1. NAME OF THE MEDICINAL PRODUCT

Artemether 20mg + Lumefantrine 120mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 20 mg Artemether and 120 mg Lumefantrine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow Coloured, circular, uncoated flat beveled edges table, having break line on one side and another side plains

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tosok 20/120 is a fixed-dose combination of artemether and lumefantrine, which acts as a blood schizontocide. It is indicated for:

Treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum. Because Tosok 20/120 is effective against both drug-sensitive and drug-resistant P. falciparum it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

Stand-by emergency treatment:

Most tourists and business travellers, considered to be non-immune, will be able to obtain prompt medical attention if malaria is suspected. However, a minority at risk of infection may be unable to obtain such care within 24 hours of the onset of symptoms, particularly if they are in an isolated location far from medical services. In such cases, prescribers are advised to issue Tosok 20/120 to be carried by the traveller for self-administration or by the parent or caregiver for administration to the traveling child (“stand-by emergency treatment”).

Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

4.2 Posology and method of administration

A six-dose regimen over 3 days is recommended, as described below:

Adults and adolescents weighing 35kg and above

1st dosage, at the time of initial diagnosis 4 Tablets

2nd dosage, at 8 hours after 1st dose 4 Tablets

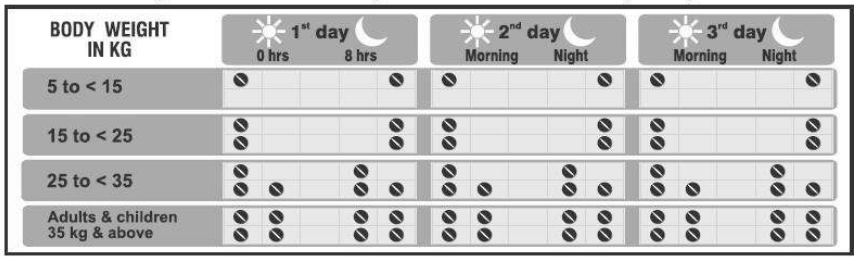
3rd dosage, at 24 hours after 1st dose 4 Tablets

4th dosage, at 36 hours after 1st dose 4 Tablets

5th dosage, at 48 hours after 1st dose 4 Tablets

6th dosage, at 60 hours after 1st dose 4 Tablets

Total number of Tablets: 24 tablets



Method of administration Tablets for oral administration

The dose should be taken with food or drinks rich in fat such as milk. A standard African diet with fat content ranging between 30 and 60 g/day or breast milk were shown to be adequate in Africa. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

In the event of vomiting within 1 hour of administration a repeat dose should be taken.

4.3 Contraindications

Artemether+ Lumefantrine tablet is contraindicated in:

- Known hypersensitivity to artemether, lumefantrine or to any of the excipients of Artemether+ Lumefantrine.
- Patients with severe malaria according to WHO definition.
- First trimester of pregnancy in situations where other suitable and effective anti-malarials are available.
- Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc

interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.

- Patients taking drugs that are known to prolong the QTc interval such as:
  - antiarrhythmics of classes IA and III,
  - neuroleptics and antidepressant agents,
  - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents,
  - certain non-sedating antihistaminics (terfenadine, astemizole),
  - cisapride.
- Patients with known disturbances of electrolyte balance e.g. hypokalemia or hypomagnesaemia.
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

4.4 Special warnings and precautions for use

Tosok 20/120 has not been evaluated for prophylaxis and is therefore not indicated for prophylaxis.

Tosok 20/120 has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure.

Tosok 20/120 is not indicated for, and has not been evaluated in, the treatment of malaria due *to P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with

P. falciparum and *P. vivax* at baseline. Tosok 20/120 is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Like other antimalarials (e.g. halofantrine, quinine, quinidine), Tosok 20/120 has the potential to cause QTc prolongation.

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

If a patient deteriorates whilst taking Tosok 20/120, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients

previously treated with Tosok 20/120.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions Resulting in a Contraindication

Interaction with drugs that are known to prolong the QTc interval

Tosok 20/120 is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as:
antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride.

