# WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).*
*The medicine may be authorised for additional or different uses by national medicines regulatory authorities.*

# 1. NAME OF THE MEDICINAL PRODUCT

SPAQ-CO® Disp 76.5mg+12.5mg/250mg [1]

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each amodiaquine (as hydrochloride) dispersible tablet contains 76.5 mg amodiaquine (equivalent to 100mg of amodiaquine hydrochloride) and each pyrimethamine/ sulfadoxine dispersible tablet contains 12.5mg pyrimethamine and 250mg sulfadoxine.

For a full list of excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Tablets
Amodiaquine (as hydrochloride) 76.5mg dispersible tablets are yellow round tablets, debossed with “AQ” on one side and a score line on the other side.
Pyrimethamine/ sulfadoxine 12.5mg/250mg dispersible tablets are white round tablets, debossed with “SP” on one side and a score line on the other side.

On both tablets, the score lines are only to facilitate breaking for ease of swallowing and not to divide into equal doses.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

SPAQ-CO® Disp 76.5mg+12.5mg/250mg is indicated for malaria prevention during the malaria season (seasonal malaria chemoprevention, SMC) in children aged 3-11 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.

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

## 4.2 Posology and method of administration

***Children aged 3-11 months***

Treatment should start at the beginning of the high transmission period and is given in 3-day courses as follows:

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

| | Dose (child aged 3–11 months) | |
|---|---|---|
| | **Amodiaquine tablet (76.5 mg)** | **Pyrimethamine/sulfadoxine tablet (12.5 mg/250 mg)** |
| **Day 1** | 1 tablet as a single dose | 1 tablet as a single dose |
| **Day 2** | 1 tablet as a single dose | – |
| **Day 3** | 1 tablet as a single dose | – |

The 3-day course is repeated after 1 month, for a maximum 4 courses during the high-transmission period.

***Children aged under 3 months***

Children who are less than 3 months of age should not receive treatment for SMC.

***Method of administration***

The tablets can be dispersed with water.

Doses on day 1 and doses on days 2 and 3 (amodiaquine) can be given by the child's carer.

For administration of SPAQ-CO® Disp 76.5mg+12.5mg/250mg on the first day of treatment 2 clean cups or glasses are needed:

(1) Add approximately 10 mL of drinking water in each cup/glass;

(2) Place one pyrimethamine/sulfadoxine dispersible tablet (only needed as the first dose for a treatment) in one cup/glass, and one amodiaquine 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 76.5mg+12.5mg/250mg on the second and third day of treatment you need one clean cup or glass.

(1) Add approximately 10 mL of drinking water in the cup/glass;

(2) Place one amodiaquine 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 a child vomits the dose within 30 minutes, the child should be allowed to rest for 10 minutes and a replacement dose given

It is important that the child receives the full 3-day course. Missing a course reduces protection but does not prevent the child receiving the next course.

## 4.3 Contraindications

SPAQ-CO® Disp 76.5mg+12.5mg/250mg is contraindicated in a 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 pyrimethamine/sulfadoxine
- history of liver injury with amodiaquine.

## 4.4 Special warnings and precautions for use

*Acute illness*

SPAQ-CO® Disp 76.5mg+12.5mg/250mg 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, SPAQ-CO® Disp 76.5mg+12.5mg/250mg should not be given if the child:

- has received pyrimethamine/sulfadoxine 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 76.5mg+12.5mg/250mg should be stopped if a child develops a rash or urticarial reaction.

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

Concomitant use of SPAQ-CO® Disp 76.5mg+12.5mg/250mg 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 SPAQ-CO® Disp 76.5mg+12.5mg/250mg is given with other drugs with hepatic or haematological toxicity.

## 4.6 Fertility, pregnancy and breast-feeding

Seasonal malaria prevention with SPAQ-CO® Disp 76.5mg+12.5mg/250mg is indicated for children and effects on pregnancy and lactation are not relevant.

*Pregnancy*

The safety of amodiaquine in pregnant women has not been established in formal studies but many years of experience with amodiaquine does not indicate reproductive toxicity.

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

Amodiaquine + 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 2$^{nd}$ or 3$^{rd}$ trimesters of pregnancy, SPAQ-CO® Disp 76.5mg+12.5mg/250mg may be used for intermittent preventive treatment in pregnancy.

*Breast-feeding*

Amodiaquine does not appear to be excreted in appreciable amounts in the breast milk. 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.

SPAQ-CO® Disp 76.5mg+12.5mg/250mg can be used during breast-feeding.

*Fertility*

No human data on the effect of SPAQ-CO® Disp 76.5mg+12.5mg/250mg on fertility are available. Animal data showed that pyrimethamine impaired fertility Amodiaquine showed effects on spermatogenesis (see section 5.3).

## 4.7 Effects on ability to drive and use machines

SPAQ-CO® Disp 76.5mg+12.5mg/250mg is indicated for children 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 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 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 76.5mg+12.5mg/250mg , 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

***Pyrimethamine/sulfadoxine***

*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 authorisation 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 authorisation holder, or, if available, via the national reporting system.

### 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

***Pyrimethamine/sulfadoxine***

*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 + pyrimethamine/sulfadoxine 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 pyrimethamine/sulfadoxine with either artesunate or amodiaquine in 2102 children. The incidence of malaria was lowest (5%) among children who received amodiaquine + pyrimethamine/sulfadoxine compared to those receiving artesunate-based regimens (9–11%).

## 5.2 Pharmacokinetic properties

No pharmacokinetic data are available for SPAQ-CO® Disp 76.5mg+12.5mg/250mg . A bioequivalence study was conducted with SPAQ-CO® Disp 76.5mg+12.5mg/250mg which is essentially the same as SPAQ-CO® Disp 76.5mg+12.5mg/250mg in qualitative terms and with respect to the ratio of active and other ingredients.

Following single dose administration of three Amodiaquine 153mg dispersible tablets in healthy volunteers, the mean (± SD) amodiaquine $C_{max}$ value was 14.7(±6.7) ng/ml and the corresponding value for AUC $_{0\text{-}t}$ was 104 (± 26) ng·h/ml. The mean (± SD) amodiaquine $t_{max}$ value was 0.81(± 0.27) hours.

Following single dose administration of pyrimethamine/sulfadoxine 25mg/500mg dispersible tablets in healthy volunteers, the mean (± SD) $C_{max}$ value for sulfadoxine was 70.2±9.2 µg/ml and the corresponding value for AUC $_{0\text{-}72hour}$ was 4125 ± 507 µg·h/ml. The mean (± SD) sulfadoxine $t_{max}$ value was 4.16 (± 1.33) hours. The mean (± SD) $C_{max}$ value for pyrimethamine was 193±29 ng/ml and the corresponding value for AUC $_{0\text{-}72hour}$ was 9.92 ± 1.24 ng·h/ml. The mean (± SD) pyrimethamine $t_{max}$ value was 3.84(± 1.47) hours.

*Absorption*

After oral administration, amodiaquine is quickly absorbed and metabolised into its main active form, desethylamodiaquine. The absolute bioavailability of amodiaquine is not known.

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

*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.

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*

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.

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*

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.

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

***Amodiaquine***

*General toxicity*

Non-clinical data reveal no special hazard for humans not already covered in other sections of the SmPC, based on conventional studies of safety pharmacology and repeated dose toxicity

*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*

Treatment of rats with amodiaquine caused disruption of the blood-testis barrier and germ cell apoptosis without affecting body weight. The adverse effects on spermatogenesis were reversible when treatment was discontinued.

***Pyrimethamine/sulfadoxine***

*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

**Amodiaquine (as hydrochloride) 76.5mg dispersible tablets**

Povidone, sodium bicarbonate, microcrystalline cellulose, crosslinking carboxymethyl cellulose sodium, sucralose and magnesium stearate

**Pyrimethamine/sulfadoxine 12.5mg/250mg dispersible tablets**

Hypromellose, low-substituted hydroxypropyl cellulose, sucralose and magnesium stearate

## 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/carton. Protect from light.

## 6.5 Nature and contents of container

The tablets are packaged in colourless transparent PVC/Al blister containing three Amodiaquine (as hydrochloride) 76.5mg dispersible tablets and one Pyrimethamine/Sulfadoxine 12.5mg/250mg dispersible tablet.

Pack size: 50 co-blister cards per box
60 boxes 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. SUPPLIER

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# 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

MA116

# 9. DATE OF PREQUALIFICATION

21 August 2018

## 10. DATE OF REVISION OF THE TEXT

January 2019

Section 7 was updated in March 2020

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