**1. Name of the medicinal product:**

OCUQUIN 600 / 750

**1.1 Name of the medicinal product:**

Combikit of Artesunate Tablets and Mefloquine Hydrochloride Tablets USP

**1.2 Strength:**

Artesunate: 200 mg
Mefloquine Hydrochloride USP : 250 mg

**1.3 Pharmaceutical form:**

Tablet

**2. Qualitative and quantitative composition**

**OCUQUIN 600 / 750 (Combikit of Artesunate Tablets and Mefloquine Hydrochloride Tablets USP)**

**Each Combikit contains:**

**Artesunate Tablets 200 mg- 3 Tablets**

Each film coated tablet contains:

Artesunate: 200 mg

Excipients: q.s.

Colour: Titanium Dioxide BP

**Mefloquine Hydrochloride Tablets USP - 250 mg: 3 Tablets**

Each film coated tablet contains:

Mefloquine Hydrochloride USP: 250 mg

Excipients: q.s.

Colour: Titanium Dioxide BP

**Quantitative declaration:**

**OCUQUIN 600 / 750 (Combikit of Artesunate Tablets and Mefloquine Hydrochloride Tablets USP)**

**Each Combikit contains:**

**Artesunate Tablets 200 mg- 3 Tablets**

Each film coated tablet contains:

Artesunate: 200 mg

Excipients: q.s.

Colour: Titanium Dioxide BP

**Mefloquine Hydrochloride Tablets USP - 250 mg: 3 Tablets**

Each film coated tablet contains:

Mefloquine Hydrochloride USP: 250 mg

Excipients: q.s.

Colour: Titanium Dioxide BP

**3. Pharmaceutical form**

Tablet

**4. Clinical particulars:**

**4.1 Therapeutic indications:**

OCUQUIN 600 / 750 are indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria, in the setting of either *P. falciparum* mono-infection or mixed infections in children and infants of 5 kg and above.

**4.2 Posology and method of administration**

As directed by Physician.

Method of administration: Oral

**4.3 Contraindications**

• Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
• Known hypersensitivity to quinine, quinidine or any artemisinin
• The recovery period from severe malaria, as mefloquine has been shown to increase the risk of convulsions
• Concurrent or recent halofantrine therapy, due to the increased risk of prolongation of the QTc interval

• Concurrent or recent ketoconazole therapy, due to the increased risk of prolongation of the QTc interval

**4.4 Special warnings and precautions for use**

Caution should be exercised in:

• Patients with underlying cardiac conduction defects or known cardiac arrhythmias:

In rare cases, treatment and prophylaxis with mefloquine have been associated with clinically significant adverse events related to cardiac conduction.

• Patients with a history of seizures.

• Patients with severe liver impairment, as mefloquine undergoes hepatic metabolism.

• Patients with thalassaemia, sickle cell anaemia or G6PD-deficiency. No studies have been done in persons with these conditions.

**4.5 Interaction with other medicinal products and other forms of interaction**

No drug-drug interaction studies have been conducted with the fixed dose combination of artesunate and mefloquine.

**Antimalarials**

Halofantrine may cause fatal prolongation of the QTc. This has occurred when halofantrine was used with or without prior administration of mefloquine. Therefore, Artesunate/Mefloquine Tablets must not be given together or within 21 days after therapy with halofantrine. Co-administration of mefloquine and quinine produced a modest increase in QTc in patients and volunteers that correlated only with quinine concentrations. There has been extensive experience with the use of a quinine loading dose (20 mg salt/kg) for treating severe falciparum malaria in patients treated earlier with mefloquine with no deleterious cardiac effects. In addition, a study in malaria patients did not find a significant cardiac interaction between the quinine (10 mg salt/kg) dose and oral mefloquine (15 mg/kg) given together. Quinidine and chloroquine have been associated with prolongation of the QTc interval. Although there are no interaction data with mefloquine for either drug, an increase in the QTc interval is theoretically possible. Concurrent use of mefloquine with chloroquine or quinine may increase the risk of convulsions.

**Cardiac Drugs**

A number of cardiac drugs (e.g. quinidine, amiodarone, sotalol, disopyramide) are known to prolong the QTc interval. Therefore, caution is advised when giving Artesunate/Mefloquine Tablets with these drugs, as this could increase the risk of QTc prolongation. Treatment of malaria results in a slowing of the heart rate because of fever resolution. This effect may be exacerbated in patients who are already taking drugs that reduce the heart rate e.g. digoxin, β-blockers, verapamil, diltiazem, or ivabradine.

**Non Cardiac Drugs Producing QTc Prolongation**

Drugs associated with QTc prolongation include tricyclic antidepressants, phenothiazines, haloperidol, pimozide, terfenadine, astemizole, ketoconazole, moxifloxacin, cisapride, and metoclopramide. Therefore, caution is advised when giving Artesunate/Mefloquine Tablets with these drugs, as this could increase the risk of QTc prolongation.

