1. NAME OF THE MEDICINAL PRODUCT

KRISDOXIN TABLETS (Sulfadoxine 500 mg. & Pyrimethamine 25mg. tablets USP**)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablets contain:
Sulfadoxine USP.....500 mg
Pyrimethamine USP.....25 mg
Excipients

Quantitative declaration

Excipients with known effect:
Maize Starch, Microcrysttaline cellulose, Gelatin , Sodium Starch Glycolate, Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc & Colloidal anhydrous Silica (Aerosil).
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral Tablets

White color, round shaped, uncoated tablet one side star mark embossed and other side embossed with KRISHAT.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

KRISDOXIN tablet is indicated for intermittent preventive treatment (IPT) of malaria in pregnancy in the second and third trimester. KRISDOXIN is effective against strains of Plasmodium falciparum resistant to chloroquine.

4.2 Posology and method of administration

Intermittent preventive treatment in pregnancy:
Adults: 3 Tablets taken as a single dose.

The dose may be repeated once every 2 to 4 weeks. The last dose should be given not later than one month before the expected date of delivery.

The tablets should be swallowed whole with plenty of fluid after a meal. The recommended dose of KRISDOXIN is as follows:

a) Curative treatment of uncomplicated malaria with a single dose

	Dose	Corresponds to	
		Sulfadoxine	Pyrimethamine
Adults According to body weight 50–70 kg	2 or 3 tablets	1000-1500 mg	50-75 mg
Children under 4 years	½ tablet	250 mg	12.5 mg
4-8 years	1 tablet	500 mg	25 mg
9-14 years	2 tablets	1000 mg	50 mg

b) Prophylaxis of malaria
KRISDOXIN is not routinely recommended for malaria prophylaxis. Prophylaxis with KRISDOXIN can only be considered for areas where P. falciparum malaria is endemic and sensitive to KRISDOXIN, and when alternative drugs are not available or contraindicated. (see CONTRAINDICATIONS).

The malaria risk must be carefully weighed against the risk of serious adverse drug reactions. If KRISDOXIN is prescribed for prophylaxis, it is important that the physician inquires about sulfonamide intolerance and points out the risk and the need for immediate drug withdrawal if skin reactions do occur (see PRECAUTIONS).

The dose given below should be taken at one time:

Semi-immune subjects Once every four weeks		Sulfadoxine	Pyrimethamine
Adults (according to body weight)	50-70 kg 2 or 3 tablets	= 1000-1500 mg	+50-75 mg
Children under 4 years 4-8 years 9-14 years	 ½ tablet 1 tablet 2 tablets	 = 250 mg = 500 mg = 1000 mg	 + 12.5mg +25 mg + 50 mg
Non-immune subjects		Sulfadoxine	Pyrimethamine
Once every two weeks			
Adults (according to body weight)	50-70 kg 2 tablets*	 = 1000 mg	 + 50 mg
Children under 4 years 4-8 years 9-14 years	 ½ tablet 1 tablet 1½ tablet	 = 250 mg = 500 mg = 750 mg	 + 12.5 mg +25 mg + 37.5 mg

* When convenient, a dosage of one tablet weekly may be given.

For malaria prophylaxis in travellers, the first dose of KRISDOXIN should be taken 1 to 2 weeks before departure for an endemic area; administration should be continued in the above dosage during the stay and also for the first 4 weeks after returning. The malaria risk must be carefully weighed against the risk of serious adverse drug reactions.

KRISDOXIN is approved for short term prophylaxis only.

4.3 Contraindications
KRISDOXIN is contra indicated in the first trimester of pregnancy and the period close to delivery because of the risk of kernicterus in the neonate.

KRISDOXIN should not be used in premature or newborn infants in the first two months of life because of the immaturity of their enzyme systems.

KRISDOXIN is contraindicated in patients who are hypersensitive to sulfonamides, pyrimethamine, or the combination, or any other ingredient in KRISDOXIN. Pyrimethamine is also contraindicated in patients with documented megaloblastic anaemia due to folate deficiency.

If skin reactions are observed, the drug must be withdrawn immediately, as these may be indicative of a lifethreatening reaction to the drug.

Prophylactic use of KRISDOXIN is also contraindicated in patients with renal or hepatic failure, or with blood dyscrasias.

Infants less than 2 months of age;

Prophylactic use of KRISDOXIN in pregnancy at term and during the nursing period.

4.4 Special warnings and precautions for use

Long-acting sulfonamides have been reported to cause erythema multiforme. KRISDOXIN contains sulfadoxine, a longacting sulfonamide.

Patients should be advised that sore throat, fever, cough, dyspnoea or purpura may be the first signs of serious side effects. The intake of KRISDOXIN must be stopped immediately at the first signs of skin eruptions, a significant decrease of blood cells, or a bacterial or fungal superinfection.

Because of the long half-lives of sulfadoxine and pyrimethamine the possibility of accumulation should be borne in mind. Care should be exercised in patients with hepatic and particularly renal impairment and dosage adjustments made if necessary. The renal clearance of sulfadoxine varies with pH. A decrease of urinary pH from 7.5 to 5.5 decreased renal clearance by a factor of 2.

Excessive exposure to the sun must be strictly avoided.

Regular blood counts are indicated whenever KRISDOXIN is administered for more than three months.

During prolonged administration of high doses, urinalysis and complete blood cell counts (CBCs), including platelet counts, should be performed periodically. Signs of folic acid deficiency can be prevented by administration of folinic acid.

Pyrimethamine has been reported to cause aplastic anaemia if used between courses of antineoplastic agents. This should be borne in mind when using KRISDOXIN.

Carcinogenicity

Pyrimethamine was not 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. Long term carcinogenicity studies have not been conducted with sulfadoxine alone, or with sulfadoxine/pyrimethamine combined.

Mutagenicity/Genotoxicity

Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test in Salmonella typhimurium. No genotoxicity studies have been conducted with sulfadoxine alone or with sulfadoxine/pyrimethamine combined.

4.5 **Interactions with other medicinal products and other forms of interaction**

There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with KRISDOXIN as compared to the use of KRISDOXIN alone. KRISDOXIN 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 KRISDOXIN for antimalarial prophylaxis. KRISDOXIN has not been reported to interfere with antidiabetic agents.

If signs of folic acid deficiency develop, KRISDOXIN 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 5-15 mg intramuscularly daily for 3 days or longer.

4.6 Pregnancy and lactation

Pregnancy

Sulphadoxine/Pyrimethamine has been shown to be teratogenic in rats when given in weekly doses approximately 12 times weekly human prophylactic dose. A teratology study in rats showed the minimum oral teratogenic dose to be approximately 18/0.9 mg/kg/day sulfadoxine/pyrimethamine. In rabbits, no teratogenic effects were noted at oral doses as high as 400/20 mg/kg/day sulfdoxine/pyrimethamine. The use of antimalarials in the treatment of malaria is accepted because the small risk to the foetus is outweighed by the benefits to the mother and foetus. Prophylaxis in high risk situations is also justified. In pregnant women, limited prophylactic and therapeutic use of Sulphadoxine/Pyrimethamine did not indicate a risk of foetal damage. Nevertheless, Sulphadoxine/Pyrimethamine should be used in pregnancy only if it is absolutely essential, and only after the expected benefit has been weighed against the potential risk to the foetus. However, women of child bearing potential who are travelling to areas where malaria is endemic should be advised against becoming pregnant. In addition, they should be advised to practice contraception during treatment with Sulphadoxine/Pyrimethamine and for three months after the last dose.

Pyrimethamine may interfere with folic acid metabolism and if pyrimethamine is given during pregnancy, folic acid supplementation may be required. Sulfadoxine may cause kernicterus in babies during the first month of life by displacing bilirubin from plasma albumin. Sulfadoxine should therefore be avoided during the last month of pregnancy.

Breastfeeding

Sulfadoxine and pyrimethamine is excreted in breast milk. Sulfonamides may cause jaundice and haemolytic anaemia in the newborn. KRISDOXIN should not be given to pregnant women at term or breast feeding mothers. If KRISDOXINe administration is considered essential, alternate arrangements should be made for feeding the infant.

Fertility

Fertility of male rats and the ability of male or female rats to mate were not adversely affected at doses of up to 210 mg/kg/day of sulfadoxine/pyrimethamine. The pregnancy rate of rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at doses of 31.5 mg/kg/day or higher, a dose approximately 30 times the weekly human prophylactic dose or higher. A 3-month gavage study rats showed delayed sperm maturation with 100/5 mg/kg/day of sulfadoxine/pyrimethamine and 15 mg/kg/day of pyrimethamine alone

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

For completeness, all major reactions to sulfonamides and to pyrimethamine are included below, even though they may not have been reported with KRISDOXIN

Hematological Changes

Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia, and eosinophilia.

Skin and Miscellaneous Sites Allergic Reactions

Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, toxic epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, allergic myocarditis, slight hair loss, Lyell's syndrome, and allergic pericarditis.

Gastrointestinal Reactions

Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pancreatitis, feeling of fullness, and transient rise of liver enzymes.

Central Nervous System Reactions

Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness, nervousness, and polyneuritis.

Respiratory Reactions

Pulmonary infiltrates resembling eosinophilic or allergic alveolitis.

Genitourinary

Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

Miscellaneous Reactions

Drug fever, chills, periarteritis nodosa and LE phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

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
Pyrimethamine combinations. ATC code P01BD51

Mechanism of Action:
Sulfadoxine and pyrimethamine, the constituents of KRISDOXIN, are folic acid antagonists. Sulfadoxine inhibits the activity of dihydropteroate synthase whereas pyrimethamine inhibits dihydrofolate reductase.

Activity in vitro:
Sulfadoxine and pyrimethamine are active against the asexual erythrocytic stages of Plasmodium falciparum. KRISDOXIN may also be effective against strains of P. falciparum resistant to chloroquine.

Drug Resistance: Strains of P. falciparum with decreased susceptibility to sulfadoxine and /or pyrimethamine can be selected in vitro or in vivo. P. falciparum malaria that is clinically resistant to KRISDOXIN occurs frequently in parts of Southeast Asia and South America, and is also prevalent in East and Central Africa. Therefore, KRISDOXIN should be used with caution in these areas. Likewise, KRISDOXIN may not be effective for treatment of recrudescent malaria that develops after prior therapy (or prophylaxis) with KRISDOXIN.

5.2 **Pharmacokinetic properties**

Absorption
After administration of 1 tablet, peak plasma levels for pyrimethamine (approximately 0.2 mg/L) and for sulfadoxine (approximately 60 mg/L) are reached after about 4 hours.

Distribution
The volume of distribution for sulfadoxine and pyrimethamine is 0.14 L/kg and 2.3 L/kg, respectively. Patients taking 1 tablet a week (recommended adult dose for malaria prophylaxis) can be expected to have mean steady state plasma concentrations of about 0.15 mg/L for pyrimethamine after about four weeks and about 98 mg/L for sulfadoxine after about seven weeks. Plasma protein binding is about 90% for both pyrimethamine and sulfadoxine. Both pyrimethamine and sulfadoxine cross the placental barrier and pass into breast milk.

Metabolism
About 5% of sulfadoxine appears in the plasma as acetylated metabolite, about 2 to 3% as the glucuronide. Pyrimethamine is transformed to several unidentified metabolites.

Elimination
A relatively long elimination half-life is characteristic of both components. The mean values are about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both pyrimethamine and sulfadoxine are eliminated mainly via the kidneys.

5.3 Preclinical safety data

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 105 mg/kg/day of KRISDOXIN 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 KRISDOXIN. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Microcrysttaline cellulose, Gelatin , Sodium Starch Glycolate, Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc & Colloidal anhydrous Silica (Aerosil).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

Store in a cool & dry place below 30°C, Protect from direct sunlight.

6.5 Nature and Contents of Container

The tablets are packed in Alu/PVC blister and inserted in a mono carton with insert.

Pack sizes: 1x3 Tablets.

6.6 Special precaution for disposal and other handling

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

Keep out of reach of children.

6 Manufacturer/Applicant

Krishat Pharma Industries Limited
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NIGERIA.
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