SUMMARY OF PRODUCT CHARACTERISTICS

Sulfadoxine/Pyrimethamine 500/25mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

SULFADOXINE/PYRIMETHAMINE 25mg/500mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pyrimethamine 25 mg and sulfadoxine 500 mg. Each tablet also contains 31 mg of lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white coloured, flat, round shaped beveled edged uncoated tablets debossed with "Swipha SP" above and "Single score line, clear" below

4. CLINICAL PARTICULARS

Therapeutic indications

SULFADOXINE/PYRIMETHAMINE is indicated for intermittent preventive treatment (IPTp) of malaria due to ***Plasmodium falciparum*** for all women in second and third trimester of pregnancy as part of antenatal care (ANC), in areas of moderate-to-high malaria transmission in Africa.

The most recent official guidelines on the use of antimalarial agents and local information (including resistance patterns) should be considered.

Official guidance will include those from WHO and public health authorities' guidelines.

Posology and method of administration

Intermittent preventive treatment of malaria in pregnancy

SULFADOXINE/PYRIMETHAMINE should be administered as directly observed therapy (DOT) of three tablets giving the total required dosage of 75 mg/1500mg pyrimethamine/sulfadoxine.

Doses should be given at each scheduled ANC visit, from the beginning of the second trimester until delivery, provided that the doses of SULFADOXINE/PYRIMETHAMINE are given at least one month apart.

WHO recommends a schedule of at least four antenatal care visits during pregnancy. The objective is to ensure that at least three doses of SULFADOXINE/PYRIMETHAMINE are received during pregnancy.

Method of administration

Tablets for oral administration.

SULFADOXINE/PYRIMETHAMINE can be given either on an empty stomach or with food.

Missing a dose reduces protection but does not prevent receiving the next dose.

Contraindications

SULFADOXINE/PYRIMETHAMINE 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)
- documented megaloblastic anemia due to folate deficiency.

Special warnings and precautions for use

Fatalities associated with the administration of Sulfadoxine/pyrimethamine have occurred due to severe reactions, including Stevens-Johnson syndrome and toxic epidermal necrosis.

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

SULFADOXINE/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.

Folic acid

A dose of 0.4 mg daily of folic acid may be safely used in conjunction with SULFADOXINE/PYRIMETHAMINE. Folic acid at a daily dose equal or above 5 mg should not be given together with SULFADOXINE/PYRIMETHAMINE as this counteracts its efficacy as an antimalarial.

Increased adverse effects

To avoid excessive effects, SULFADOXINE/PYRIMETHAMINE should not be given if the patient:

- has received pyrimethamine/sulfadoxine in the past 30 days.
- is HIV-positive and is receiving sulfamethoxazole/trimethoprimprophylaxis.

Hypersensitivity reactions

Because of a rare risk of severe hypersensitivity reactions (see section 4.3), treatment with SULFADOXINE/PYRIMETHAMINE should be stopped if one develops a rash or urticarial reaction.

Excipients

SULFADOXINE/PYRIMETHAMINE 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.

Interaction with other medicinal products and other forms of interaction

Concomitant use of SULFADOXINE/PYRIMETHAMINE with trimethoprim, or sulfamethoxazole/trimethoprim, or another sulfonamide can increase hematological side effects and the risk of severe cutaneous reactions. Concomitant use should therefore be avoided.

The risk of hepatic and hematological adverse effects may increase if SULFADOXINE/PYRIMETHAMINE is given with other drugs with hepatic or hematological toxicity.

If signs of folic acid deficiency develop, SULFADOXINE/PYRIMETHAMINE should be discontinued.

Fertility, pregnancy and breast-feeding

Pregnancy

Pyrimethamine/sulfadoxine showed reproductive toxicity in animal studies (see section 5.3).

Pyrimethamine/sulfadoxine 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, SULFADOXINE/PYRIMETHAMINE may be used for intermittent preventive treatment of malaria.

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 above conditions, Sulfonamides including Sulfadoxine/Pyrimethamine are compatible with breastfeeding.

SULFADOXINE/PYRIMETHAMINE can be used during breast-feeding.

Fertility

No human data on the effect of SULFADOXINE/PYRIMETHAMINE on fertility are available. Animal data showed that pyrimethamine impaired fertility (see section 5.3).

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.

Undesirable effects

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.

Gastrointestinal reactions

glossitis, stomatitis, nausea, emesis, abdominal pain, diarrhea, 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, 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 anemia, thrombocytopenia, leucopoenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia, 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 edema, conjunctival and scleral injection

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 suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorization holder, or, if available, via the national reporting system.

Overdose

Symptoms: headache, anorexia, nausea, vomiting, agitation, convulsions, hematologic changes (megaloblastic anemia, leucopoenia, thrombocytopenia), glossitis, crystalluria.

Treatment: the patient should be urgently transferred to a specialized 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

Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial Pyrimethamine combinations. 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 pyrimethamine/sulfadoxine.

Clinical efficacy

Intermittent preventive treatment of malaria in pregnancy

Seven trials enrolling 2190 participants showed that three or more monthly doses of pyrimethamine/sulfadoxine, 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)

Pharmacokinetic properties

Absorption of SULFADOXINE/PYRIMETHAMINE

The absorption characteristics of SULFADOXINE/PYRIMETHAMINE have been determined after administration of one (1) tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value (± standard deviation)**	
	Pyrimethamine	**Sulfadoxine**
Maximum concentration (C_{max}) (µg/ml)	0.153±0.03	56.347±6.75
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption (µg.h/ml)	8.00±1.57	3304.4±467.71
Time to attain maximum concentration (t_{max})[#]	2.00 (1.00-24.00)	4.50 (2.00-12.00)

#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 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.

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.

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 in human bone marrow following 3 or 4 consecutive daily doses totaling 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

List of Excipients

Maize starch, Hydroxypropyl cellulose, Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Sodium starch glycolate, Sodium Lauryl sulphate, Colloidal Silicon Dioxide.

Incompatibilities

Not applicable.

Shelf life

2 years

Special precautions for storage

Do not store above 30°C. Store the tablets in blisters in the provided box or carton.

Nature and contents of container

- Primary packaging:

Transparent PVC sealed with an aluminum foil lid.

Pack Sizes

1 blister card of 3 tablets per box

10 blister cards of 3 tablets each per box.

50 blister cards of 3 tablets each per box.

7 Manufacturer

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8 WHO REFERENCE NUMBER (WHO Prequalification Programme)

<XXXXXX>

9 DATE OF PREQUALIFICATION

<{DD/MM/YYYY}> <{DD month YYYY}>

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

References

WHO (2015) Guidelines for the treatment of malaria. Third edition. Accessed 2 February 2019 http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1

WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) April 2013 (revised January 2014). Accessed 2 February 2019 https://www.who.int/malaria/publications/atoz/iptp-sp-updated-policy-brief-24jan2014.pdf

Section 4.6

Transfer of drugs and other chemicals into human milk. American Academy of Pediatrics Committee on Drugs. Pediatrics (2001);108(3):776-89.

Section 4.8

Fansidar FDA label https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/18557slr015_fansidar

Section 5.2

De Kock M, Tarning J, Workman L, Nyunt MM, Adam I, Barnes KI, Denti P. Pharmacokinetics of Sulfadoxine and Pyrimethamine for Intermittent Preventive Treatment of Malaria During Pregnancy and After Delivery. CPT Pharmacometrics Syst Pharmacol (2017); 6(7): 430–438.

Section 5.3

Kalla NR, Saggar SK, Puri R, Mehta U: Regulation of male fertility by pyrimethamine in adult mice. Res Exp Med Berl (1997); 197: 45-52.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .