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

# Registration & Regulatory Affairs (R & R) Directorate

# SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

/Instructions in this font/colour are from the World Health Organisation Public Assessment Report WHOPAR guidelines.]

## 1. NAME OF THE MEDICINAL PRODUCT

**PRODUCT NAME:** Amodiaquine (as hydrochloride) 150 mg + Sulfadoxine/Pyrimethamine 500/25mg Dispersible Tablets

**BRAND NAME:** SUPYRA DISPERSIBLE

Co blister of- 3 Dispersible tablets of Amodiaquine + 1 Dispersible tablet Sulfadoxine/Pyrimethamine

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**PRODUCT NAME:** Sulfadoxine/Pyrimethamine (500/25mg) Dispersible Tablets

Each uncoated dispersible tablet contains:
Sulfadoxine Ph.Eur……..500 mg
Pyrimethamine Ph.Eur…….25 mg
Excipients……q.s.
For complete list of excipients refer section 6.1.

- Contains Isomalt 51.00 mg per tablet
- Total Sodium content per tablet 0.133 mMol

**PRODUCT NAME:** Amodiaquine 150 mg Dispersible Tablets

Each uncoated dispersible tablet contains :

Amodiaquine Hydrochloride equivalent to Amodiaquine …….150 mg

Excipients……q.s.
For complete list of excipients refer section 6.1.

- Contains Mannitol 35.00 mg per tablet
- Total Sodium content per tablet 0.205 mMol

## 3. PHARMACEUTICAL FORM:

Solid oral dosage form: dispersible tablets

Amodiaquine Dispersible Tablets

Pale yellow to yellow, mottled circular, biconvex, uncoated tablets with break-line on one side and plain on other side.

Tablet having functional scoring which can be divided into equal halves.

Sulfadoxine/Pyrimethamine Dispersible Tablets

White to off white, flat beveled edged, uncoated dispersible tablets, debossed with "525" on one side and with breakline on other side.

Tablet having functional scoring which can be divided into equal halves.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indication:

SUPYRA DISPERSIBLE is seasonal malaria chemoprevention drugs indicated for malaria prevention during the malaria transmission season in children aged 12-59 months.

**4.2 Posology and method of administration:**

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

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

Children aged 12-59 months

| Dose (children aged 12-59 months) | | |
|---|---|---|
| | Sulfadoxine/pyrimethamine Dispersible tablet (500 mg/25mg) | Amodiaquine Dispersible Tablet (150 mg) |
| Day 1 | 1 tablet | 1 tablet |
| Day 2 | NA | 1 tablet |
| Day 3 | NA | 1 tablet |

Method of administration

- First day both tablets Sulfadoxine/pyrimethamine Dispersible tablet and Amodiaquine Dispersible Tablet should be administered separately, Sulfadoxine/pyrimethamine Dispersible tablet followed by Amodiaquine Dispersible Tablet.
- Put each tablet into the cup with a little of water (about 10 ml).
- Stir gently until a uniform suspension is obtained and administer to the child within 5 minutes.
- Then rinse with water about 10 ml, administer now. Make sure the child drinks all the medicine.

If your child vomits within 30 minutes of taking the tablet then you may need to give another tablet. Wait for 10 minutes before giving the replacement dose. If you have any questions on the use of this medicine, ask your health care provider.
There should be a gap of 1 month between the courses.

**Children aged under 12 months**

Dividing SUPYRA DISPERSIBLE tablets into two has been shown to result in half the dose and the tablets are therefore suitable for use in children aged between 3-12 months.

**4.3 Contraindications:**

These tablets are contraindicated in a child with:
- Hypersensitivity to any of the active ingredients or to any of the excipients.
- History of blood disorders with amodiaquine or Sulfadoxine/Pyrimethamine.
- History of liver injury with amodiaquine.

**4.4 Special warning and precautions for use**

Acute illness

- These tablets should not be given if the child has an acute illness.
- If the child has malaria, specific treatment should be given according to current official guidelines.

Increased adverse effects

To avoid excessive effects, these tablets should not be given if the child:

- Has received Sulfadoxine / Pyrimethamine or amodiaquine in the past 30 days.
- Is HIV-positive and is receiving sulfamethoxazole/ trimethoprim for prophylaxis.

Hypersensitivity reactions

Because of a rare risk of severe hypersensitivity reactions, treatment with these tablets should be stopped if a child develops a rash or urticarial reaction.

Sugar intolerance : SUPYRA DISPERSIBLE contains Isomalt :

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

**4.5 Drug Interactions**

Concomitant use of these tablets 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 tablets + Amodiaquine dispersible tablets are given with other drugs with hepatic or haematological toxicity.

**4.6 Pregnancy & Lactation**

Seasonal malaria prevention with these tablets is indicated for children aged 3- 59 months and effects on fertility, pregnancy and lactation are not relevant.

**4.7 Effects on ability to drive and use machines:**

These tablets are indicated for children aged up 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.

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

  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

Sulfadoxine / Pyrimethamine

- 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, generalized 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 anemia, 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, anaphylactic 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 specialized unit for close monitoring and supportive therapy.

Sulfadoxine / Pyrimethamine

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 polymerizing 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 schizonticide 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**

**Amodiaquine**

**Absorption**

After oral administration, amodiaquine is quickly absorbed and metabolized into its main active form, desethylamodiaquine. The absolute bioavailability of amodiaquine is not known.

**Distribution**

The volume of distribution of amodiaquine is estimated at 20–40 l/kg

**Metabolism**

The hepatic first-pass metabolism of amodiaquine is high.

**Elimination**

Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine.

**Sulfadoxine / Pyrimethamine**

**Absorption**

Following single-dose administration of the Sulfadoxine / Pyrimethamine tablet in healthy volunteers (n = 46), the mean (± SD) Cmax value for sulfadoxine was 183 ± 18 µg/ml, and the corresponding value for $AUC_{0\text{-}72hour}$ was 11037 ± 1142 µg·hour/ml. The median (range) sulfadoxine tmax value was 5.5 hours (range 4–48 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.

**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:**

**With reference to available literatures.**

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

Sulfadoxine/Pyrimethamine (500/25mg) Dispersible Tablets
List of Excipients:
Methacrylic Acid-Methyl Methacrylate Copolymer, Povidone, Polyethylene Glycol, Isomalt, Sodium bicarbonate, Citric acid Monohydrate, Sucralose, Flavour orange SD, Silica colloidal anhydrous, Crospovidone, Sodium Stearyl fumarate.

Amodiaquine 150mg Dispersible Tablets
List of Excipients:
Magnesium Hydroxide, Silica colloidal anhydrous, Mannitol, Crospovidone, Polysorbate 80, Sodium Bicarbonate, Citric acid Monohydrate, Sucralose, Flavour Orange SD, Purifed talc, Sodium Stearyl fumarate.

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf Life

Proposed shelf life of 24 Months.

### 6.4 Special precautions for storage:

Do not store above 30°C.
Avoid excursion above 30°C.
Store tablet in blister in the provided carton in order to protect from light.
Keep the medicine out of reach of children.

### 6.5 Nature and contents of container

3 dispersible tablets of Amodiaquine + 1 dispersible tablet of Sulfadoxine/pyrimethamine in a ALU – PVC/PVDC blister pack

a) Such 25 blisters in a carton with insert or
b) Such 50 blisters in a carton with insert

### 6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirement

## 7. APPLICANT

**Manufactured by:**

S Kant
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