SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

(G-COSPE® Dispersible)
Sulfadoxine/Pyrimethamine 500mg/25mg Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pyrimethamine 25 mg and sulfadoxine 500 mg.
Each tablet also contains 7.20 mg of Sucralose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablets. White round tablet, debossed with “SP” on one side and a score line on the other side.
The score line is intended for subdivision of tablets when half a tablet dose is to be administered as supported by divisibility studies.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

G-COSPE® Dispersible is indicated for intermittent preventive treatment of malaria in first or second pregnancy as part of antenatal care, in areas of moderate-to-high malaria transmission in Africa.

G-COSPE® Dispersible 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 diphtheria, 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 Method of administration and posology

Intermittent preventive treatment of malaria in pregnancy

G-COSPE® Dispersible should ideally 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 antenatal care (ANC) visit, from the beginning of the second trimester until delivery, provided that the doses of G-COSPE® Dispersible 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 G-COSPE® Dispersible are received during pregnancy.

Intermittent preventive treatment in 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 of the Expanded Programme on Immunization (EPI).

The correct dosage of G-COSPE® Dispersible depends on the weight of the child.
Children weighing 5 kg or more should be given half a tablet.
For children weighing less than 5 kg, appropriate dose adjustments cannot be made and other formulations should be used.

Method of administration
Dispersible tablets for oral administration.
G-COSPE® Dispersible 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.
(1) Add approximately 10 mL of drinking water in the cup/glass; place the G-COSPE® Dispersible Tablets in the cup/glass;
(2) Let the tablets disperse, then shake thoroughly the mixtures obtained and give immediately to drink to the child the contents of the cup/glass;
(4) Rinse the cup/glass with additional approximately 10 mL of drinking water respectively and have the child drink the contents to assure that the whole dose is taken.

For **infants**, the following procedure should be used.
(1) Add approximately 10 mL of drinking water in the cup/glass; place the G-COSPE® Dispersible Tablets in the cup/glass;
(2) Let the tablets disperse, then shake thoroughly the mixtures obtained and give immediately to drink to the child the contents of the cup/glass;
(4) Rinse the cup/glass with additional approximately 10 mL of drinking water respectively and have the child drink the contents to assure that the whole dose is taken.

If a child vomits within 30 minutes of taking the tablet then she or he may need to give another tablet. Wait for 10 minutes before giving the replacement dose.

4.3 Contraindications
G-COSPE® Dispersible 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
- documented megaloblastic anaemia due to folate deficiency.

4.4 Special warnings and precautions for use
If skin eruptions, cytopenia or a bacterial or fungal super-infection occurs, use of G-COSPE® Dispersible should be discontinued. Caution is advised in repeated administration of G-COSPE® Dispersible 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 G-COSPE® Dispersible. Folic acid at a daily dose equal or above 5 mg should not be given together with G-COSPE® Dispersible as this counteracts its efficacy as an antimalarial.

Acute illness
G-COSPE 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, G-COSPE® Dispersible 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 G-COSPE® Dispersible should be stopped if one develops a rash or urticarial reaction.

Excipients
G-COSPE® Dispersible contains Sucralose. If you have been told by your health care provider that you have an intolerance to some sugars, contact your health care provider before taking this medicinal product.
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 form of interaction
Concomitant use of G-COSPE® Dispersible 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 G-COSPE® Dispersible is given with other drugs with hepatic or haematological toxicity.

4.6 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, G-COSPE® Dispersible 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.
G-COSPE® Dispersible can be used during breast-feeding.

Fertility
No human data on the effect of G-COSPE® Dispersible 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
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, 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, 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.

4.9 Overdose
Symptoms: headache, anorexia, nausea, vomiting, agitation, convulsions, hematologic 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
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 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.

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

Pharmacokinetic variable	**Mean value**	
	Pyrimethami	**Sulfadoxine**
Maximum concentration (C_{max})	0.55 (0.07) µ mL	183 (18) µg/m
Area under the curve ($AUC_{0–72h}$) measure of the extent of absorption	29.8(3.4) µg. mL	1 1 0 3 7 (1 1 4 2 µg.h/mL
Time to attain maximum concentra	5.5 (1.0 – 10.(	5.5 (4.0 – 48.(

#Median (range)

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

<u>*Distribution*</u>
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.

<u>*Metabolism*</u>
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 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

6.1 List of excipients
Hypromellose E5, Hyprolose LH-22, Hyprolose LH-11, Sucralose, Magnesium Stearate, and Purified water (removable)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30°C. Store the tablets in blisters in the provided box or carton.

6.5 Nature and contents of container
● The primary packs are: Blister cards (comprised of colourless transparent PVC blisters sealed with an aluminium foil lid), 3 tablets packaged in a PVC/ aluminium blister pack.
● The pack size are as follows:

1 blister card per box, 450 boxes per carton.
10 blister cards per box, 100 boxes per carton.
50 blister cards per box, 27 boxes per carton.
100 blister cards per box, 18 boxes per carton.

6.6 Special precautions for disposal

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

6.7 Distribution category

POM (Prescription only medicine)

7. MARKETING AUTHORISATION HOLDER

Manufacturer

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8. MARKETING AUTHORISATION NUMBER(S):

TAN 22 HM 0425

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21st September, 2022

10. DATE OF REVISION OF THE TEXT