Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

SPAQ-CO ®Disp

Sulfadoxine/Pyrimethamine250mg/12.5mg + Amodiaquine (as Hydrochloride) 76.5mg co- blistered dispersible tablets
Sulfadoxine/Pyrimethamine500mg/25mg + Amodiaquine (as Hydrochloride) 153mg co- blistered dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SPAQ-CO Disp(Amodiaquine (100 mg as hydrochloride) 76.5mg dispersible tablets+ Sulfadoxine / Pyrimethamine (250/12.5mg) dispersible tablet)

Each amodiaquine dispersible tablet contains 76.5mg amodiaquine (as hydrochloride).
Each sulfadoxine/pyrimethamine dispersible tablet contains 250mg sulfadoxine and 12.5mg pyrimethamine.
For a full list of excipients, see section 6.1.

SPAQ-CO Disp(Amodiaquine (200 mg as hydrochloride) 153mg dispersible tablets+ Sulfadoxine / Pyrimethamine (500/25mg) dispersible tablet)

Each amodiaquine dispersible tablet contains 153mg amodiaquine (as hydrochloride).
Each sulfadoxine/pyrimethamine dispersible tablet contains 500 mg sulfadoxine and 25 mg pyrimethamine.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Amodiaquine dispersible tablets are tablets with yellow core debossed with “AM” on one side and a score line on the other side. The score-line is to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.
Sulfadoxine /pyrimethamine dispersible tablets are white round tablets, debossed with “SP” on one side and a score line on the other side. The score-line is to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indication

SPAQ-CO Disp is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention,SMC) in infant aged 3- 12 months and children aged 12–59 months throughout the Sahel sub-region of Africa, provided that amodiaquine and pyrimethamine/sulfadoxine retain sufficient antimalarial efficacy.
The most recent official guidelines on the use of antimalarial agents and local information (including resistance patterns) should be considered.

4.2. Posology and method of administration

The dose of SPAQ-CO Disp is determined by the age of the child. Number of SPAQ-CO Disp tablets for treatment by age group:

Age range	Day 1		Day 2		Day 3	
	SP*	AQ*	SP*	AQ*	SP*	AQ*

3 months to <12 months	1 tablet (250mg/ 12.5mg)	1 tablet (76.5 mg)	/	1 tablet (76.5 mg)	/	1 tablet (76.5 mg)
12 months to 59 months	1 tablet (500mg/ 25mg)	1 tablet (153 mg)	/	1 tablet (153 mg)	/	1 tablet (153 mg)
Treatment schedule	Once daily for 3 days First dose directly observed treatment Given at monthly intervals Maximum 4 doses a year (transmission season)					

*SP: Sulfadoxine/Pyrimethamine dispersible tablets; AQ: Amodiaquine (as Hydrochloride) dispersible tablets.

The tablets should be given after a meal.

For administration of SPAQ-CO Disp on the *first day of treatment* you need 2 clean cups or glasses, one clean spoon and water that is suitable for drinking (potable water) or boiled water that has cooled down.

(1) Add approximately 10 mL of drinking water in each cup/glass;
(2) Place one SP dispersible tablet (only needed as the first dose for a treatment) in one cup/glass, and one AQ dispersible tablet in the other cup/glass;
(3) Let the tablets disperse, then shake thoroughly the mixtures obtained and give immediately to drink to the child the contents of the two cups/glasses;
(4) Rinse the two cups/glasses 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 administration of SPAQ-CO Disp on the *second and third day of treatment* you need one clean cup or glass, one clean spoon and water that is suitable for drinking (potable water) or boiled water that has cooled down.

(1) Add approximately 10 mL of drinking water in the cup/glass;
(2) Place one AQ dispersible tablet in the cup/glass;
(3) Let the tablet disperse, then shake thoroughly the mixture 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 child vomits within half an hour of taking the tablets, give him/her another dose as soon as you can.

SPAQ-CO Disp should not be used in children less than 3 months of age.

4.3. Contraindications

SPAQ-CO Disp is contraindicated in a infant or child with:

- hypersensitivity to any of the active ingredients to sulfonamide drugs or to any of the excipients (see section 6.1)
- history of blood disorders with amodiaquine or sulfadoxine / pyrimethamine
- history of liver injury with amodiaquine.
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4.4. Special warnings and precautions for use

Acute illness

SPAQ-CO Disp should not be given if the infant or child has an acute illness. If the infant or child has malaria, specific treatment should be given according to recent official guidelines.

Increased adverse effects

To avoid excessive effects, SPAQ-CO Disp should not be given if the child:

- has received sulfadoxine / pyrimethamine or amodiaquine 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 SPAQ-CO Disp should be stopped if a child develops a rash or urticarial reaction.

Lactose intolerance

The sulfadoxine/pyrimethamine tablets contain lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may have gastrointestinal symptoms of lactose intolerance.

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

Concomitant use of SPAQ-CO Disp with trimethoprim, or sulfonamide/ trimethoprim, or another sulfonamide can increase antifolate effect and haematological side effects, and should be avoided.

The risk of hepatic and haematological adverse effects may increase if SPAQ-CO Disp is given with other drugs with hepatic or haematological toxicity.

4.6. Fertility, pregnancy and lactation

Seasonal malaria prevention with SPAQ-CO Disp is indicated for infant and children aged up to 59 months and effects on pregnancy and lactation are not relevant.

Pregnancy

SPAQ-CO Disp is not indicated for pregnant women.

The safety of amodiaquine in pregnant women has not been established in formal studies but many years of experience with amodiaquine does not indicate teratogenicity. Sulfadoxine/pyrimethamine is recommended for intermittent preventative treatment in pregnancy in many countries.

Amodiaquine + Sulfadoxine/yrimethamine has been found effective for the treatment of malaria in pregnancy in West Africa and in Tanzania.

Amodiaquine + Sulfadoxine/pyrimethamine 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.

Breastfeeding

SPAQ-CO Disp is not indicated for breastfeeding women. No studies are available in breastfeeding women.

Fertility

Animal data showed that pyrimethamine impaired fertility (see section 5.3). There are no fertility data in humans.

4.7. Effects on ability to drive and use machines

SPAQ-CO Disp is indicated for infant and children aged 3 to 59 months and effects on driving and use of machines are not relevant. Side effects are not expected to affect attention or reduce co-ordination but care should be taken if the child feels dizzy or balance is affected.

4.8. Undesirable effects

Of the mild adverse events associated with amodiaquine, the most common are vomiting, abdominal pain, fever, diarrhoea, itching, headaches and rash. Aplastic anaemia and fatal hepatotoxicity are rarely associated with weekly prophylactic use of amodiaquine; such events have not been reported with use of amodiaquine for seasonal malaria chemoprophylaxis (see also section 5.1).

Mild adverse events associated with Sulfadoxine/pyrimethamine 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 and no frequencies are given for many events. Side effects most relevant to seasonal malaria prevention in children are shown in bold.

Adverse events reported with SPAQ-CO Disp, are listed below by body system, organ class. Where they can be estimated, frequencies are defined as *very common* (≥ 1/10), *common* (1/100–1/10), *uncommon* (1/1000–1/100), *rare* (1/10 000–1/1000) or *very rare* (≤ 1/10 000). ***Amodiaquine***

Nervous system disorders

Very common: weakness, headache, dizziness

Rare: neuromyopathy

Gastrointestinal disorders

Very common: anorexia, nausea, vomiting, abdominal pain, diarrhoea

Skin and subcutaneous disorders

slate-grey pigmentation, notably of the fingers and mucous membranes (usually associated with malaria treatment rather than seasonal chemoprophylaxis)

Common: pruritus

General disorders and administration site conditions Common: fever

Eye disorders

transient accommodation disorders, corneal opacity (usually associated with malaria treatment rather than seasonal chemoprophylaxis) which reverses on stopping treatment *Very rare:* irreversible retinopathy requiring care from eye specialist

Blood and lymphatic disorders

leucopoenia and neutropenia (agranulocytosis)—but see notes above

Hepato-biliary disorders

severe and sometimes fatal hepatitis but see notes above—development of hepatic disorders may be delayed

Sulfadoxine/Pyrimethamine

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

4.9. Overdose

Amodiaquine

Symptoms: headache, dizziness, visual disorders, cardiovascular collapse and convulsions, followed by early respiratory and cardiac arrest

Treatment: the patient should be urgently transferred to a specialised unit for close monitoring and supportive therapy

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. Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial
Amodiaquine ATC code: P01BA06
Pyrimethamine combinations. ATC code
P01BD51

Amodiaquine is a synthetic 4-aminoquinoline antimalarial. It has schizonticidal action on
Plasmodium falciparum, *P. vivax*, and *P. ovale* by destroying intraerythrocytic forms.
The mechanism of action of 4-aminoquinoline derivatives like amodiaquine against plasmodium is not yet completely known. It is nonetheless accepted that these derivatives penetrate the infected red blood cells and prevent the parasite from polymerising haeme into an insoluble product called haemozoin, leading to parasite death.
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.
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.
Clinical efficacy
Three randomised placebo-controlled studies have looked at the efficacy of seasonal malaria prevention with amodiaquine + sulfadoxine/pyrimethamine added to other measures such as insecticidal bed-nets or home malaria management. Over 7300 children aged 3–59 months participated in the studies, all in west Africa. The protective efficacy, measured as the incidence of malaria, ranged from 66 to 82%.
A previous study had compared regimens containing sulfadoxine/pyrimethamine with either artesunate or amodiaquine in 2102 children. The incidence of malaria was lowest (5%) among children who received amodiaquine + sulfadoxine/pyrimethamine compared to those receiving artesunate-based regimens (9–11%).

5.2. Pharmacokinetic properties

Amodiaquine

Absorption
After oral administration, amodiaquine is quickly absorbed and metabolised into its main active form, desethylamodiaquine. The absolute bioavailability of amodiaquine is not known.
Following single-dose administration of three Amodiaquine Hydrochloride Tablets (i.e. 450 mg amodiaquine base) in healthy volunteers, the mean (± SD) amodiaquine C_{max} value was 30.3 ± 12.6 ng/ml and the corresponding value for AUC_{0-t} was 309.4 ± 76.0 ng·ho ur/ml. The median (± SD) amodiaquine t_{max} value was 0.91 ± 1.13 hours.
Distribution
The volume of distribution of amodiaquine is estimated at 20–40 l/kg. Desethylamodiaquine, the main metabolite of amodiaquine, is assumed to be the main active form. It is mainly found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4–6 times higher than in plasma.
Metabolism
The hepatic first-pass metabolism of amodiaquine is high, with formation of the active metabolite, desethylamodiaquine, presumably via the CYP2C8 isoenzyme. Further metabolism includes oxidation and glucuronidation.
Elimination
Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Desethylamodiaquine is eliminated slowly with a terminal half- life of 9–18 days.

Sulfadoxine/Pyrimethamine

Absorption
Following single-dose administration of the sulfadoxine/pyrimethamine tablet in healthy volunteers (n = 46), the mean (± SD) C_{max} value for sulfadoxine was 183 ± 18 µg/ml, and the corresponding value for $AUC_{0-72hour}$ was 11037 ± 1142 µg·hour/ml. The median (range) sulfadoxine t_{max} value was 5.5 hours (range 4–48 hours).
The mean (± SD) pyrimethamine C_{max} value was 0.55 ±0.07 µg/ml, and the

corresponding value for AUC was 29.8 ± 3.4 μg·hour/ml. The median (range) pyrimethamine t_{max} value was 5.5 hours (range 1–10 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.

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

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 data

Amodiaquine

General toxicity

Single dose toxicity studies reported a LD_{50} (mouse intraperitoneal) of 225 mg/kg; LD_{50} (mouse oral) of 550 mg/kg and a LD_0 (mouse intraperitoneal) of 137 mg/kg. Histopathological changes (pigmentation) were seen in the heart at 30 mg/kg/day in rats. The statistically significant

effects seen in vitro on ion channels in the heart at 0.1 µm in the hERG current (expressed in human embryonic kidney cells) as well as the increase in QRS complex and QT interval durations at concentrations higher than 0.1 µm in the isolated rabbit Purkinje fibres appeared to be due to a non-specific multi-ion channel blockade. Transient prolongation of QT interval was observed at 30 mg/kg given orally. This dose corresponds to about twice the maximum recommended therapeutic dose. At a dose of 100 mg/kg given orally (about 6.7-fold the maximum recommended therapeutic dose), slight respiratory depressant and natriuretic effects occurred. Pigmentation was also seen in liver, kidney and thyroid glands in rats as well as in kidneys, liver and lymph nodes in dogs (at doses of 25 mg/kg daily). Also an increase in haemosiderosis in the spleen and bone marrow as well as thymus lymphoid depletion were observed.

Genotoxicity

In vitro (Ames test) and in vivo tests (sister chromatid exchange and chromosome aberration tests) showed that amodiaquine, like chloroquine, has both, a mutagenic and a clastogenic potential.

Carcinogenicity

No studies on the carcinogenic potential of amodiaquine have been conducted.

Reproductive toxicity

No data on toxicity on the reproductive system and embryofetal development is available for amodiaquine alone. The combination of amodiaquine and artesunate did not demonstrate any particular effects on fertility or associated parameters. In the peri-postnatal study, the offspring from the F1 generation did not show any effect on sexual development, and despite an early slowing of bodyweight increases with some effect on testicular and epididymal weights, no sequelae were noted on reproductive capacity.

Pyrimethamine/sulfadoxine

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 Sulfadoxine/ Pyrimethamine 5/100 mg/kg daily 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 Sulfadoxine/Pyrimethamine doses of up to 10/200 mg/kg daily. 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. Sulfadoxine/Pyrimethamine was teratogenic in rats when given in weekly doses about 12 times the normal human dose.

Sperm motility and sperm count were significantly decreased in pyrimethamine-treated male mice, and their fertility rate fell to zero.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The active substances are: Amodiaquine(as Hydrochloride), Sulfadoxine and Pyrimethamine The other ingredients are:

Amodiaquine(as Hydrochloride)dispersible tablets in SPAQ-CO Disp:

Povidone K30

Sodium
bicarbonate
Microcrystalline cellulose
Cross linking carboxymethyl cellulose
sodium Sucralose
Magnesium stearate

Sulfadoxine/Pyrimethamine dispersible tablets in SPAQ-CO Disp

Hypromellose E5
Low-substituted Hydroxypropyl Cellulose
LH-22 Low-substituted Hydroxypropyl
Cellulose LH-11 Sucralose
Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Keep out of reach and sight of children.

Store below 30°C.Store in the original container. Protect from light.

6.5. Nature and contents of container

3 Amodiaquine (as Hydrochloride) + 1 Sulfadoxine/Pyrimethamine dispersible tablets per co- blister comprised of colourless transparent PVC blisters sealed with an aluminium foil lid, 50 such co-blisters in a box, 60 boxes in a 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.

6.7.Classification

List I. Drug under medical prescription. Respected the prescribed doses.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0289

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

19th July, 2022

10. DATE OF REVISION OF THE TEXT