Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

S-Pyrimac

2. Qualitative and quantitative composition

Each dispersible tablet contains 25 mg pyrimethamine and 500 mg sulfadoxine.

Excipients with known effect:

Each tablet contains 18 mg of aspartame.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Dispersible tablets.

White to off-white, capsule shaped, biconvex, uncoated tablet debossed with 'F' and '41' on either side of the break line on one side, and plain on the other side.

The tablets can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

S-Pyrimac is indicated for intermittent preventive treatment of malaria as part of antenatal care for women in their first or second pregnancy, in areas of moderate-to-high malaria transmission in Africa.

S-Pyrimac is also indicated for intermittent preventive treatment of malaria in infants aged less than 12 months at the time of the second and third rounds of vaccination against diphteria, tetanus and pertussis and vaccination against measles, in areas of moderate-to-high malaria transmission of Africa (annual entomological inoculation rate ≥ 10), where the combination of sulfadoxine and pyrimethamine is still effective (prevalence of the Pfdhps 540 mutation of ≤ 50%).

The most recent official guidelines on the use of antimalarial agents and local information (including resistance patterns) should be considered. Official guidance will normally include those from WHO and public health authorities' guidelines.

4.2 Posology and method of administration

S-Pyrimac should ideally be administered as directly observed therapy (DOT).

Intermittent preventive treatment of malaria in pregnancy

The recommended dose is 3 tablets, supplying a total dose of 75 mg/1500 mg pyrimethamine/sulfadoxine.

Doses should be given at least 1 month apart at scheduled antenatal care visits, from the beginning of the second trimester until delivery. The objective is to ensure that at least 3 doses of S-Pyrimac are received during pregnancy.

Intermittent preventive treatment of malaria in infants

Treatment is given 3 times during the first year of life at approximately 10 weeks, 14 weeks, and 9 months of age, at the same time as children attend for routine vaccination.
The correct dosage of S-Pyrimac depends on the weight of the child:

Weight	**Dose (number of tablets)**	**Amount of active substances supplied per dose**
Under 5 kg	S-Pyrimac not suitable; an alternative formulation allowing appropriate dose adjustment should be used	Not applicable
5 kg and over	1⁄2 tablet	12.5 mg pyrimethamine/250 mg sulfadoxine

Method of administration
Dispersible tablets for oral administration.
S-Pyrimac can be given either on an empty stomach or with food.
The tablets should be dispersed in drinking water before administration of the dose.
Missing a dose reduces protection but does not prevent receiving the next dose.
Instructions for use
For **adults**, the following procedure should be used.

- Around 30 mL of clean drinking water should be taken in a small and clean cup or glass and the tablets added.
- The container should be gently swirled until tablets disperse, and the entire mixture should be given/taken immediately.
- The container should be rinsed with an additional 10 mL of water, which should be drunk by the patient to ensure the entire dose is taken.

For use in **infants**:

- The tablet should be divided into half along the break line.
- Around 10 mL of clean drinking water should be taken in a small and clean cup or glass, and the half tablet added.
- The cup should be gently swirled until the half tablet disperses and the entire mixture should be given to the child to drink immediately.
- The container should be rinsed with an additional 5-10 mL of water, and given to the child to drink to ensure the whole dose is taken.

If a child vomits the dose within 30 minutes, they should be allowed to rest for 30 minutes and a replacement dose given. If they vomit a second time, no further dose should be attempted.

4.3 Contraindications

S-Pyrimac 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)
- premature or newborn infants in the first 2 months of life, because of the immaturity of their enzyme systems
- patients with documented megaloblastic anaemia due to folate deficiency.

4.4 Special warnings and precautions for use

If skin eruptions, cytopenia or a bacterial or fungal superinfection occurs, use of S-Pyrimac should be discontinued. Caution is advised in repeated administration of S-Pyrimac 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 S-Pyrimac. Folic acid at a daily dose equal or above 5 mg should not be given together with S-Pyrimac as this counteracts its efficacy as an antimalarial.

Acute illness

S-Pyrimac 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, S-Pyrimac should not be given if the patient:

- has received pyrimethamine/sulfadoxine 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 S-Pyrimac should be stopped if one develops a rash or urticarial reaction.

Excipients

Each tablet of S-Pyrimac contains 18 mg of aspartame. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Therefore, S-Pyrimac may be harmful for people with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

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

Bbb Concomitant use of S-Pyrimac 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 S-Pyrimac is given with other drugs with hepatic or haematological toxicity.

4.6 Fertility, pregnancy, and lactation

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, S-Pyrimac may be used for intermittent preventative treatment in pregnancy.

Breastfeeding

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.

S-Pyrimac can be used during breastfeeding.

Fertility

No human data on the effect of S-Pyrimac 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

Bbb 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, 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, leucopenia, haemolytic anaemia, purpura, hypoprothrombinaemia, methaemoglobinaemia, and eosinophilia

Cardiac disorders

allergic myocarditis/pericarditis

Ear and labyrinth disorders tinnitus, vertigo

Endocrine disorders

Sulfadoxine, a sulfonamide, is similar to some diuretics (acetazolamide and the thiazides), and sulfonylurea hypoglycaemics. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulfonamide.
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, 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
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the Pharmacy and Poison Board website (https://pv.pharmacyboardkenya.org).

4.9 Overdose

Symptoms:
headache, anorexia, nausea, vomiting, agitation, convulsions, haematologic changes (megaloblastic anaemia, leucopenia, 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

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/sulfadoxime, 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 pyrimethamine/sulfadoxime 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%). Pyrimethamine/sulfadoxime 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

The absorption characteristics S-Pyrimac have been determined after administration of single tablets (containing 25 mg pyrimethamine and 500 mg sulfadoxine) in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**	
	Pyrimethamine	**Sulfadoxine**
Maximum concentration (C_{max})	192 ± 35 ng/ml	75.2 ± 7.7 µg/ml

Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	9323 ± 1676 ng·h/ml	4429 ± 547 µg·h/ml
Time to attain maximum concentration (t_{max})	2.44 ± 1.29 h	4.34 ± 1.19 h

* Arithmetic mean

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.

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

Pregelatinized starch
Croscarmellose sodium
Colloidal silicon dioxide
Microcrystalline cellulose
Aspartame
Orange flavour
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage:

Store below 30°C. Store tablets in blisters in the provided carton in order to protect from light.

6.5 Nature and contents of container

Clear PVC/PVDC-Alu blister card containing 3 tablets of pyrimethamine/sulfadoxine 25 mg/500 mg. Pack sizes: 1, 10 or 50 blister cards per carton.

Clear PVC/PVDC-Alu blister card containing 10 tablets of pyrimethamine/sulfadoxine 25mg/500mg. Pack sizes: 10 blister cards per 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. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Macleods Pharmaceuticals Limited
304, Atlanta Arcade,
Marol Church Road,
Andheri (East), Mumbai
400 059, India
Tel: +91-22-66762800

Manufacturing site address:

M/s. Macleods Pharmaceuticals Limited.
Plot No. 25-27, Survey No.366, premier Industrial Estate,
Daman-396 210

8. Marketing authorization number
CTD9779

9. Date of first registration
20/12/2022

10. Date of revision of the text:
15/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable