SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

WIMAL 500/25 TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Dispersible Tablet contains
Sulfadoxine……. 500mg
Pyrimethamine……25mg

Excipient of known effect
Each tablet contains Lactose Monohydrate Ph. Eur.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White to off-white, round shaped flat bevel edged tablet, Scored on one side and plain on the reverse.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sulfadoxine and pyrimethamine Dispersible Tablets are used to prevent malaria in pregnant women as of week 13 of pregnancy and it can also be used for prevention in children aged less than 12 months.

The health care provider will use the most recent official guidelines on the use of malaria medicines to check that the medicine is the right one and on when to start giving it to you and your child.

4.2 Posology and method of administration

Sulfadoxine and pyrimethamine Dispersible Tablets should ideally be administered as directly observed therapy (DOT).

IPTp (Intermittent Preventive Treatment in pregnant women)
Pregnancy
The usual dose is 1500mg/75 mg sulfadoxine/pyrimethamine (three tablets).
This preventive treatment should be given to all pregnant women starting as early as possible in the second trimester (i.e. not during the first trimester). The women should receive Sulfadoxine + Pyrimethamine Dispersible Tablets at least

3 times during her pregnancy, with each dose of three tablets being given at least 1-month apart. Sulfadoxine + Pyrimethamine Dispersible Tablets can safely be administrated up to the time of delivery.

Infants

Treatment is given 3 times during the first year of life at approximately 10 weeks, 14 weeks, and 9 months of age, corresponding to the routine vaccination schedule.

The correct dosage of Sulfadoxine + Pyrimethamine Dispersible Tablets depends on the weight of your child.

Children weighing 5 kg or more should be given half a tablet of Sulfadoxine and Pyrimethamine Dispersible Tablets. For children weighing less than 5 kg, appropriate dose adjustments cannot be made, and your health care provider will choose another formulation.

Method of administration

Dispersible Tablets for oral administration.

Sulfadoxine + Pyrimethamine Dispersible Tablets can be given either on an empty stomach or with food.

For use in Pregnant Women,

Three tablets are to be taken at once and it should be dispersed in a glass with clean water (minimum. 100ML). Dispersible tablet must be used immediately after removal from the blister packaging. This can be slowly stirred to aid the dispersion before administration

For use in infants,

The tablets should be dispersed in small amount of water or added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. 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

4.3 Contraindications

WIMAL is contraindicated in patients with hypersensitivity to any of the active ingredients, to sulfonamide drugs or to any of the excipients (see section 6.1)

4.4 Special warnings and precautions for use

If skin eruptions, cytopenia or a bacterial or fungal super-infection occurs, use of WIMAL should be discontinued. Caution is advised in repeated administration of WIMAL to patients with blood dyscrasias and those with renal hepatic failure, in whom the drugs accumulate.

Folic acid

A dose of 0.4 mg daily of folic acid may be safely used in conjunction with

WIMAL. Folic acid at a daily dose equal or above 5 mg should not be given together with WIMAL as this counteracts its efficacy as an antimalarial.

Acute illness
WIMAL 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, WIMAL should not be given if the patient:

- has received Sulfadoxine/pyrimethamine 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 WIMAL should be stopped if one develops a rash or urticarial reaction.
Excipients
WIMAL contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.
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 WIMAL with trimethoprim, or sulfamethoxazole /trimethoprim, or another sulfonamide can increase haematological side effects and the risk of severe cutaneous reactions. Concomitant use should therefore be avoided. The risk of hepatic and haematological adverse effects may increase if WIMAL is given with other drugs with hepatic or haematological toxicity.

4.6 Pregnancy and lactation

Pregnancy
Sulfadoxine/pyrimethamine showed reproductive toxicity in animal studies (see section 5.3). Sulfadoxine/pyrimethamine 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.
During 2nd or 3rd trimesters of pregnancy, WIMAL may be used for intermittent preventive treatment in pregnancy.

Breast-feeding
Pyrimethamine is excreted in human milk. Some sulfonamides are excreted in human milk.
Sulfonamides are avoided in premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency. Except

for the preceding conditions, sulfonamides are compatible with breastfeeding. WIMAL can be used during breast-
feeding. Fertility
No human data on the effect of WIMAL on fertility are available. Animal data showed that pyrimethamine impaired fertility (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

Like all medicines, this medicine can cause side effects but not everybody gets them. Sulfadoxine/pyrimethamine can cause skin rash and side effects on moist areas such as the lining of the nose and the mouth.
Serious but rare side effects include blood disorder, liver damage and severe skin reactions.
Other side effects have occurred with sulfadoxine/pyrimethamine usually in adults treated for malaria but not when these medicines are used for intermittent preventive treatment of malaria during pregnancy. These side effects include:

General disorders
Fever, chills, lupus-like effects (joint pain and stiffness, swollen glands and skin rashes), swelling of blood vessels to the gut, kidneys and nerves with periarteritis nodosa.

Mental and nervous system disorders:
Depression, apathy, nerve disorders (peripheral neuritis and polyneuritis), fits, inability to move properly, sleeplessness, muscle weakness, hallucinations, headache and fatigue.

Digestive system:
Feeling sick, inflammation of the tongue and in the mouth, stomach feeling full, vomiting, abdominal pain and diarrhoea.

Liver and pancreas
Inflammation of the pancreas and blood test showing a temporary increase in liver enzymes, hepatitis and hepatocellular necrosis

Skin
Serious reactions with flu-like symptoms and blistering rashes, skin reactions caused by sunlight, slight hair loss, hives, itching, inflammatory skin rash., exfoliative dermatitis, Lyell's syndrome, erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions and toxic epidermal necrolysis.

Eyes
Temporary problems with focussing, clouding of the clear layer at the front of the eye (which gets better when the medicine is stopped), damage to the light-sensitive layer at the back of the eye, swelling around the eyes, and redness

Ear
Ringing or buzzing sound in the ear, sense of losing balance or feeling giddy.

Heart
Inflammation of the heart and of the sac that surrounds the heart

Blood sugar and kidneys
Kidney disorders, reduced urine, Sulfadoxine can increase urine volume, hypoglycemia, renal failure, interstitial nephritis, increased blood urea nitrogen and serum creatinine, toxic nephrosis, oliguria/anuria and crystalluria.

Allergic reactions
Allergic reactions including skin rashes, joint stiffness and fever, swelling of the throat, face, and other parts of the body, serum sickness and anaphylactoid reactions.

Bones
Joint pain

Lungs
Allergic reactions in the lungs

Psychiatric disorders
Depression, nervousness, apathy

Blood and lymphatic disorders
agranulocytosis, aplastic anaemia, megaloblastic anaemia, thrombocytopenia, leucopenia, haemolytic anaemia, purpura, hypoprothrombinaemia, methaemoglobinaemia, and eosinophilia

Respiratory disorders
pulmonary infiltrates resembling eosinophilic or allergic alveolitis

Reporting of side effects
If you or your child gets any side effects, talk to your health care provider. This includes unwanted effects not listed in this leaflet.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

'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

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, 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.

P. falciparum can become resistant to the effects of sulfadoxine/pyrimethamine.

Clinical efficacy
Intermittent preventive treatment of malaria in pregnancy
Seven trials enrolling 2190 participants showed that three or more monthly doses of sulfadoxine/pyrimethamine, in comparison with two doses, increased the mean birth weight by about 56 g (95% CI, 29-83), reduced the number of low-birth-weight infants by about 20% (RR 0.80, 95% CI 0.69-0.94) and maternal parasitaemia by about 33% (RR 0.68, 95% CI 0.52-0.89). Six trials based on 1436 participants showed that three or more monthly doses compared to two doses reduced placental parasitaemia by about 50% (RR 0.51,

CI 95%, 0.38-0.68)

Intermittent preventive treatment of malaria in infants
A pooled analysis of six randomised placebo controlled studies, conducted in areas of moderate to high transmission of malaria, showed that the use of sulfadoxine/pyrimethamine in intermittent preventive treatment of malaria in infants delivered through EPI provides an overall protection in the first year of life against clinical malaria (30.3%, CI 19.8%-39.4%), anaemia (21.3%, 95% CI 8.3%-
32.5%), hospital admissions associated with malaria parasitaemia (38.1%, 95% CI 12.5%-56.2%) and all-cause hospital admissions (22.9%, 95% CI 10%-34%). sulfadoxine/pyrimethamine in intermittent preventive treatment of malaria in infants offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

5.2 Pharmacokinetic properties

Absorption of WIMAL
The absorption characteristics of WIMAL have been determined after administration of three (3) tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value (± standard deviation)**	
	Pyrimethamine	**Sulfadoxine**
Maximum concentration (Cmax)	0.55 (0.07) µg/mL	183 (18) µg/mL
Area under the curve (AUC0–72h), a measure of the extent of absorption	29.8(3.4) µg.h/mL	11037(1142) µg.h/mL
Time to attain maximum concentration (tmax)#	5.5 (1.0 – 10.0) h	5.5 (4.0 – 48.0) h

#Median (range)

Absorption
After oral administration both sulfadoxine and pyrimethamine are well absorbed (bioavailability of >90%) in healthy adults.

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.

5.3 Preclinical safety data

General toxicity
Non-clinical data reveal no special hazard for humans not already covered in other sections of SmPC based on conventional studies of safety pharmacology and repeated dose toxicity.

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

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 blisters containing three Sulfadoxine and Pyrimethamine Dispersible Tablet 500/25mg

Secondary pack size:
10 blisters in a carton (10x3's) 30 blisters in a carton (30x3's) 50 blisters in a carton (50x3's) 100 blisters in a carton (100x3'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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