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

Oral Solid Dosage form – Uncoated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adult, children and infants of 5 kg and above.

4.2 Posology and method of administration

Artemether 20mg + Lumefantrine 120mg tablets-24 tablets

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

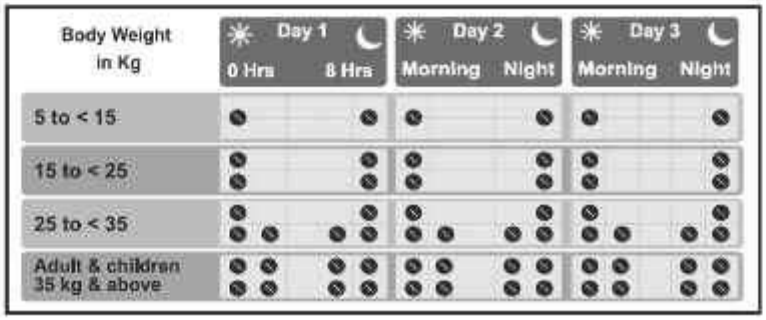
2nd dosage, at 8 hours after 1st dose 4 Tablets

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



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:

- Patients with severe malaria.
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (eg. flecainide, metoprolol, imipramine, amitryptyline, clomipramine).
- Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- Patients taking drugs known to prolong que are the QTc interval.

  These drugs include.
  - 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 a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

4.4 Special warnings and precautions for use

How to take drug: Artemether + Lumefantrine Tablets should be taken with food or drinks rich in fat such as milk.

If any dose missed: Try to make sure that you do not miss any doses. However, if you do

forget a dose of Artemether + Lumefantrine Tablets, take the missed dose as soon as you remember unless it is almost time

for your next dose. Then take your next dose at the usual time. Ask doctor for advice. Do not take a double dose to make up for a forgotten dose.

4.5 Interaction with other medicinal products and other forms of interaction

Some medicines must not be taken with Artemether + Lumefantrine Tablets.

These include:

- Medicines used for the treatment of heart rhythm disturbances (eg. Flecainide, metoprolol),
- Certain medicines used to treat depression (such as imipramine, amitriptyline, clomipramine),
- Certain types of medicine used to treat infection, such as:
  - Rifampicin, an antibiotic to treat leprosy or tuberculosis
  - Antibiotics, including medicines of the classes: macrolides, fluoroquinolones, imidazole,
  - Triazole antifungal agents
- Certain medicines used to treat allergies or inflammation (eg. Nonsedating antihistaminics such as terfenadine or astemizole),
- A medicine called cisapride used to treat stomach disorders,
- Certain medicines used to treat epilepsy (such as carbamazepine, phenytoin)
- St. John's wort (Hypericum perforatum) a medicinal plant or extract of this medicinal plant used to treat for example depressed mood.
- Any other anti-malarial medicines
- Any anti-retroviral medicines or protease inhibitor
- A hormonal birth control medicine.

4.6 Pregnancy and Lactation

Pregnancy - Artemether + Lumefantrine Tablets are suspected to cause serious birth defects when administered during the first trimester of pregnancy, so it must not be used during the first 3 months of pregnancy. If it is possible use an alternative medicine first. However, it should not be withheld in life threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should't only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Lactation - Women taking Artemether + Lumefantrine Tablets should not breast- feed

during their treatment. Due to the long elimination half-life of Lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Artemether + Lumefantrine Tablets unless potential benefits to the mother and child outweigh the risks of Artemether + Lumefantrine Tablets treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Artemether + Lumefantrine Tablets should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

Most of the side effects are mild to moderate and generally disappear after a few days to a few weeks after treatment. Some side effects are more commonly reported in children and others are more commonly reported in adults. Some side effects could be serious and need immediate medical attention (affecting less than 1 in 1,000 patients). If you get a rash, swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing, tell your doctor straight away. These are signs of an allergic reaction.

4.9 Overdose

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antimalarials, blood schizonticide. ATC code: P01 BF01

Mechanism of Action: Artemether is rapidly metabolized into an active metabolite - dihydroartemisinin (DHA). The antimalarial activity of Artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which Lumefantrine exerts its antimalarial effect is not well defined. Available data suggest that Lumefantrine inhibits the formation of hematin by forming a complex with hemin. Both Artemether + Lumefantrine were shown to inhibit nucleic acid and protein synthesis.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of tablet 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 Artemether + Lumefantrine Tablets 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 metabolized (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 Artemether + Lumefantrine Tablets, 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 Artemether + Lumefantrine Tablets.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether + Lumefantrine Tablets, 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 Artemether + Lumefantrine Tablets dose. No conclusive data is available for artemether.

Bioavailability /bioequivalencestudies

Systemic exposure to Lumefantrine, Artemether and dihydroartemisinin was similar following administration of Artemether + Lumefantrine Tablets as crushed tablets of 20 mg/120 mg in healthy adults.

Systemic exposure to Lumefantrine was similar following administration of Artemether/Lumefantrine dispersible 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 dispersible 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.

Special populations 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 pediatric 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 Artemether + Lumefantrine Tablets 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 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

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a dry place below 30°C. Protect from light.

Keep out of reach of Children.

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

Aluminium-PVDC coated PVC foil containing 1X6, 1X12, 1X18 and 1X24 tablets in one blister, and 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 S KANT NIGERIA LIMITED

Alshonny Place, No 1A Shonny Highway,

Shonibare Estate, Ikeja,

Lagos Nigeria

Manufactured by:

S Kant

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