1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTIC (SMPC)

Enclosed

1. NAME OF THE MEDICINAL PRODUCT

1.1 (Invented) name of the medicinal product

CHEMAL (Artemether and Lumefantrine Tablets (80+480)

1.2 Strength

80+ 480 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CHEMAL (Artemether and Lumefantrine Tablets (80+480)

Each film coated tablet contains:

Artemether ……...80 mg.

Lumefantrine USP ……..480 mg

Excipients ……..Q.S.

Colour: Tartrazine Supra

3 PHARMACEUTICAL FORM

Film Coated Tablets

A Yellow coloured, Round shaped, Biconvex, Film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHEMAL 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 CHEMAL 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, consider ed 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 CHEMAL 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 standard 3 days treatment schedule with a total of 6 doses is recommended as follows.
One tablet of 80 mg/480 mg at the time of initial diagnosis, again 1 tablet after 8 hours and then 1 tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 tablets of 80 mg/480 mg).

Treatment and stand-by emergency treatment

The treatment should be administered at the time of initial diagnosis or at onset of symptoms.

New and recrudescent infections
Data for a limited number of patients with CHEMAL show that new and recrudescent infections can be treated with a second course of the medication.

Special populations

Geriatric patients
There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Dosage in patients with renal impairment
No specific studies have been carried out in this groups of patients. There was no significant renal excretion of lumefantrine, artemether and dihydroartemisinin (DHA) in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of CHEMAL in patients with renal impairment is recommended.

Dosage in patients with hepatic impairment
No specific studies have been carried out in this group of patients. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution should be exercised in dosing patients with severe hepatic impairment (see section WARNINGS AND PRECAUTIONS). Most patients with acute malaria present with some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with CHEMAL.

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

Known hypersensitivity to artemether, lumefantrine or to any of the excipients of CHEMAL.

- Patients with severe malaria according to WHO definition*.
- First trimester of pregnancy in situations where other suitable and effective anti-malarials are available (see section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).
- 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

CHEMAL has not been evaluated for prophylaxis and is therefore not indicated for prophylaxis.

CHEMAL has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure. CHEMAL is not indicated for, and has not been evaluated in, the treatment of malaria due to P. vivax, P. malariaeor P. ovale, although some patients in clinical studies had co-infection with P. falciparum and P. vivax at baseline. CHEMAL is active against blood stages of Plasmodium vivax , but is not active against hypnozoites.

Like other antimalarials (e.g. alofantrine, quinine, quinidine), CHEMAL has the potential to
cause QTc prolongation (see section CLINICAL PHARMACOLOGY – QT/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 CHEMAL, 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 CHEMAL.

4.5 Interaction with other medicinal products and other forms of interaction

Caution in case of concomitant administration of medicines With other antimalarials:
Data on safety and efficacy are limited, and CHEMAL should therefore not be given concurrently with other antimalarials unless there is no other treatment option. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with CHEMAL. Patients previously treated with other antimalarials:If CHEMAL is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised

In patients previously treated with halofantrine, CHEMAL should not be administered earlier than one month after the last halofantrine dose

With other drugs:
Caution is recommended when combining CHEMAL with substrates, inhibitors or weak to moderate inducers of CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with cautionin patients taking CHEMAL (see sections INTERACTIONS and CLINICAL PHARMACOLOGY - Pharmacokinetics).

With hormonal contraceptives
: CHEMAL may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control (see sections INTERACTIONS and WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).

Special populations
CHEMAL has not been studied for efficacy and safe ty in patients with severe hepatic or renal impairment and therefore no recommendations can be made for these groups of patients. In patients with severe hepatic impairment, a clinically relevant 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 (see section CLINICAL PHARMACOLOGY - Pharmacokinetics).

4.6 Pregnancy and lactation

As CHEMAL is contraindicated during the first trimester of pregnancy, women should not
conceive while on CHEMAL treatment for malaria. This includes women prescribed CHEMAL 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

CHEMAL 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 (see section WARNINGSAND PRECAUTIONS).

Pregnancy

Based on animal data, CHEMAL is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections CONTRAINDICATIONS and NON-CLINICAL SAFETY DATA).

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 (see section NON-CLINICAL SAFETY DATA)

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to CHEMAL (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether-lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

CHEMAL treatment is contraindicated during the first trimester of pregnancy in situations

where other effective anti-malarials are available. However, it should not be withheld in life-threatening situations where no other effective anti-malarials are available (see section CONTRAINDICATIONS). During the second and the third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Breast-feeding women should not take CHEMAL. 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 CHEMAL treatment.

Fertility

There is no information on the effects of CHEMAL on human fertility (see section NON-CLINICAL SAFETY DATA – Fertility).