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Tosok 20/120 with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4such as rifampicin

Oral administration of rifampicin (600 mg daily), a strong CYP3A4 inducer, with Tosok 20/120 Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis co-infected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Tosok 20/120 alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with Tosok 20/120.

Interactions resulting in concomitant use not being recommended Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Tosok 20/120 should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If Tosok 20/120 is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half- life of lumefantrine must be taken into account when administering quinine in patients previously treated with Tosok 20/120. In patients previously treated with

halofantrine, Tosok 20/120 should not be administered earlier than one month after the last halofantrine dose. As patients to be treated with Tosok 20/120 may have recently been treated with other antimalarials, interactions with mefloquine and quinine were studied in healthy volunteers. The sequential oral administration of mefloquine prior to Tosok 20/120 had no effect on plasma concentrations of artemether or the artemether/ dihydroartemisinin ratio but there was a significant (around 30 to 40%) reduction in plasma levels (Cmax and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for this decrease in bioavailability.

The concurrent i.v. administration of quinine (10 mg/kg BW) with Tosok 20/120 had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Tosok 20/120 to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Tosok 20/120 in 14 additional subjects. It would thus appear that the inherent risk of QTc- prolongation associated with i.v. quinine was enhanced by prior administration of Tosok 20/120. In a clinical trial in Thailand some adult patients received Tosok 20/120 following treatment failures with mefloquine or quinine. One hundred and twenty-one patients received Tosok 20/120 without any previous antimalarial treatment whereas 34 and 9 patients had measurable quinine or mefloquine, respectively, at enrolment. These patients showed similar safety and pharmacokinetic profiles of Tosok 20/120 to patients who had no detectable levels of other antimalarials.

Interactions to be considered

Interactions affecting the use of Tosok 20/120 Interaction with CYP 3A4 inhibitors

Both artemether and lumefantrine are metabolized by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with Tosok 20/120 led to a modest increase (121-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Tosok 20/120 is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for

increased concentrations of lumefantrine which could lead to QT prolongation, Tosok 20/120 should be used cautiously with drugs that inhibit CYP3A4. Administration of artemether with double concentrated grapefruit juice in healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug. Grapefruit juice should be avoided during Tosok 20/120 treatment.

Interaction with anti-retroviral drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3-fold, and efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to lopinavir/ritonavir and efavirenz were not significantly affected by concomitant use of Tosok 20/120 should be used cautiously in patients on anti-retroviral drugs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Tosok 20/120, and increased lumefantrine concentrations may cause QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Tosok 20/120 is co-administered with weak to moderate inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy.

Interactions resulting in effects of Tosok 20/120 on other drugs Interaction with drugs metabolized by CYP450 enzymes

When Tosok 20/120 is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Whereas in- vitro studies with artemether at therapeutic concentrations revealed no significant inhibition of CYP450 enzymes, artemether and DHA were reported to have a mild inducing effect on CYPs (2C19, 2B6 and 3A4) activity. Although the magnitude of the changes was generally low and is not expected to present a problem in the general patient population, it is possible that CYP3A4 induction could alter the therapeutic effects of drugs that are predominantly metabolised by this enzyme.

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Tosok 20/120 may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non- hormonal method of birth control.

Drug-food/drink interactions

Tosok 20/120 should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased.

Grapefruit juice should be avoided during Tosok 20/120 treatment.

4.6 Pregnancy and Lactation

Women of child-bearing potential and contraceptive measures

As Tosok 20/120 is contraindicated during the first trimester of pregnancy, women should not conceive while on Tosok 20/120 treatment for malaria. This includes women prescribed Tosok 20/120 for stand-by emergency treatment of malaria during their travel, in case they may require treatment for malaria.

Women of child-bearing potential should be advised to practice contraception during travel with stand-by emergency treatment, while on Tosok 20/120 and until the start of the next menstruation after the treatment.

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.

Pregnancy

Based on animal data, Tosok 20/120 is suspected to cause serious birth defects when administered during the first trimester of pregnancy.

Reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats. Other artemisinin derivatives have in addition demonstrated teratogenic potential with an increased risk during early gestation.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Breast-feeding women should not take Tosok 20/120. Due to the long elimination half-life of

lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume before day 28 unless potential benefits to mother and child outweigh the risks of Tosok 20/120 treatment.

