials in adults. Frequency estimates are highly variable across the studies and no frequencies are given for many events. Side effects most relevant to seasonal malaria prevention in children are shown in **bold**.
Adverse events reported with Sulfadoxine/pyrimethamine, are listed below by body system, organ class. Where they can be estimated, frequencies are defined as *very common* (≥ 1/10), *common* (1/100–1/10), *uncommon* (1/1000–1/100), *rare* (1/10 000–1/1000) or *very rare* (≤ 1/10 000).

*Gastrointestinal reactions*
glossitis, stomatitis, nausea, emesis, **abdominal pain**, **diarrhoea**, feeling of fullness
*Skin and subcutaneous tissue disorders*
photosensensitivity, **urticaria**, **pruritus**, exfoliative dermatitis, slight hair loss, Lyell's syndrome, erythema multiforme, Stevens-Johnson syndrome, **generalised skin eruptions**, toxic epidermal necrolysis
*General disorders*
**fever**, chills, periarteritis nodosa and lupus erythematosus phenomenon *Nervous system disorders*
**headache**, peripheral neuritis, convulsions, ataxia, hallucinations, insomnia, fatigue, muscle weakness, polyneuritis
*Psychiatric disorders*
depression, **nervousness**, apathy
*Blood and lymphatic disorders*
agranulocytosis, aplastic anaemia, megaloblastic anaemia, thrombocytopenia, leucopoenia, haemolytic anaemia, purpura, hypoprothrombinaemia, methaemoglobinaemia, and eosinophilia
*Cardiac disorders*
allergic myocarditis/pericarditis
*Ear and labyrinth disorders*
tinnitus, vertigo
*Endocrine disorders*
Sulfadoxine, a sulphonamide is similar to some diuretics (acetazolamide and the thiazides), and sulfonylurea hypoglycaemics. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulphonamide.
*Eye disorders*
periorbital oedema, conjunctival and scleral injection
*Hepatobiliary disorders*

hepatitis, hepatocellular necrosis, pancreatitis, transient rise of liver enzymes
*Immune system disorders*
hypersensitivity reactions, serum sickness, anaphylactoid reactions.
*Musculoskeletal and connective tissue disorders*
arthralgia
*Renal and urinary disorders*
renal failure, interstitial nephritis, blood-urea nitrogen and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria
*Respiratory disorders*
pulmonary infiltrates resembling eosinophilic or allergic alveolitis

**4.9 Overdose**
*Symptoms:* headache, anorexia, nausea, vomiting, agitation, convulsions, haematologic changes (megaloblastic anaemia, leucopoenia, thrombocytopenia), glossitis, crystalluria.
*Treatment:* the patient should be urgently transferred to a specialised unit for close monitoring and supportive therapy including, where appropriate, activated charcoal and fluid administration; a parenteral benzodiazepine, phenytoin or a barbiturate can be given for convulsions,. Liver and renal function should be monitored and blood counts checked repeatedly for up to four weeks after the overdose. Should blood dyscrasia occur, folinic acid (leucovorin) may be used.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Antimalarial
Pyrimethamine combinations. ATC code P01BD51
Pyrimethamine is a diaminopyrimidine. It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It has in vitro activity against the four long-established human malaria parasites. There has been rapid emergence of clinical resistance.
Sulfadoxine is a sulfonamide. Sulfonamides are competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the enzyme in *P. falciparum*, which is responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid. Therefore, by acting at a different step in folate synthesis, sulfadoxine increases the effect of pyrimethamine.
Strains of *P. falciparum* resistant to 4-aminoquinolines (chloroquine, amodiaquine) are present in many areas, and their geographical distribution is constantly changing. However, amodiaquine remains active against some chloroquine-resistant *P. falciparum* strains. *P. falciparum* can also become resistant to the effects of pyrimethamine/sulfadoxine.

**5.2 Pharmacokinetic properties**
***Pyrimethamine/sulfadoxime***
*Absorption*
Following single-dose administration of the pyrimethamine/sulfadoxine tablet in healthy volunteers (n = 46), the mean (± SD) Cmax value for sulfadoxine was 183 ± 18 µg/ml, and the corresponding value for AUC0-72hour was 11037 ± 1142 µg·hour/ml. The median (range) sulfadoxine tmax value was 5.5 hours (range 4–48 hours).
The mean (± SD) pyrimethamine Cmax value was 0.55 ±0.07 µg/ml, and the corresponding value for AUC was 29.8 ± 3.4 µg·hour/ml. The median (range) pyrimethamine tmax value was 5.5 hours (range 1–10 hours).
*Distribution*
The volume of distribution for pyrimethamine and sulfadoxine is 2.3 l/kg and 0.14 l/kg, respectively. Plasma protein binding is about 90% for both pyrimethamine and sulfadoxine. Both cross the placental barrier and pass into breast milk.
Pyrimethamine is transformed to several unidentified metabolites. About 5% of sulfadoxine appears in the plasma as acetylated metabolite, about 2 to 3% as the glucuronide.
*Elimination*
Pyrimethamine and sulfadoxine both have long elimination half-lives: about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both are eliminated mainly through the kidneys.

### 5.3 Preclinical safety data

*Genotoxicity*
Pyrimethamine was not found mutagenic in the Ames test.
*Carcinogenesis*
Pyrimethamine was not found carcinogenic in female mice or in male and female rats. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200–300 mg.
*Reproductive toxicity*
Testicular changes have been observed in rats treated with pyrimethamine/sulfadoxine 5/100 mg/kg daily and with 15 mg/kg/day of pyrimethamine alone. Fertility of male rats and the ability of male or female rats to mate were not adversely affected at pyrimethamine/sulfadoxine doses of up to 10/200 mg/kg daily. The pregnancy rate of female rats was not affected following treatment with 10.5 mg/kg daily, but was significantly reduced at doses of 31.5 mg/kg daily or higher. Pyrimethamine/sulfadoxine was teratogenic in rats when given in weekly doses about 12 times the normal human dose.
Sperm motility and sperm count were significantly decreased in pyrimethamine-treated male mice, and their fertility rate fell to zero.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients
Sodium Starch Glycollate
Maize Starch
Docusate Sodium
Avicel PH 101
Magnesium Stearate

### 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
Alu/PVC blister containing three Tablets.

### 6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. Applicant/manufacturer
Avro Pharma Limited
Daid House, Plot 2, Block J, Limca Way,
Isolo Industrial Estate, Oshodi-Apapa Expressway,
Isolo, Lagos State, Nigeria
Email: avro@rumon-org.com