4.7 Effects on ability to drive and use machines

May make you feel sleepy, dizzy or generally weak. If this happens to you, do not drive or use any tools or machines

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 CHEMAL although a causal relationship with the use of CHEMAL 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, concomitantinfections) or the information provided was too scarce to draw any conclusion. Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials (Table 1 and 2) are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.
Table 1
Adverse drug reactions compiled from a pooled safety analysis in clinical trials in adults and adolescents >12 years of age using the recommended 6-dose regimen
Metabolism and nutrition disorders
Very common:
Decreased appetite
Psychiatric disorders
Very common:
Sleep disorder
Nervous system disorders
Very common: Headache, dizziness
Common:
Clonus
Uncommon:
Somnolence, hypoesthesia, ataxia
Cardiac disorders
Very common: Palpitations
Respiratory, thoracic and mediastinal disorders
Common:
Cough
Gastrointestinal disorders
Very common:
Vomiting, abdominal pain, nausea
Common:
Diarrhea
Skin and subcutaneous tissue disorders
Common:
Rash, pruritus
Uncommon:
Urticaria
Musculoskeletal and connective tissue disorders
Very common:
Arthralgia, myalgia
General disorders and administration site conditions
Very common:
Asthenia, fatigue
Uncommon:
Gait disturbance
Investigations
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CHEMAL
Uncommon:

Electrocardiogram QT prolonged, liver function tests increased
Table 2
Adverse drug reactions compiled
from a pooled safety analysis of 4
studies in infants and children
≤
12 years of age receiving a 6-dose
regimen of CHEMAL or CHEMAL/CHEMAL Dispersible
Immune system disorders
Rare:
Hypersensitivity
Metabolism and nutrition disorders
Very common:
Decreased appetite
Psychiatric disorders
Uncommon:
Sleep disorder
Nervous system disorders
Common:
Headache, dizziness
Uncommon:
Clonus, somnolence
Cardiac disorders
Uncommon:
Palpitations
Respiratory, thoracic and mediastinal disorders
Very common: Cough
Gastrointestinal disorders
Very common: Vomiting
Common:
Abdominal pain, diarrhea, nausea
Skin and subcutaneous tissue disorders
Common:
Rash
Uncommon:
Urticaria, pruritus
Musculoskeletal and connective tissue disorders
Common:
Arthralgia, myalgia
General disorders and administration site conditions
Common:
Asthenia, fatigue
Investigations
Common:
Liver function tests increased
Rare:
Electrocardiogram QT prolonged
Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (1.2% of adolescents and adults, no cases in children). The

following adverse reactions were reported in adults with a frequency of uncommon but were not reported in infants or children: hypoesthesia, ataxia, and gait disturbance.

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 Pharmacodynamic properties

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 CHEMAL 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 CHEMAL is limited by the lack of an intravenous formulation, and the very high inter- and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C max).
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 CHEMAL 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 (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS). During repeated administration of CHEMAL, 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. The clinical evidence of induction is consistent with the in vitrodata described in section INTERACTIONS. 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 vitroantiparasitic 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 (see sections CONTRAINDICATIONS and INTERACTIONS).

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 characteristic s such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of CHEMAL. In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of CHEMAL, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.
In animals (rats and dogs), no unchanged artemetherwas 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 ofboth drug components were eliminated in bile/faeces and urine.

5.3 Preclinical safety data

Based on conventional studies, repeated dose toxicity, and genotoxicity, preclinical data reveal no special hazard for humans administered artemether/lumefantrine in adults and children weighing at least 5 kg for the treatment of malaria when used in accordance with the Product Information. Adverse drug reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels, and with possible

relevance to clinical use, were as follows: post-implantation losses and teratogenicity of artemisinin derivatives

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Colliodal Anhydrous silica BP
Dibasic Calcium Phosphate BP
Kyron T-314 (IH)
Ethyl Cellulose RT-N-50 USP
Sodium Starch Glycollate BP
Magnesium Stearate BP
Purified Talc BP
Isopropyl alcohol BP
Methylene chloride BP
Ready mix of Tartrazine (IH)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months from the date of Manufacturing.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Alu-PVC Blister is used as primary packaging material for packing of **Chemal (Artemether and Lumefantrine Tablets (80+480).6** Tablets are packed in a One blister. Such 1 blister is packed in one carton along with Pack Insert.

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. REGISTRANT

MIKCHEMA GLOBAL SERVICES AND INVESTMENT LIMITED.
ADDRESS: # 37, Modern Market Road,
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8. MANUFACTURER

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Vadodara – 390010
Gujrat.

9. DATE OF REVISION OF THE TEXT
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10 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable