Product Name	*KWAMAL TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets)*

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

Attached

REGULATORY EXECUTIVE	Q.A.MANAGER
Prepared By	Approved By

Summary of Product Characteristic

Contents

Summary of Product Characteristic

1. **Name of the Medicinal Product:**
   KWAMALTABLET (Artemether 80mg&Lumefantrine480mg tablet)

2. **Quality and Quantitative Composition:**

2.1 Qualitative Declaration

Each film coated tablet contains:
Artemether 80mg
Lumefantrine USP 480mg
Excipients q.s.
Colour :Tartrazine Supra

2.2 Quantitative Declaration

Components	Amount / Unit (mg)	Reference
Artemether	80	In-House
Colloidal Silicon Dioxide	6	Ph Eur (BP)
Kyron T-314	14	USP (NF)
Light Magnesium Oxide	10	Ph Eur (BP)
Povidone K-30%	25	Ph Eur (BP)
Lumefantrine	480	USP (NF)
Purified Talc	5	Ph Eur (BP)
Magnesium Stearate	8	Ph Eur (BP)
Crosspovidone	12	Ph Eur (BP)
PEG 6000	10	Ph Eur (BP)
Isopropyl Alcohol	q.s	Ph Eur (BP)
Ready Mix of Tartrazine	19	In-House
Methylene Chloride	q.s	Ph Eur (BP)

3. **Pharmaceutical Form:**
   Tablet

4. **Clinical Particulars:**

4.1 Therapeutic indications

- Kwamal Tablets (Artemether and lumefantrine) are indicated for treatment of acute, uncomplicated malaria infections due to Plasmodium falciparum in patients of 5 kg bodyweight and above (1)
- Kwamal Tablets (Artemether and lumefantrine) have been shown to be effective in geographical regions where resistance to chloroquine has been reported (1)
- Kwamal Tablets (Artemether and lumefantrine) should not be used to treat severe malaria or to prevent malaria

Summary of Product Characteristic

4.2 Posology and method of administration

Oral use

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferablethat the patient has a positive diagnostic test before administration.

One tablet should be taken twice a day for three days (total six doses).The first dose should be followedby asecond dose after 8 hours. The following two days the doses of Kwamal tablet should be given twice daily,morning and evening (i.e. 12 hours apart).

To increase absorption, Kwamal tablet should be taken with food or a milky drink. If a patient is unable to tolerate food, Kwamal tablet should still be administered, but the systemic exposure may be reduced.

Patients who vomit within 1 hour of taking the medication should repeat the dose. If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued untilthe full course of treatment has been completed.

Renal or hepatic impairment
No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advisedwhen administering Kwamal tablet to patients with severe renal or hepatic problems.

Paediatric patients weighing less than 35 kg:
Appropriate dose adjustments cannot be achieved with this product. Other formulations containing loweramounts of artemether/lumefantrine are available for these patients.

Elderly
No special precautions or dosage adjustments are necessary in such patients.

4.3 Contraindications

Kwamal tablet is contraindicated in:

- patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- patients with severe malaria according to WHO definition.
- patients with a personal or 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, clinically relevant bradycardia or severe cardiac diseases.
- patients taking drugs that are known to prolong 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 antihistamines (terfenadine, astemizole)
- cisapride
- patients with known disturbances of electrolyte balance e.g. hypokalaemia 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, StJohn's wort.

4.4 Special warning and precautions for use

- Talk to your health care provider before taking Kwamal tablet
- If you have severe liver or kidney problems.

Take special care with Kwamal tablet:

- If your condition worsens, or if you feel too unwell to eat and drink, contact your health care provider immediately. Your health care provider may want to perform a test called an electrocardiogram (ECG) and check the levels of electrolytes, such as potassium and magnesium in your blood before and during treatment.
- If you are taking or have taken any other medication for the treatment of malaria, talk to your health care provider, because some of these medicines must not be given together with Kwamal tablet.
- If you are infected with both, Plasmodium falciparum and Plasmodium vivax, your health care provider will give you another medicine for you to take after completing Kwamal tablet treatment

4.5 Interaction with other medicinal products and other forms of interaction

It is important that you tell your health care provider if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of Kwamal tablet, or Kwamaltablet may affect their action. Side effects of either medicine may become worse and/or the medicines may become less effective.

Especially tell your health care provider if you take or have recently taken:

- Any other medicines to treat or prevent malaria
- Medicines for your heart
- Antipsychotic medicines (for treatment of abnormal condition of the mind)
- Antidepressants (medication to alleviate mood disorders)
- Antibiotics
- Antihistamines (for treatment of, e.g., allergies)
- Cisapride (a medicine for improving gastric motility)
- Medicines to treat HIV infection
- Medicines to treat hepatitis B or hepatitis C infection
- Medicines against fungal infection
- Hormonal methods of birth control (for example birth control pills or contraceptive patch)

4.6 Pregnancy and lactation

Pregnancy

Kwamal tablet can be used during pregnancy.

