



# NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL

NAFDAC CORPORATE HQ:

Plot 2032 Olusegun Obasanjo Way,  
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LAGOS LIAISON OFFICE:

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DRUG REGISTRATION AND REGULATORY AFFAIRS DIRECTORATE

[registration@nafdac.gov.ng](mailto:registration@nafdac.gov.ng)

21/04/2022

Your Ref..... Our Ref.....: Date•.....

The Managing Director,  
Tridem Pharmaceuticals Nig. Ltd,  
Km. 4, Ijoko Road, Opp. AP Filling Station, Junction. Bus Stop, Otta,  
Ogun State.

Attention; Supt Pharmacist:

## RE: NOTIFICATION OF CHANGE OF NAME OF APPLICANT

The above subject matter refers, please.

We hereby acknowledge the change of name of Applicant from **Guilin Pharmaceuticals Nig. Ltd** to **Tridem Pharmaceuticals Nig. Ltd** with same address at **Km. 4, Ijoko Road, Opp. AP Filling Station, Junction Bus Stop, Otta, Ogun State.**

Please note that subsequent applications should be made in the new Applicant's name.

Regards,

**Pharm. Chukwuma P. Oligbu**  
For: Director-General (NAFDAC)

112010052

Read the package leaflet before use.  
Keep out of the reach and sight of children.

**Storage :**  
Store in a dry place below 30°C in its original pack.  
Protect from light.



**Composition:**  
Sulfadoxine/Pyrimethamine ..... 500 mg/25 mg  
Amodiaquine ..... 153 mg



Mfr. / Fab.: Guilin Pharmaceutical Co., Ltd.  
No. 43 Qilidian Road, Guilin 541004, Guangxi, China  
43 Rue Qilidian, Guilin 541004, Guangxi, Chine

# **SPAQ-CO<sup>®</sup>** Dispersible Tablets Comprimés Dispersible 12-

*Sulfadoxine/Pyrimethamine + Amodiaquine  
(500 mg/25 mg) (153 mg)*

-  Sulfadoxine/Pyrimethamine dispersible tablets  
Sulfadoxine/Pyriméthamine comprimés dispersible
-  Amodiaquine dispersible tablets  
Amodiaquine comprimés dispersible

**50 blister strips  
plaquettes**

**FOSUN**

sulfadoxine-pyriméthamine inhibite dihydrofolate reductase. Amodiaquine est un synthétique 4-aminoquinoline antimalarial. Sa activité est caractérisée par une action schizonticide sur Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale et Plasmodium malariae en détruisant les formes intraérythrocytaires.

SPAQ-CO Dispersible Tablets est un médicament chimio-préventif saisonnier de la malaria. Il est utilisé pour prévenir, mais pas pour traiter la malaria pendant la saison de transmission de la malaria chez les enfants et les jeunes dont l'âge est compris entre 3 et 59 mois. SPAQ-CO Dispersible Tablets contient deux médicaments, amodiaquine et sulfadoxine/pyriméthamine, qui agissent ensemble pour prévenir la malaria.

Si votre médecin trouve que votre enfant doit être protégé contre la malaria et vous prescrit SPAQ-CO Dispersible Tablets.

SPAQ-CO Dispersible Tablets n'est pas adapté pour traiter la malaria.

Pour une prévention complète, il est important que votre enfant prenne la dose prescrite par votre médecin, votre pharmacien ou un professionnel de santé.

## 2. AVANT D'ADMINISTRER SPAQ-CO DISPERSIBLE TABLETS

Il est important de signaler à votre médecin si votre enfant a d'autres problèmes médicaux ou s'il prend d'autres médicaments.

### Ne pas donner SPAQ-CO Dispersible Tablets

- Si votre enfant est allergique (hypersensible) à l'amodiaquine ou à la sulfadoxine/pyriméthamine, ou à l'un des autres ingrédients de SPAQ-CO Dispersible Tablets (voir section 6, Que contient SPAQ-CO Dispersible Tablets).
- Si votre enfant a eu des problèmes de foie pendant le traitement avec l'amodiaquine.
- Si votre enfant a eu des fièvres soudaines élevées, des frissons, une gorge douloureuse ou des ulcères à la bouche (symptômes suggérant un danger pour les globules blancs) pendant le traitement avec l'amodiaquine.
- Si votre enfant a une maladie de l'œil avec des dommages à sa rétine.
- Si votre enfant a une insuffisance rénale ou hépatique ou une dyscrasie sanguine pendant l'utilisation prophylactique de la sulfadoxine/pyriméthamine.
- Si votre enfant a une anémie mégaloblastique documentée due à une carence en folate.
- Si votre enfant est un bébé de moins de 3 mois.

Si vous avez le moindre doute, il est essentiel de demander conseil à votre médecin, votre pharmacien ou un professionnel de santé.

### Prenez des précautions particulières avec SPAQ-CO Dispersible Tablets

L'amodiaquine peut causer des dommages au foie et/ou au sang qui peuvent être mortels.

- Si votre enfant présente une asthénie (fatigue), des troubles gastro-intestinaux (nausées, vomissements, douleurs abdominales), une jaunisse (urines foncées, selles décolorées), une gorge douloureuse ou des ulcères à la bouche, arrêtez le traitement et consultez immédiatement un médecin ; votre médecin peut avoir besoin de faire un prélèvement sanguin.

Informez votre médecin, votre pharmacien ou un professionnel de santé si votre enfant a utilisé ce médicament ou un autre médicament contenant de l'amodiaquine très récemment, car votre enfant pourrait alors être plus susceptible d'expé-

riencer des effets secondaires, une attention particulière est requise. Si l'un des problèmes suivants s'applique à votre enfant, informez votre médecin avant de donner SPAQ-CO Dispersible Tablets. Parce que la prudence doit être exercée chez certains patients, il est important d'informer votre médecin si votre enfant a, ou a eu, l'un des problèmes suivants :

- une condition cardiaque, telle que des changements dans le rythme ou la fréquence du cœur, ou d'autres troubles cardiaques,
- une histoire familiale de problèmes cardiaques ou de décès soudains,
- de faibles niveaux d'électrolytes tels que le potassium ou le magnésium,
- des problèmes de foie ou de reins,
- des crises épileptiques,

识别码印刷位置  
印刷时需删除虚线框

## NOTICE D'INFORMATIONS POUR L'UTILISATEUR

### SPAQ-CO® Comprimés Dispersible Sulfadoxine/Pyriméthamine + Amodiaquine

**Veillez lire attentivement toutes les informations ci-dessous avant d'administrer SPAQ-CO Comprimés Dispersible.**

- Conservez cette notice au cas où vous auriez besoin de la lire à nouveau.
- Si vous avez d'autres questions, contactez votre médecin, votre prestataire de soins de santé ou votre pharmacien.
- Ce médicament a été prescrit pour votre enfant. Ne le donnez pas à quelqu'un d'autre, même en cas de symptômes identiques, cela pourrait lui être nocif.
- En cas d'effet indésirable grave, ou si vous observez un effet non décrit dans cette notice, contactez votre médecin ou votre pharmacien.

#### Contenu de cette notice :

1. Qu'est-ce que SPAQ-CO Comprimés Dispersible et dans quel cas doit-il être utilisé
2. Avant d'administrer SPAQ-CO Comprimés Dispersible à votre enfant
3. Comment administrer SPAQ-CO Comprimés Dispersible à votre enfant
4. Effets indésirables éventuels
5. Comment conserver SPAQ-CO Comprimés Dispersible
6. Informations supplémentaires

### 1. QU'EST-CE QUE SPAQ-CO COMPRIMÉS DISPERSIBLE ET DANS QUEL CAS DOIT-IL ÊTRE UTILISÉ

Sulfadoxine et de pyriméthamine sont des antagonistes de l'acide folique. Sulfadoxine inhibe l'activité de synthase dihydroptéroate alors pyriméthamine inhibe la dihydrofolate réductase. L'amodiaquine est une 4-aminoquinoline synthétique antipaludique. Son activité est caractérisée par une action schizonticide sur Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale et Plasmodium paludisme en détruisant les formes intra-érythrocytaires.

SPAQ-CO est destiné à la chimioprévention du paludisme saisonnier. Il est utilisé pour prévenir le paludisme et non pour le traiter, pendant la saison de transmission du paludisme chez le petit enfant âgé de 3 à 59 mois.

SPAQ-CO Comprimés Dispersible contient deux principes actifs, l'amodiaquine et la sulfadoxine/pyriméthamine, qui agissent ensemble pour prévenir le paludisme.

Le médecin a estimé que la prévention du paludisme était importante pour votre enfant et lui a donc prescrit SPAQ-CO Comprimés Dispersible.

Ce médicament est indiqué uniquement pour la prévention et non pour le traitement du paludisme.

Pour une prévention efficace, il est important que le traitement soit pris par votre enfant dans son intégralité aux doses prescrites selon les instructions du médecin, de l'agent de santé ou du pharmacien.

### 2. AVANT D'ADMINISTRER SPAQ-CO COMPRIMÉS DISPERSIBLE A VOTRE ENFANT

Il est important de signaler au médecin si votre enfant a des antécédents médicaux et si il ou elle a un traitement en cours.

#### Ne pas administrer SPAQ-CO Comprimés Dispersible chez un enfant

- Allergique (hypersensible) à l'amodiaquine ou à la sulfadoxine/pyriméthamine, ou à tout autre ingrédient de SPAQ-CO Comprimés Dispersible (voir section 6, Que contient SPAQ-CO Comprimés Dispersible).

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# Receipt

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*Directorate*

**Registration and Regulatory**

*Company Name*

**GUILIN PHARMACEUTICALS NIGERIA LIMITED**

*Application Number*

**RNW-PP-247658**

*Product Name*

**SPAQ-CO DISPERSIBLE TABLETS 500MG/25MG/153MG**

*Remita Reference Number*

**290603565704**

*Pack Size*

**50X3X1 Milligram (mg)**

*Payment Type*

**Renewal Fee**

*Payment Breakdown*

**451,239.94**

*Payment Date*

**1/19/2022**

**Total Amount:**

**N451,239.94**





**NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL**  
**OFFICE OF THE DIRECTOR**  
**DRUG EVALUATION AND RESEARCH DIRECTORATE**  
Plot 1, Isolo Industrial Scheme, Oshodi-Apapa Expressway, Isolo, Lagos  
Director's E-mail: ijeoma.nwankwo@nafdac.gov.ng Office E-mail: der.headquarters@nafdac.gov.ng

REF NO: NAF/DER/HQ/OFF/208/VOL 1

Date: 28/6/2021

The Managing Director,  
Guilin Pharm Nigeria Limited,  
Km 4, Iyoko Road, Opposite AP Filling Station,  
Junction Bus Stop, Ota, Ogun State

Dear Sir,

**CLEARANCE IN LIEU OF ONSITE INSPECTION**

Following your application for Good Manufacturing Practice (GMP) inspection of your foreign manufacturer's site at **GUILIN PHARMACEUTICAL COMPANY LIMITED, NO. 43, QILIDIAN ROAD, GUILIN 541004, GUANGXI, P.R OF CHINA.**; I wish to inform you that a provisional clearance in lieu of on-site GMP inspection of your foreign manufacturer's site has been granted you. This is to enable further processing of your application for the registration of the following products,

**NAME OF DRUG-STRENGTH PACKSIZE**

1. ARTESUN (ARTESUNATE FOR INJECTION INJECTIONS 30MG)
2. ARTESUN (ARTESUNATE FOR INJECTION INJECTIONS 60MG)
3. ARTESUN (ARTESUNATE FOR INJECTION INJECTIONS 120MG)
4. D-ARTEPP DISPERSIBLE TABLETS (DIHYDROARTEMISININ 20MG, PIPERAQUINE PHOSPHATE 160MG)
5. D-ARTEPP DISPERSIBLE TABLETS (DIHYDROARTEMISININ 40MG, PIPERAQUINE PHOSPHATE 320MG)
6. D-ARTEPP TABLETS (DIHYDROARTEMISININ 40MG, PIPERAQUINE PHOSPHATE 320MG)
7. D-ARTEPP TABLETS (DIHYDROARTEMISININ 80MG, PIPERAQUINE PHOSPHATE 640MG)

Please note that the inspection of the site will be carried out at a later date after the COVID -19 pandemic and that any failure to meet minimum NAFDAC GMP requirements at the time will invalidate this approval. Also, in view of the above you are required to give your commitment to provide a seamless involvement in processing of staff visas when the time comes, otherwise the approval shall be reversed.

You may reach out to Director Drug Registration and Regulatory Affairs Directorate for further processing of your application.

Thank you,

**Mrs. Ijeoma U. Nwankwo**  
Director (DER)  
For: Director General (NAFDAC)



**National Agency for Food & Drug Administration  
& Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R)  
Directorate**

**SUMMARY OF PRODUCT CHARACTERISTICS  
(SmPC)**

## Summary of Product Characteristics

### 1. NAME OF THE MEDICINAL PRODUCT

#### **SPAQ-CO<sup>®</sup> Disp**

Sulfadoxine/Pyrimethamine 250mg/12.5mg + Amodiaquine (as Hydrochloride) 76.5mg co-blistered dispersible tablets

Sulfadoxine/Pyrimethamine 500mg/25mg + Amodiaquine (as Hydrochloride) 153mg co-blistered dispersible tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### **SPAQ-CO<sup>®</sup> 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<sup>®</sup> 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 yellow round tablets, debossed with “AQ” on one side and a score line on the other side.