**Antimicrobial Agents / Ketoconazole**

Mefloquine concentrations are increased by the co-administration with ampicillin and tetracycline. Mefloquine concentrations are reduced with concomitant use with rifampicin. Ketoconazole, an inhibitor of CYP3A4, results in increased mefloquine concentrations. There has been a report of convulsions in three patients treated with mefloquine combined with the quinolones ciprofloxacin, ofloxacin or sparfloxacin. As noted above, moxifloxacin and ketoconazole are known to induce QTc prolongation in both clinical and preclinical models. Therefore, caution is advised when giving Artesunate/Mefloquine Tablets with either drug because of the risk of a prolongation of the QTc interval**.**

**Anticonvulsants**

Artesunate/Mefloquine Tablets should not be given to epileptic patients, as mefloquine reduces the plasma levels of anticonvulsants e.g. carbamazepine, phenobarbital, phenytoin, valproic acid. However, if no other choice is available, dose adjustment of anti-seizure medication may be necessary during treatment with Artesunate/Mefloquine Tablets.

**Anticoagulants**

There are reports of serious bleeding in patients co-administered mefloquine and coumadin. Close monitoring of coagulation parameters is advised. Dose adjustment of oral anticoagulants may be necessary.

**Metoclopramide**

The concurrent use of metoclopramide with Artesunate/Mefloquine Tablets may increase the plasma concentrations of mefloquine. Antiretrovirals Coadministration of mefloquine and

ritonavir (200 mg) decreased ritonavir AUC (31%) and Cmax (36%). Ritonavir did not affect the pharmacokinetics of mefloquine. Clinical consequences are not expected.

**Food**

There are no food interaction data with Artesunate/Mefloquine Tablets. Data in P. falciparum-infected patients treated with mefloquine and artesunate given as loose tablets did not indicate any consistent effect of food on mefloquine AUC.

**4.6 Pregnancy and lactation**

**Pregnancy**

Artesunate + mefloquine may be used in the second and third trimester of pregnancy. In the first trimester artesunate + mefloquine should be used only if this is the only treatment immediately available or if first-line therapy with quinine plus clindamycin has failed.

**Lactation**

Mefloquine is secreted into breast milk. Lactating women should receive the recommended antimalarial treatment (including artesunate+mefloquine).

**4.7 Effects on ability to drive and use machines:**

Mefloquine can cause dizziness and severe vertigo. Patients who experience such side-effects during or after treatment with Artesunate/Mefloquine Tablets should not drive, operate machinery or perform tasks that require a high degree of manual and/or psychomotor dexterity for at least 3 weeks following use of Artesunate/Mefloquine Tablets.

**4.8 Undesirable effects:**

The most frequent adverse events were headache, dizziness, vomiting, nausea, fatigue, pyrexia, arthralgias, myalgias, anorexia, sleep disorders, and palpitations.

Other adverse events which have been reported to occur with artesunate, mefloquine, or combinations of the two include anxiety, abnormal dreams, weakness, urticaria, hypersensitivity (allergic) reactions and skin rashes (including erythematous maculapapular rash, erythema multiforme, and Stevens-Johnson syndrome), rigors, tremor, confusion, and numbness. Serious psychiatric adverse events (seizure, depressive syndrome, acute psychosis) and acute intravascular haemolysis with haemoglobinuria have been reported rarely. There have also been reports of mild electrocardiogram (ECG) changes (QTc and PR increases), atrial extrasystoles,

nonspecific T-wave changes, and bradycardia, as well as elevations of transaminases. Their frequencies cannot be estimated from the available data.

**4.9 Overdose:**

**Symptoms**

In the event of an overdose the symptoms may be more pronounced: cardiac, hepatic and neurological symptoms have been reported.

**Treatment**

Patients should be monitored by ECG and observed for neuropsychiatric symptoms for at least 24 hours. The use of oral activated charcoal to limit mefloquine absorption may be considered within one hour of ingestion of an overdose. Supportive care should be given as clinically indicated.

**5. Pharmacological properties:**

**5.1 Pharmacodynamics properties:**

Pharmacotherapeutic group: Antimalarial

ATC-Code: Artemisinin and derivatives, combinations (P01BF02)

**Mechanism of action**

**Artesunate**

Artesunate, an artemisinin derivative, and its principal metabolite dihydroartemisinin (DHA) are toxic to malaria parasites at nanomolar concentrations. There is enhanced uptake of the drug by red blood cells infected with parasites, which is rapid and saturable. It is active against all Plasmodium species. It has broad activity against asexual parasites, killing all stages from young rings to schizonts. In *P. falciparum* malaria, artemisinin also kills the gametocytes—including the stage 4 gametocytes.

The peroxide moiety in artemisinin reacts in the presence of haeme. A primary radical alkylates haeme via an intramolecular process to produce covalent haeme-drug adducts. The accumulation of nonpolymerizable redox-active haeme derivatives, a consequence of haeme alkylation, is thought to be toxic for the parasite. The alkylation of haeme by artemisinin has been demonstrated in malaria infected mice, indicating that haeme is acting as the trigger and target of artemisinin.

**Mefloquine**

Mefloquine is an antimalarial agent with highly active schizontocide activity but is not gametocidal. It is active against chloroquine-resistant *P. falciparum*. The exact mechanism of action of mefloquine is unclear but it is has a high affinity for erythrocyte membranes.

**5.2 Pharmacokinetic Properties**

**Artesunate**

According to published data, orally administered artesunate is rapidly hydrolyzed to DHA, primarily by plasma or tissue choline esterases. Due to the rapid conversion, artesunate is often considered as pro-drug of DHA. Following oral administration of artesunate, the ratio of AUC for DHA to AUC for artesunate can be as high as 10:1. Artesunate Cmax concentrations are achieved within 1 hour, and it is eliminated with a half-life of 20 to 45 minutes. Plasma protein binding of artesunate and DHA is moderate (62 to 93%) and albumin is the principal binding protein for DHA in human plasma. The metabolic pathways for DHA was studied in humans by analyzing metabolites in urine collected from patients who had received intravenous AS and metabolites produced by human liver microsomes. It was shown that DHA is metabolized by UGT1A9 and UGT2B7, but not UGT1A1 and UGT1A6. The major metabolite identified was α-DHA-β-glucuronide. AS and DHA undergo extensive first-pass metabolism with very high extraction ratio. For drugs with high extraction ratio, clearance approaches blood flow and is therefore perfusion rate limited. No urinary excretion data are available for humans.

**Mefloquine**

Mefloquine is absorbed from the gastrointestinal tract and is widely and rapidly distributed throughout the body. The mean times to maximum concentrations range from 6 to 24 hours in healthy volunteers. Plasma levels are higher in patients with malaria than in healthy volunteers. Mefloquine is 98% bound to plasma proteins and is metabolised in the liver by cytochrome P450 isoenzymes to inactive 4- carboxylic acid metabolite, and several other metabolites. Mefloquine has a long half-life of 14- 28 days. Excretion is mainly in the faeces and bile.

**5.3 Preclinical safety data**

Artesunate and mefloquine have been extensively and safely used for many years for the treatment of malaria at doses similar to those used in Artesunate/Mefloquine Tablets.

Artemisinin derivatives, of which artesunate is one, have been associated with neurotoxicity following prolonged exposure to very high doses in animals. To date, there is no convincing clinical evidence of neurotoxicity in treated patients. Furthermore, the potential for neurotoxicity in man is highly unlikely given the rapid clearance of artesunate and short exposure (3 days of treatment). Artemisinins are also known to be embryotoxic and artesunate has been shown to cause increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats and rabbits.

In rats and mice, mefloquine has been shown to cross the placenta and is teratogenic in early gestation. Mefloquine is also secreted into breast milk. In vitro, mefloquine blocks preferentially the slow (IKs) component of the delayed rectifier potassium (K+) channel in cardiac muscle and, therefore theoretically has the potential to exacerbate the QTc prolongation produced by other drugs.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

| Sr. No. | Excipients Name | Specification |
|---|---|---|
| 1 | Microcrystalline Cellulose | BP |
| 2 | Lactose | BP |
| 3 | Hydrophobic Colloidal Anhydrous Silica | BP |
| 4 | Starch | BP |
| 5 | Povidone K-30 | BP |
| 6 | Isopropyl Alcohol | BP |
| 7 | Sodium Starch Glycolate | BP |
| 8 | Magnesium Stearate | BP |
| 9 | Purified Talc | BP |
| 10 | Polacrillicn Potassium (Kyron T 314) | USP |
| 11 | Titanium Dioxide | BP |
| 12 | Hypromellose (HPMC 15 CPS ) | BP |
| 13 | Propylene Ethylene Glycol (400) | BP |
| 14 | Dichloromethane | BP |

| | | |
|---|---|---|
| 15 | Sodium Lauryl Sulfate | BP |
| 16 | Crosscarmellose Sodium | BP |
| 17 | Cross povidone | BP |
| 18 | Macrogol 6000 (P.E.G.6000) | BP |

**6.2 Incompatibilities**

None

**6.3 Shelf life**

36 Months (3 Years) from date of manufacturing

**6.4 Special precautions for storage**

Store below 30°C in a dry place. Keep medicines out of reach of children.

**6.5 Nature and contents of container**

OCUQUIN 600 / 750 is available in 1 Combikit of 6 Tablets packed in Alu-PVC blister. 1 Blister packed in a carton along with pack insert.

**6.6 Special precautions for disposal:**

None

**7. Registrant:**

**M/s NOMEDI PHARMACEUTICALS LTD**
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**8. MANUFACTURER**

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