SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

WIMAL PLUS ADULT TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Co-blister pack contains:
One Sulfadoxine and Pyrimethamine Dispersible Tablet 500/25mg
Each Dispersible Tablet contains
Sulfadoxine……. 500mg
Pyrimethamine……25mg

Excipients with known effect
Product contains Lactose Monohydrate.

Three Amodiaquine (as Hydrochloride) Dispersible Tablets 150mg
Each dispersible tablet contains
Amodiaquine Hydrochloride 196mg
Equivalent to Amodiaquine… … … … … … … … … … 150mg.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sulfadoxine and Pyrimethamine Dispersible Tablets description: White to off-white, round shaped flat bevel edged tablet, Scored on one side and plain on the reverse.

Amodiaquine (as Hydrochloride) dispersible Tablets description: yellow, round shape flat, bevel edged tablet, plain on one side and scored on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This product is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SCM) in children aged 12-59 months.

4.2 Posology and method of administration

Children aged 12-59 months

Treatment should start at the beginning of the high transmission period and is

given in 3day courses as follows,

	Dose (child aged 12 -59 months)	
	Amodiaquine (as Hydrochloride) Dispersible tablet 150mg	Sulfadoxine and Pyrimethamine Dispersible Tablet 500/25mg
Day 1	1 Tablet	1 Tablet
Day 2	1 Tablet	
Day 3	1 Tablet	

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

Method of administration

The tablets should not be broken.

The tablets should be dispersed in water.

Doses on day 1 should be given under the supervision of the health care provider, whereas doses on days 2 and 3 (amodiaquine only) can be taken by the patient at home.

For administration of Wimal Plus Junior on the first day of treatment, there is a need for two clean cups or glasses, and (depending on the patient's age) either 1 or 2 tablets of amodiaquine dispersible tablets, and either 1 or 2 tablets sulfadoxine/pyrimethamine dispersible tablets:

For children aged 1 to 5 years, add approximately 10 mL of drinking water into each cup/glass; o Place 1 amodiaquine dispersible tablet into one cup/glass, and 1 sulfadoxine/pyrimethamine dispersible tablet into the other cup/glass;

For children aged 5 to 10 years, add approximately 20 mL of drinking water into each cup/glass; o Place 2 amodiaquine dispersible tablets into one cup/glass, and 2 sulfadoxine/pyrimethamine dispersible tablets into the other cup/glass;

The cups/glasses should be gently swirled until the tablets disperse and the contents are fully mixed, and then taken immediately;

Rinse the cups/glasses with about another 10 mL of drinking water and have the patient drink the contents to be sure that the whole dose is taken.

For administration of Wimal Plus Adult on the second and third day of treatment only one clean cup or glass is needed and either 1 or 2 tablets of amodiaquine (depending on the patient's age):

For children aged 1 to 5 years, add approximately 10 mL of drinking water into the cup/glass; o Place 1 amodiaquine dispersible tablet into the cup/glass;

For children aged 5 to 10 years, add approximately 20 mL of drinking water into the cup/glass; o Place 2 amodiaquine dispersible tablets into the cup/glass;

The cup/glass should be gently swirled until the tablet disperses and the contents are fully mixed, and then taken immediately by the patient;

Rinse the cup/glass with about another 10 mL of drinking water and have the patient drink the contents to be sure that the whole dose is taken. If a patient vomits the dose within 30 minutes, they should rest for 10 minutes and a replacement dose taken.

If a patient vomits the dose within 30 minutes, they should rest for 10 minutes and a replacement dose taken

4.3 Contraindications

WIMAL PLUS ADULT is contraindicated in children

who is hypersensitive to any of the active substances, to sulfonamide drugs or to any of the excipients of Wimas plus adult (see section 6.1)
with an acute febrile illness or a severe illness;
taking co-trimoxazole (e.g. HIV-positive child receiving co-trimoxazole prophylaxis);
who has received a dose of either amodiaquine or pyrimethamine/sulfadoxine during the previous 4 weeks;
with a history of blood disorders with amodiaquine or pyrimethamine/sulfadoxine;
with documented megaloblastic anaemia due to folate deficiency;
with liver disease;
with retinopathy

4.4 Special warnings and precautions for use

Acute illness
Wimas Plus Adult should not be given if the patient has an acute illness. If the patient has malaria, specific treatment should be given according to the most recent official guidelines.

Renal or hepatic impairment
Caution should be exercised in children with renal or hepatic impairment.

Hypersensitivity reactions
Because of a rare risk of severe hypersensitivity reactions (see section 4.3), treatment with Wimas Plus Adult should be stopped if a patient develops a rash or urticarial reaction.

Excipients
Wimas Plus adult contains lactose. Children with congenital lactase deficiency, galactosaemia or glucosegalactose intolerance must not be given this medicine unless strictly necessary. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other children.
Wimas Plus adult contain 24.4 mg sodium, equivalent to 1, 22% of the WHO recommended maximum daily intake of 2 g sodium for an adult. It is important to consider the contribution of excipients from all the medicines that the patient is taking

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of this product 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 it is given with other drugs with hepatic or haematological toxicity.

Seasonal malaria chemoprevention is not recommended for individuals receiving other forms of malaria chemoprevention (e.g. mass drug administration [MDA] or perennial malaria chemoprevention [PMC]).

Concomitant administration of Wimas Plus adult is not recommended with:
medicines that inhibit the liver enzymes cytochrome (CYP) 2A6 (e.g., some beta-blockers, antidepressants, and antipsychotic drugs);
medicines that inhibit CYP2C8 (e.g. trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast).

4.6 Pregnancy and lactation

Seasonal malaria prevention with this product is indicated for children aged up to 59 months and effects on pregnancy and lactation are not relevant.

Pregnancy
The safety of amodiaquine in pregnant women has not been established in formal studies but many years of experience with amodiaquine do not indicate reproductive toxicity.
Pyrimethamine/sulfadoxine showed reproductive toxicity in animal studies (see 5.3).
Amodiaquine + pyrimethamine/sulfadoxine should not be used during the first trimester of pregnancy unless the benefit is considered to outweigh the risks and alternative medicines are not available.
During second or third trimesters of pregnancy, Wimal Plus Adult may be used for intermittent preventive treatment in pregnancy.

Breastfeeding
Amodiaquine does not appear to be excreted in appreciable amounts in the breast milk. Pyrimethamine is excreted in human milk. Some sulfonamides are excreted in human milk.
Sulfonamides should be avoided in premature infants and in infants with hyperbilirubinaemia or glucose-6- phosphate dehydrogenase deficiency. Except for the preceding conditions, Wimal Plus Adult can be used during breastfeeding.

Fertility
No human data on the effect of Wimal Plus Adult on fertility are available. Animal data showed that pyrimethamine impaired fertility. Amodiaquine showed effects on spermatogenesis (see section 5.3).

4.7 Effects on ability to drive and use machines

Side effects are not expected to affect attention or reduce co-ordination but undesirable effects such as dizziness may occur, in which case patients should not drive or use machines.

4.8 Undesirable effects

Of the mild adverse events associated with amodiaquine, the most common are vomiting, abdominal pain, fever, diarrhea, itching, headaches and rash. Aplastic anemia 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 (Stevens–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 Wimas Plus Adult 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)

Hepato-biliary disorders
severe and sometimes fatal hepatitis; 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, methemoglobinaemia, 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 icterus

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

'**Reporting of suspected adverse reactions:**
Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'

4.9 Overdose

Amodiaquine (as hydrochloride)
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

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 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 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. P. falciparum can become resistant to the effects of sulfadoxine/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 (as hydrochloride)
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. 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.

Elimitation:
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.

Parameter	Pyrimethamine	Sulfadoxine	Amodiaquine
Absorption – Oral bioavailability	NA*	NA*	NA*
Absolute bioavailability	NA*	NA*	Amodiaquine is metabolized to its main active form, desethylamodiaquine.
Food effect	–	–	The Cmax and AUC(0-t) of the active metabolite desethylamodiaquine increased 18% and 12% respectively with a high-fat meal, compared to

			fasting.
Distribution – Volume of distribution (mean)	2.3 L/kg	0.14 L/kg	20 to 40 L/kg
Plasma protein binding in vitro	90%	90%	>90% (amodiaquine as well as desethylamodiaquine)
Tissue distribution	Widely distributed. Crosses the placental barrier and excreted in breast milk	Widely distributed. Crosses the placental barrier and excreted in breast milk	Distributed into red blood cells; blood/plasma ratio is 4–6
Metabolism	Transformed to several unidentified metabolites.	5% acetylated; 2–3% glucuronated	Metabolism of amodiaquine into the active metabolite, desethylamodiaquine, by CYP2C8
Active metabolite(s)	–	–	Desethylamodiaquine; further metabolized by oxidation and glucuronidation
Elimination half-life	100 hours	200 hours	Amodiaquine: 12 h; Desethylamodiaquine: 9–18 days
Mean systemic clearance (Cl/F)	NA*	NA*	Amodiaquine: 1.1 L/h*
% of dose excreted in urine	NA*	Approximately 60% is present as the acetyl derivative and 10% as the glucuronide	2% excreted unchanged
% of dose excreted in faeces	–	–	–
Pharmacokinetic linearity	NA*	NA*	Linear PK over the 200–600 mg dose range
Drug interactions – Transporters	–	–	–
Drug interactions – Metabolizing enzymes	–	May inhibit CYP2D6	—
Special populations – Renal impairment	In patients with renal insufficiency, delayed elimination of sulfadoxine and pyrimethamine is expected.	Same	—

Special populations – Pregnant women	During pregnancy, sulfadoxine clearance is increased. Pyrimethamine is not significantly affected.	Same	—

Sulfadoxine and Pyrimethamine:

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 t max value was 5.5 hours (range 1–10 hours).

Distribution
The volume of distribution for sulfadoxine and pyrimethamine is 0.14 l/kg and 2.3 l/kg, respectively. Plasma protein binding is about 90% for both sulfadoxine and pyrimethamine. Both cross the placental barrier and pass into breast milk.

Metabolism
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
The elimination half-lives are about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both are eliminated mainly through the kidneys.

Pharmacokinetic variable	Pyrimethamine	Sulfadoxine	Amodiaquine
Maximum concentration (Cmax)	207 ± 30 ng/mL	78.9 ± 12.8 µg/mL	8634 ± 3758 pg/mL
Area under the curve (AUC0–72h)	10890 ± 1508 ng·h/mL	4438 ± 509 µg·h/mL	86151 ± 40416 pg·h/mL
Time to attain maximum concentration (tmax)	3.54 ± 1.85 h	4.18 ± 1.62 h	1.27 ± 1.23 h

5.3 Preclinical safety data

Amodiaquine

General toxicity Non-clinical data reveal no special hazard for humans not

already covered in other sections of the SmPC, based on conventional studies of safety pharmacology and repeated dose toxicity.

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 Treatment of rats with amodiaquine caused disruption of the blood-testis barrier and germ cell apoptosis without affecting body weight. The adverse effects on spermatogenesis were reversible when treatment was discontinued.

Pyrimethamine/sulfadoxine

Genotoxicity

Pyrimethamine was not found mutagenic in the Ames test. 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.

Carcinogenesis

Pyrimethamine was not found carcinogenic in female mice or in male and female rats

Reproductive toxicity

Sperm motility and count were significantly decreased in pyrimethamine-treated male mice, and their fertility rate fell to zero. These adverse effects were reversible when pyrimethamine was discontinued. Testicular changes have been observed in rats treated with pyrimethamine/sulfadoxine. 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amodiaquine (as hydrochloride) Dispersible Tablets contains:
Microcrystaliine Cellulose
Croscarmelose Sodium,Silica

Colloidal Anhydrous
Cross Povidone
Sucralose
Vanilla flavor
Purified Talc
Magnesium Stearate
Sodium Bicarbonate
Maize Starch.

Sulfadoxine and Pyrimethamine Dispersible tablet contains:
Lactose monohydrate (Pharmatose 200m)
Microcrystalline cellulose (102)
Sodium bicarbonate
Magnesium stearate
Maize starch
Sucralose
Povidone (PVP K 30)
Silica colloidal Anhydrous
Croscarmellose sodium (Ac – Dc-sol)
Orange flavour
Purified Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.Protect from light and moisture Store the tablets in blisters in the provided box or carton. Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date stated on the carton or blister card, after 'EXP'. The expiry date refers to the last day of that month.
Do not use this medicine if you notice visible signs of deterioration.

6.5 Nature and contents of container

Primary Packing:

Tablets are packed in Alu/PVDC opaque co-blisters containing one Sulfadoxine and Pyrimethamine Dispersible Tablet 500/25mg + Three Amodiaquine (as hydrochloride) Dispersible Tablets 150mg.

Secondary pack size:
25 blisters in a carton (25x4's) 30 blisters in a carton (30x4's) 50 blisters in a carton (50x4's)

6.6 Special precautions for disposal

Do not throw away any medicines in wastewater or household waste. Ask your health care provider how to throw away medicines you no longer use. These measures will help protect the environment.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

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8. MARKETING AUTHORIZATION NUMBER

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9. DATE OF PREQUALIFICATION/RENEWAL OF PREQUALIFICATION

09/23/2021

10. DATE OF REVISION OF THE TEXT

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