1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME: Sulfadoxine 500 mg and Pyrimethamine 25 mg Tablets USP

BRAND NAME: Vitadar

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRODUCT NAME: Sulfadoxine 500 mg and Pyrimethamine 25 mg Tablets USP

Each uncoated tablet contains:
Sulfadoxine ……..500 mg
Pyrimethamine……25 mg
Excipients……..…q.s

For complete list of excipients refer section 6.1.

3. *PHARMACEUTICAL FORM:*

Tablet
White to off white, circular, biconvex, uncoated, tablets with break line on one side and VITADAR engraved on other side

4. *CLINICAL PARTICULARS*

4.1 Therapeutic Indication:

Treatment of Acute Malaria

VITADAR (sulfadoxine and pyrimethamine) is indicated for the treatment of acute, uncomplicated P. falciparum malaria for those patients in whom chloroquine resistance is suspected. However, strains of P. Falciparum may be encountered which have developed resistance to VITADAR (sulfadoxine and pyrimethamine), in which case alternative treatment should be administered.

Prevention of Malaria

Malaria prophylaxis with VITADAR (sulfadoxine and pyrimethamine) is not routinely recommended and should only be considered for travelers to areas where chloroquine-resistant P. falciparum malaria is endemic and sensitive to VITADAR (sulfadoxine and pyrimethamine), and when alternative drugs are not available or are contraindicated. However, strains of P. falciparum may be encountered which have developed resistance to VITADAR (sulfadoxine and pyrimethamine).

4.2 Posology and method of administration:

The dosage should be swallowed whole, and not chewed, with plenty of fluids after a meal.

Treatment of Acute Malaria

Adults	2 to 3 tablets taken as a single dose.

Pediatric patients (>2 months to 18 years)	The dosage for treatment of malaria in children is based upon body weight:
Weight (kg)	**Number of Tablets Taken as a Single Dose**
>45	3
31 to 45	2
21 to 30	1 ½
11 to 20	1
5 to 10	½

4.3 Contraindications:

- Repeated prophylactic (prolonged) use of VITADAR (sulfadoxine and pyrimethamine) is contraindicated in patients with renal or hepatic failure or with blood dyscrasias;
- Hypersensitivity to pyrimethamine, sulfonamides, or any other ingredient of VITADAR (sulfadoxine and pyrimethamine) ;
- Patients with documented megaloblastic anaemia due to folate deficiency;
- Infants less than 2 months of age;

Prophylactic use of VITADAR (sulfadoxine and pyrimethamine) in pregnancy at term and during the nursing period.

4.4 Special warning and precautions for use

Warning

Fatalities associated with the administration of VITADAR (sulfadoxine and pyrimethamine) have occurred due to severe reactions, including stevens-johnson syndrome and toxic epidermal necrolysis. VITADAR (sulfadoxine and pyrimethamine) prophylaxis must be discontinued at the first appearance of skin rash, if a significant reduction in the count of any formed blood elements is noted, or upon the occurrence of active bacterial or fungal infections.

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including fulminant hepaticnecrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. VITADAR (sulfadoxine and pyrimethamine) prophylacticregimen has been reported to cause leukopenia during a treatment of 2 months or longer. This leukopenia is generally mild and reversible.

PRECAUTIONS

General

Oral VITADAR (sulfadoxine and pyrimethamine) has not been evaluated for the treatment of cerebral-malaria or other severe manifestations of complicated malaria, including

hyperparasitemia, pulmonary edema or renal failure. Patients with severe malaria are not candidates for oral therapy. In the event of recrudescent P. falciparum infections after treatment with VITADAR (sulfadoxine and pyrimethamine) or failure of chemoprophylaxis with VITADAR (sulfadoxine and pyrimethamine), patients should be treated with a different blood schizonticide.

VITADAR (sulfadoxine and pyrimethamine) should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. As with some sulfonamide drugs, in glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. Urinalysis with microscopic examination and renal function tests should be performed during therapy of those patients who have impaired renal function. Excessive sun exposure should be avoided.

Laboratory Tests

Regularly scheduled complete blood counts, liver enzyme tests and analysis of urine for crystalluria should be performed whenever VITADAR (sulfadoxine and pyrimethamine) is administered for more than three months.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Pyrimethamine was not found 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. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totaling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test. Testicular changes have been observed in rats treated with 105 mg/kg/day of VITADAR (sulfadoxine and pyrimethamine) 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 dosages of up to 210 mg/kg/day of VITADAR (sulfadoxine and pyrimethamine). The pregnancy rate of female rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at dosages of 31.5 mg/kg/day or higher, a dosage approximately 30 times the weekly human prophylactic dose or higher.