Sulfadoxine /pyrimethamine 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-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<sup>®</sup> 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.

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

#### 4.2 Posology and method of administration

The dose of SPAQ-CO<sup>®</sup> Disp is determined by the age of the child. Children who are less than 3 months of age should not receive treatment for SMC.

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

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 (153mg)	/	1 tablet (153 mg)	/	1 tablet (153 mg)
Treatment schedule	Once daily for 3 days First dose directly observed treatment The 3-day course is repeated after 1 month, for a maximum 4 courses during the high-transmission period.					

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

### **Method of administration**

The tablets should be given after a meal.

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<sup>®</sup> 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<sup>®</sup> 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 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<sup>®</sup> 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.

### **4.4 Special warnings and precautions for use**

#### *Acute illness*

SPAQ-CO<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> Disp 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.

#### *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<sup>®</sup> Disp with trimethoprim, or sulfonamide/trimethoprim, or another sulfonamide can increase antifolate effect and 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<sup>®</sup> Disp is given with other drugs with hepatic or haematological toxicity.

#### **4.6 Fertility, pregnancy and lactation**

Seasonal malaria prevention with SPAQ-CO<sup>®</sup> Disp is indicated for infant and children aged up to 59 months 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<sup>nd</sup> or 3<sup>rd</sup> trimesters of pregnancy, SPAQ-CO<sup>®</sup> Disp may be used for intermittent preventive treatment in pregnancy.

##### *Breastfeeding*

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<sup>®</sup> Disp can be used during breastfeeding.

##### *Fertility*

No human data on the effect of SPAQ-CO<sup>®</sup> Disp 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<sup>®</sup> 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<sup>®</sup> Disp, are listed below by body system, organ class. Where they can be estimated, frequencies are defined as *very common* ( $\geq 1/10$ ), *common* ( $1/100-1/10$ ), *uncommon* ( $1/1000-1/100$ ), *rare* ( $1/10000-1/1000$ ) or *very rare* ( $\leq 1/10000$ ).

##### ***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*

leucopenia 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*

photosensitivity, 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 sulphonamide is similar to some diuretics (acetazolamide and the thiazides), and sulfonyleurea 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, SmPC of SPAQ-CO® Disp tablets

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, 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, folic 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 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.

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**

No pharmacokinetic data are available for SPAQ-CO<sup>®</sup> Disp. A bioequivalence study was conducted with SPAQ-CO<sup>®</sup> Disp which is essentially the same as SPAQ-CO<sup>®</sup> Disp 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 ( $\pm$  SD) amodiaquine C<sub>max</sub> value was 14.7( $\pm$ 6.7) ng/ml and the corresponding value for AUC<sub>0-t</sub> was 104 ( $\pm$  26) ng·h/ml. The mean ( $\pm$  SD) amodiaquine t<sub>max</sub> value was 0.81( $\pm$  0.27) hours.

Following single dose administration of pyrimethamine/sulfadoxine 25mg/500mg dispersible tablets in healthy volunteers, the mean ( $\pm$  SD) C<sub>max</sub> value for sulfadoxine was 70.2 $\pm$ 9.2  $\mu$ g/ml and the corresponding value for AUC<sub>0-72hour</sub> was 4125  $\pm$  507  $\mu$ g·h/ml. The mean ( $\pm$  SD) sulfadoxine t<sub>max</sub> value was 4.16 ( $\pm$  1.33) hours. The mean ( $\pm$  SD) C<sub>max</sub> value for pyrimethamine

was  $193 \pm 29$  ng/ml and the corresponding value for  $AUC_{0-72\text{hour}}$  was  $9.92 \pm 1.24$  ng·h/ml. The mean ( $\pm$  SD) pyrimethamine  $t_{\text{max}}$  value was  $3.84(\pm 1.47)$  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**

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**

36 months.

### **6.4 Special precautions for storage**

Keep out of reach and sight of children.

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) dispersible tablets and one Pyrimethamine/Sulfadoxine dispersible tablet.

Pack size: 50 co-blisters 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.

### **6.7 Classification**

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

## **7. MANUFACTURER**

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## **8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)**

MA116, MA117

## **9. DATE OF FIRST PREQUALIFICATION**

August 2018

## **10. DATE OF REVISION OF THE TEXT:**

February 2019