Fertility

There is no information on the effects of Tosok 20/120 on human fertility

4.7 Effects on ability to drive and use machines

Not reported.

4.8 Undesirable effects

Summary of the safety profile

Most of the reported events were of mild to moderate severity and duration, and likely related to the underlying malaria and/or to an unsatisfactory response to the treatment rather than to Tosok 20/120 although a causal relationship with the use of Tosok 20/120 could not be excluded for some reports. For other reports alternative factors were identified as the more likely cause of the events (e.g. concomitant drugs, concomitant infections) or the information provided was too scarce to draw any conclusion.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Tosok 20/120 via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Hypersensitivity reactions including urticaria and angioedema.

4.9 Overdose

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeuticgroup: Antimalarial ATCcode:

QT/QTc Prolongation

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of Tosok 20/120 was associated with prolongation of QTcF. The mean changes compared to placebo from baseline at 68, 72, 96, and 108 h post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 h after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec.

Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 h after the single dose with a maximal change at 1 h after dose of 14.1 msec.

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Tosok 20/120 is limited by the lack of an intravenous formulation, and the very high inter-and intra subject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6 to 8 hours after administration. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen- fold compared with fasted conditions when Tosok 20/120 was taken after a high-fat meal. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100 % absorption after a high-fat meal, the amount absorbed under fasted conditions would

be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin (DHA) is also bound to human serum proteins (47% to 76%). Protein binding to human plasma protein is linear.

Biotransformation/Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans in vivo. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity, which is not expected to present a problem in the general patient population.

During repeated administration of Tosok 20/120, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for the metabolism of artemether.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation.

In humans, the systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent compound.

In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours, while lumefantrine is eliminated very slowly with an elimination half-

life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Tosok 20/120.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Tosok 20/120, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of both drug components were eliminated in bile/faeces and urine.

5.3 Preclinical safety data

Dose Proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the Tosok 20/120 dose. No conclusive data is available for artemether.

Bioavailability /bioequivalencestudies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Tosok 20/120 as dispersible tablets and crushed tablets of 20 mg/120 mg in healthy adults.

Systemic exposure to Lumefantrine was similar following administration of Artemether/Lumefantrine tablets and intact tablets of 20 mg/120 mg in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet of 20 mg/120 mg. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the pediatric population since adequate efficacy of Artemether/Lumefantrine tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

The 80 mg/480 mg tablet was shown to be bioequivalent to 4 tablets of 20 mg/120 mg in healthy adults.

Specialpopulations Elderly patients

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Pediatrics

Systemic exposure to artemether, DHA, and lumefantrine when dosed on a mg/kg body weight basis in paediatric malaria patients (≥5 to <35 kg body weight) is comparable to that of the recommended dosing regimen in adult malaria patients.

Renal impairment

No specific pharmacokinetic studies have been performed in patients with renal impairment. However, based on the pharmacokinetic data in healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of Tosok 20/120 in patients with renal impairment is advised.

Hepatic impairment

No specific pharmacokinetic studies have been performed in patients with hepatic impairment. Metabolism is the primary clearance mechanism of both artemether and lumefantrine and may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose Powder BP, Hypromellose E15 (Dry Mix) (Hydroxy Propyl Methyl Cellulose E15) BP, Polysorbate 80 BP, Maize Starch BP, Purified Water BP, Purified Talc BP, Magnesium Stearate BP, Crospovidone BP, Colloidal Anhydrous Silica BP.

6.2 Incompatibilities

Nil

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30^0C in a dry place, Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Aluminium-PVDC coated PVC foil containing 24 tablets in one blister, such blister is packed in a printed carton along with pack insert

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/MANUFACTURER

M/s Hikmeg Pharma Limited

71, Ire-Akari Estate Road, Isolo, Lagos, Nigeria.

Manufactured by:

S Kant

HEALTHCARE Ltd.
1802-1805, G.I.D.C.,Phase III,
Vapi - 396 195. Gujarat, INDIA.