Pregnancy

Teratogenic Effects: Pregnancy Category C

VITADAR (sulfadoxine and pyrimethamine) has been shown to be teratogenic in rats when given in weekly doses approximately 12 times the weekly human prophylactic dose. Teratology studies with pyrimethamine plus sulfadoxine (1:20) in rats showed the minimum oral teratogenic dose to be approximately 0.9 mg/kg pyrimethamine plus 18 mg/kg sulfadoxine. In rabbits, no teratogenic effects were noted at oral doses as high as 20 mg/kg pyrimethamine plus 400 mg/kg sulfadoxine.

There are no adequate and well-controlled studies in pregnant women. However, due to the teratogenic effect shown in animals and because pyrimethamine plus sulfadoxine may interfere with folic acid metabolism, VITADAR (sulfadoxine and pyrimethamine) therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant, and should be advised to practice contraception during prophylaxis with VITADAR (sulfadoxine and pyrimethamine) and for three months after the last dose.

Pediatric Use

VITADAR (sulfadoxine and pyrimethamine) should not be given to infants less than 2 months of age because of inadequate development of the glucuronide-forming enzyme system.

Geriatric Use

Clinical studies of VITADAR (sulfadoxine and pyrimethamine) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

4.5 Drug Interactions

There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with VITADAR (sulfadoxine and pyrimethamine) as compared to the use of VITADAR (sulfadoxine and pyrimethamine) alone. VITADAR (sulfadoxine and pyrimethamine) is compatible with quinine and with antibiotics. However, antifolic drugs such as sulfonamides, trimethoprim, or trimethoprim-sulfamethoxazole combinations should not be used while the patient is receiving VITADAR (sulfadoxine and pyrimethamine) for antimalarial prophylaxis. VITADAR (sulfadoxine and pyrimethamine) has not been reported to interfere with antidiabetic agents.

If signs of folic acid deficiency develop, VITADAR (sulfadoxine and pyrimethamine) should be discontinued. When recovery of depressed platelets or white blood cell counts in patients with drug-induced folic acid deficiency is too slow, folinic acid (leucovorin) may be administered in doses of 5 to 15 mg intramuscularly daily for 3 days or longer.

4.6 Pregnancy & Lactation

Prophylactic use of VITADAR (sulfadoxine and pyrimethamine) in pregnancy at term and during the nursing period.

VITADAR (sulfadoxine and pyrimethamine) has been shown to be teratogenic in rats when given in weekly doses approximately 12 times the weekly human prophylactic dose. Teratology studies with pyrimethamine plus sulfadoxine (1:20) in rats showed the minimum oral teratogenic dose to be approximately 0.9 mg/kg pyrimethamine plus 18 mg/kg sulfadoxine. In rabbits, no teratogenic effects were noted at oral doses as high as 20 mg/kg pyrimethamine plus 400 mg/kg sulfadoxine.

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prophylaxis with VITADAR (sulfadoxine and pyrimethamine) and for three months after the last dose.

4.7 Effects on ability to drive and use machines:

Side effects are not expected to affect attention or reduce co-ordination but care should be taken if the person feels dizzy or balance is affected.

4.8 Adverse Effects

Sulfadoxine / Pyrimethamine

- Gastro-intestinal reactions glossitis, stomatitis, nausea, emesis, abdominal pain, diarrhoea, feeling of fullness
- Skin and subcutaneous tissue disorders
  Photosensitivity, 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, periarteritisnodosa 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, 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

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 Pharmacodynamics properties

Pharmacotherapeutic group: Anti-malaria

ATC code: P01BD51

Mechanism of action:

Pyrimethamine is a diaminopyrimidine. It exerts its antimalarial activity by inhibiting plasmodialdihydrofolate 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

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 AUC0-72hour 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 Dat:

None

6. *PHARMACEUTICAL PARTICULARS*

6.1 List of excipients

Sulfadoxine 500 mg and Pyrimethamine 25 mg Tablets USP

List of Excipients:

- Maize Starch
- SSG
- Aerosil
- Cross Carmellose Sodium
- Lactose
- Sodium Lauryl Sulphate
- Magnesium stearate
- PVPK-30

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months.

6.4 Special precautions for storage:

Do not store above 30°C. Protect from light.
Keep the medicine out of reach of children.

6.5 Nature and contents of container

1 blister of 3 tablets packed in a printed carton.

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*

Name of the Applicant:

SAGAR VITACEUTICALS NIGERIA LIMITED

Business Address:
SAGAR VITACEUTICALS NIGERIA LIMITED
Plot 6, New Makun City,
Along Lagos/Ibadan expressway,
K/m 53/55 Sagamu.
Ogun State,
NIGERIA

Manufactured by:

SAGAR VITACEUTICALS NIGERIA LIMITED.
Plot 6, New Makun City,
Along Lagos/Ibadan expressway,
K/m 53/55 Sagamu.
Ogun State,
NIGERIA

8. *WHO PREQUALIFICATION REFERENCE NUMBER*
Not applicable

9. *DATE OF PREQUALIFICATION / RENEWAL OF PREQUALIFICATION*
Not applicable

10. *DATE OF REVISION OF THE TEXT*
Not applicable