Breast-feeding

The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small.Therefore,breastfeeding women can receive artemisinin-based combination therapies (including 80/480) formalaria treatment.

Fertility
There is no information on the effects of Kwamal tablet on fertility in humans.

4.8 Undesirable effects

Like all medicines, Kwamal tablet can cause side effects, although not everybody gets them. It is important that you inform the health care provider of any change in your health.

The following side effects have been reported in adults and adolescents above 12 years of age using the recommended 6-dose regimen. A similar side effect profile was reported for children

The most commonly reported side effects (greater than 1 in every 10 patients treated) include palpitations, headache, dizziness, nausea, vomiting, abdominal pain, decreased appetite, joint pain, muscle pain, weakness, tiredness, sleep disorders.

Commonly (greater than 1 in every 100 patients treated) reported side effects include cough, rash, itching, diarrhoea and involuntary, rhythmic, muscular contractions (clonus).

Uncommon side effects (greater than 1 in every 1000 patients treated but less than 1 in 100): alterations to the electrocardiogram (QT-prolongation), lack of voluntary coordination of muscle movements, which may present e.g. as gait disturbance, numbness (hypoesthesia), somnolence, urticaria, blood tests for liver function abnormal.

Allergic reactions and anaemia (low red blood cell count) have been reported in patients treated with Kwamal tablet. However, frequency estimates for this side effect are not available. Allergic reactions may present with rash, hives, rapid swelling of the face and throat (angioedema).

If any of the side effects gets serious, or if you notice any side effects not listed, please tell your health care provider as soon as possible.

4.9Overdose and treatment

Experience of overdosage with artemether and lumefantrine is limited. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include monitoring of ECG and serum electrolytes.

5. Pharmacological Properties:

5.1Pharmacodynamic Properties

Pharmacodynamic effects

Artemether/Lumefantrine 80/480 comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site ofantiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

5.2 Pharmacokinetic Properties

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 while Kwamal 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).

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47–76%).

Metabolism

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism both in vitro and in humans). Human liver microsomes metabolized 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 ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity.

Lumefantrine is N-debutylated, mainly by CYP3M in human liver microsomes in vivo in animals (dogs and rats) glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In vitro lumefantrine significantly inhibits the activity of CYP2D6 attherapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-6 days.
Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Kwamal.
No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine.
Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and gods, qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dole being recovered as parent drug.

5.3Preclinical safety Data

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxicartemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Cardiovascular Pharmacology

In toxicity studies in dogs at doses > 600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man. In an in vitro assay of HERG channels, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. From the estimated IC50 values, the order of potency of HERG current block was halofantrine (IC50 = 0.04 μM) >chloroquine (2.5 μM) >mefloquine (2.6 μM) >desbutyl-lumefantrine (5.5 μM) >lumefantrine (8.1

μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether/lumefantrine.

6. Pharmaceutical Particulars:

6.1 List of excipients

Colloidal Silicon Dioxide, Kyron T-314, Light Magnesium Oxide, Povidone K-30%, Purified Talc, Magnesium Stearate, Crosspovidone, PEG 6000, Isopropyl Alcohol, Ready Mix of Tartrazine, Methylene Chloride.

6.2 Incompatibilities

None known

6.3Shelf life

36 months

6.4Special precautions for storage

Store in below 30°C. Protect from light.
Keep out of reach of children

6.5 Nature and contents of container

06 Tablets are packed in Alu-PVC blister, such 1 blisterispacked in carton with pack insert.

7. Marketing Authorization Holder:

NAME: NOVOPHARM FORMULATIONS (P) LTD.
ADDRESS:105.Rajmandir, 62- Alkapuri Society,
R.C Dutt Road, Vadodara – 390007,
GUJARAT, INDIA.
COUNTRY: INDIA
TELEPHONE: +91– 265–2342033
E-MAIL:novopharm.export@gmail.com

8. Marketing Authorization Number (s):

Product license / registration Number (s)

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9. Manufacturer Name:

Name:NOVOPHARM FORMULATIONS (P) LTD.
C/O RELAX BIOTECH PVT. LTD.
Address: 862/1 G.I.D.C, Industrial Estate, Makarpura,
Vadodara-390010, Gujarat, India.

10. Date of first authorization/renewal of the authorization:

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11. Date of revision of the text:

Jul 2022