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® Sulphadoxine/Pyrimethamine + Amodiaquine (SPAQ) Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sulfadoxine/pyrimethamine tablet contains 500 mg sulfadoxine and 25 mg pyrimethamine.
Each amodiaquine tablet contains 150 mg amodiaquine (as hydrochloride).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pyrimethamine/sulfadoxine tablets are white round tablets, debossed with "SP" and a scoreline on single side. The score-line is to facilitate breaking for ease of administration.
Amodiaquine tablets are tablets yellow-coloured tablets debossed and a scoreline on single side. The score-line is to facilitate breaking for ease of administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

AVRO® sulfadoxine/pyrimethamine + amodiaquine is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in children aged 12–59 months, provided that amodiaquine and pyrimethamine/sulfadoxine retain sufficient antimalarial efficacy.

4.2 Posology and method of administration

Children aged 3–59 months
Treatment should start at the beginning of the high transmission period and is given in 3-day courses as follows:

AGE	DAY 1	DAY 2	DAY 3
3 to 11 Months	Half tablet of Sulphadoxine/Pyrimethamine And Half Tablet of Amodiaquine as a single dose	Half Tablet of Amodiaquine as a single dose	Half Tablet of Amodiaquine as a single dose
12 to 59 Months	One tablet of Sulphadoxine/Pyrimethamine And One Tablet of Amodiaquine as a single dose	One Tablet of Amodiaquine as a single dose	One Tablet of Amodiaquine as a single dose

The 3-day course is repeated after 1 month, for a maximum 4 courses during the high-transmission period.

Method of administration
Tablets for oral administation.
The tablets should be dispersed in little water and administered to the child with a spoon (3 to 11 months) or a cup (12 months to 5 years).
If a child vomits the dose within 30 minutes, the child should be allowed to rest for 10 minutes and a replacement dose given

It is important that the child receives the full 3-day course. Missing a course reduces protection but does not prevent the child receiving the next course.

WARNING:

This medicine is for prevention of malaria and not for treatment of children sick with malaria. Do not give to children who have fever or who are sick from malaria or other conditions.

Only recommended doses should be taken except otherwise directed by a physician.

4.3 Contraindications

Sulfadoxine/pyrimethamine + amodiaquine tablets are contraindicated in a child with:

- Hypersensitivity to any of the active ingredients to sulfonamide drugs or to any of the excipients (see section 6.1)
- History of blood disorders with amodiaquine or pyrimethamine/sulfadoxine
- History of liver injury with amodiaquine.
- Patients with severe impairment of liver or kidney function.
- Patients with serious haematological disorders.
- Patients with folate deficiency due either to innate disease or malnutrition.

4.4 Special warnings and precautions for use

Acute illness

Sulfadoxine/pyrimethamine + amodiaquine should not be given if the child has an acute illness. If the child has malaria, specific treatment should be given according to recent official guidelines.

Increased adverse effects

To avoid excessive effects, Sulfadoxine/pyrimethamine + amodiaquine should not be given if the child:

- has received pyrimethamine/sulfadoxine or amodiaquine in the past 30 days
- is HIV-positive and is receiving sulfamethoxazole/trimethoprim prophylaxis

Hypersensitivity reactions

Because of a rare risk of severe hypersensitivity reactions (see section 4.3), treatment with Sulfadoxine/pyrimethamine + amodiaquine should be stopped if a child develops a rash or urticarial reaction.

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant use of Sulfadoxine/pyrimethamine + amodiaquine with trimethoprim, or sulfonamide/trimethoprim, or another sulfonamide can increase antifolate effect and haematological side effects, and should be avoided.

The risk of hepatic and haematological adverse effects may increase if Sulfadoxine/pyrimethamine + amodiaquine is given with other drugs with hepatic or haematological toxicity.

4.6 Fertility, pregnancy and lactation

Seasonal malaria prevention with Sulfadoxine/pyrimethamine + amodiaquine is indicated for children aged 3 to 59 months and effects on pregnancy and lactation are not relevant.

Pregnancy

Sulfadoxine/pyrimethamine + amodiaquine is not indicated for pregnant women.

The safety of amodiaquine in pregnant women has not been established in formal studies but many years of experience with amodiaquine does not indicate teratogenicity. Pyrimethamine/sulfadoxine is recommended for intermittent preventative treatment in pregnancy in many countries.

Sulfadoxine/pyrimethamine + amodiaquine has been found effective for the treatment of malaria in pregnancy in West Africa and in Tanzania.

Sulfadoxine/pyrimethamine + amodiaquine should not be used during the first trimester of pregnancy unless the benefit is considered to outweigh the risks and alternative drugs are not available.

Breastfeeding
Sulfadoxine/pyrimethamine + amodiaquine is not indicated for breastfeeding women. No studies are available in breastfeeding women.

Fertility
Animal data showed that pyrimethamine impaired fertility (see section 5.3). There are no fertility data in humans.

4.7 Effects on ability to drive and use machines
Sulfadoxine/pyrimethamine + amodiaquine is indicated for children aged 3 to 59 months and effects on driving and use of machines are not relevant. Side effects are not expected to affect attention or reduce co-ordination but care should be taken if the child feels dizzy or balance is affected.

4.8 Undesirable effects
Of the mild adverse events associated with amodiaquine, the most common are vomiting, abdominal pain, fever, diarrhoea, itching, headaches and rash. Aplastic anaemia and fatal hepatotoxicity are rarely associated with weekly prophylactic use of amodiaquine; such events have not been reported with use of amodiaquine for seasonal malaria chemoprophylaxis (see also section 5.1).
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 + amodiaquine, 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).

Amodiaquine
Nervous system disorders
Very common: weakness, **headache**, dizziness
Rare: neuromyopathy
Gastrointestinal disorders
Very common: anorexia, nausea, **vomiting**, **abdominal pain**, **diarrhoea**
Skin and subcutaneous disorders
slate-grey pigmentation, notably of the fingers and mucous membranes (usually associated with malaria treatment rather than seasonal chemoprophylaxis)
Common: **pruritus**
General disorders and administration site conditions
Common: **fever**
Eye disorders
transient accommodation disorders, corneal opacity (usually associated with malaria treatment rather than seasonal chemoprophylaxis) which reverses on stopping treatment
Very rare: irreversible retinopathy requiring care from eye specialist
Blood and lymphatic disorders
leucopoenia and neutropenia (agranulocytosis)—but see notes above
Hepato-biliary disorders
severe and sometimes fatal hepatitis but see notes above—development of hepatic disorders may be delayed

Pyrimethamine/sulfadoxine
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
Amodiaquine
Symptoms: headache, dizziness, visual disorders, cardiovascular collapse and convulsions, followed by early respiratory and cardiac arrest
Treatment: the patient should be urgently transferred to a specialised unit for close monitoring and supportive therapy.
Pyrimethamine/sulfadoxine
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
Amodiaquine ATC code: P01BA06
Pyrimethamine combinations. ATC code P01BD51
Amodiaquine is a synthetic 4-aminoquinoline antimalarial. It has schizonticidal action on *Plasmodium falciparum*, *P. vivax*, and *P. ovale* by destroying intraerythrocytic forms.
The mechanism of action of 4-aminoquinoline derivatives like amodiaquine against plasmodium is not yet completely known. It is nonetheless accepted that these derivatives penetrate the infected red blood cells and prevent the parasite from polymerising haeme into an insoluble product called haemozoin, leading to parasite death.
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.

Clinical efficacy
Three randomised placebo-controlled studies have looked at the efficacy of seasonal malaria prevention with amodiaquine + pyrimethamine/sulfadoxine added to other measures such as insecticidal bed-nets or home malaria management. Over 7300 children aged 3–59 months participated in the studies, all in west Africa. The protective efficacy, measured as the incidence of malaria, ranged from 66 to 82%.
A previous study had compared regimens containing pyrimethamine/sulfadoxine with either artesunate or amodiaquine in 2102 children. The incidence of malaria was lowest (5%) among children who received amodiaquine + pyrimethamine/sulfadoxine compared to those receiving artesunate-based regimens (9–11%).

5.2 Pharmacokinetic properties

Amodiaquine
Absorption
After oral administration, amodiaquine is quickly absorbed and metabolised into its main active form, desethylamodiaquine. The absolute bioavailability of amodiaquine is not known.
Following single-dose administration of three Amodiaquine Hydrochloride Tablets (i.e. 450 mg amodiaquine base) in healthy volunteers, the mean (± SD) amodiaquine Cmax value was 30.3 ± 12.6 ng/ml and the corresponding value for AUC0-t was 309.4 ± 76.0 ng·hour/ml. The median (± SD) amodiaquine tmax value was 0.91 ± 1.13 hours.
Distribution
The volume of distribution of amodiaquine is estimated at 20–40 l/kg. Desethylamodiaquine, the main metabolite of amodiaquine, is assumed to be the main active form. It is mainly found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4–6 times higher than in plasma.

Metabolism
The hepatic first-pass metabolism of amodiaquine is high, with formation of the active metabolite, desethylamodiaquine, presumably via the CYP2C8 isoenzyme. Further metabolism includes oxidation and glucuronidation.
Elimination
Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Desethylamodiaquine is eliminated slowly with a terminal half-life of 9–18 days.

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

Amodiaquine
General toxicity
Single dose toxicity studies reported a LD50 (mouse intraperitoneal) of 225 mg/kg; LD50 (mouse oral) of 550 mg/kg and a LD0 (mouse intraperitoneal) of 137 mg/kg. Histopathological changes (pigmentation) were seen in the heart at 30 mg/kg/day in rats. The statistically significant effects seen in vitro on ion channels in the heart at 0.1 µM in the hERG current (expressed in human embryonic kidney cells) as well as the increase in QRS complex and QT interval durations at concentrations higher than 0.1 µM in the isolated rabbit Purkinje fibres appeared to be due to a non-specific multi-ion channel blockade. Transient prolongation of QT interval was observed at 30 mg/kg given orally. This dose corresponds to about twice the maximum recommended therapeutic dose. At a dose of 100 mg/kg given orally (about 6.7-fold the maximum recommended therapeutic dose), slight respiratory depressant and natriuretic effects occurred. Pigmentation was also seen in liver, kidney and thyroid glands in rats as well as in kidneys, liver and lymph nodes in dogs (at doses of 25 mg/kg daily). Also an increase in haemosiderosis in the spleen and bone marrow as well as thymus lymphoid depletion were observed.
Genotoxicity
In vitro (Ames test) and in vivo tests (sister chromatid exchange and chromosome aberration tests) showed that amodiaquine, like chloroquine, has both, a mutagenic and a clastogenic potential.
Carcinogenicity
No studies on the carcinogenic potential of amodiaquine have been conducted.
Reproductive toxicity
No data on toxicity on the reproductive system and embryofetal development is available for amodiaquine alone. The combination of amodiaquine and artesunate did not demonstrate any particular effects on fertility or associated parameters. In the peri-postnatal study, the offspring from the F1 generation did not show any effect on sexual development, and despite an early slowing of bodyweight

increases with some effect on testicular and epididymal weights, no sequelae were noted on reproductive capacity.

Pyrimethamine/sulfadoxine

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

Amodiaquine tablets

Crospovidone, Maize Starch, Microcrystalline Cellulose, Aspartame Powder, Stearic Acid Powder,

Pyrimethamine/sulfadoxine tablets

Povidone K.30, Crospovidone, microcrystalline cellulose, Aspartame Powder, Stearic Acid Powder

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Colourless transparent PVC/Al blister containing three Amodiaquine (as hydrochloride) 150 mg Tablets and three Pyrimethamine/Sulfadoxine 25 mg/500 mg Tablets.

6 X 25 blister cards per box.

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

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