1. NAME OF THE MEDICINAL PRODUCT

Artemether & Lumefantrine 80/480 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Artemether & Lumefantrine 80/480 tablets is a fixed dose combination and each tablet contains artemether 80 mg and lumefantrine 480 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

Therapeutic indications

Artemether & Lumefantrine is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adult, children and infants. Because Artemether and lumefantrine 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 anti-malarials.

Contraindications

Artemether & Lumefantrine is contraindicated in:

- Hypersensitivity to Artemether, Lumefantrine or to any of the excipients
- 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 Pregnancy and Lactation).
- 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.

Special warnings and precautions for use

Must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available

Artemether/Lumefantrine 80/480 mg has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Due to limited data on safety and efficacy, Artemether & Lumefantrine 80/480 tablets should not be given concurrently with any other antimalarial unless there is no other treatment option.

If a patient deteriorates whilst taking Artemether/Lumefantrine 80/480 mg, 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 Artemether & Lumefantrine

If quinine is given after Artemether & Lumefantrine close monitoring of the ECG is advised

If Artemether & Lumefantrine is given after mefloquine, close monitoring of food intake is advised

In patients previously treated with halofantrine, Artemether & Lumefantrine should not be administered earlier than one month after the last halofantrine dose.

Artemether & Lumefantrine 20/120 tablets [Uncoated] is not indicated and has not been evaluated for prophylaxis.

Caution is recommended when combining Artemether & Lumefantrine tablets [Uncoated] with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered

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

Drug interaction:

The likelihood of Artemether and lumifantrine interaction with other drug is minimal in views of its short duration of administration and wide therapeutic index; three specific pharmacokinetic and pharmacodynamic drug-drug interaction studies with ketaconazole, mefloquine and quinine have been conducted in healthy volunteers.

Interaction with anti malarial:

A drug interaction study with Artemether and lumifantrine in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3 dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of Artemether and lumifantrine were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels 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 the decrease in bioavailability.

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 h) was given sequentially 2 h after the last (sixth) dose of Artemether and lumifantrine (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemether and lumifantrine 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 cardio toxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and lumifantrine 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 Artemether and lumifantrine. Effects on ability to drive and use machines.

Interaction with CYP450 3A4 inhibitors (ketoconazole)

Dose adjustment of Artemether and lumifantrine is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Interaction with CYP450 enzymes

Whereas in vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisinins have some capacity to induce the production of the cytochrome enzyme CYP2C19, and perhaps also CYP3A4. It is possible that iso-enzyme induction could alter the therapeutic effects of drugs that are predominantly metabolised by these enzymes.

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 Artemether and lumifantrine with drugs that are metabolised by this iso-enzyme is contraindicated. In vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with Artemether and lumifantrine, requires clinical surveillance and monitoring of clinical response/undesirable effects.

Other interactions

Administration of Artemether and lumifantrine is contra-indicated in patients taking drugs that are known to prolong the QT interval.

In patients previously treated with halofantrine, Artemether and lumifantrine should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, Artemether and lumifantrine should not be given concurrently with any other anti-malarial agent.

In addition, due to the propensity of some anti-malarial agents to prolong the QT interval, caution is advised when administering Artemether and lumifantrine to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

Pregnancy and lactation
Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Artemether and lumifantrine treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective anti-malarials are available. However, it should not be withheld in life-threatening situations, where no other effective anti-malarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.
Lactation
Women taking Artemether and lumifantrine 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 and lumifantrine unless potential benefits to the mother and child outweigh the risks of Artemether and lumifantrine treatment.
Effects on ability to drive and use machines
Patients receiving Artemether and lumifantrine should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

Adverse Reactions

The frequency of adverse events reported during clinical trial with Artemether and lumifantrine was similar to or lower than that of other anti-malarial drugs used as comparators.
Artemether and lumifantrine was generally well tolerated by children and adults, with most sdverse events being of mild to moderate severity and duration. Many of the reported events are likely to be related to the underlying malaria and/or to an unsatisfactory response to the treatment rather than to Artemether and lumifantrine. For other reports other alternative factors were identified as the more likely cause of the events (e.g. concomitant drugs, concomitant infection) or the information provided was too scarce to draw any conclusion.
The casual relationship with the use of Artemether and lumifantrine could not be excluded for the following adverse events.
Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic effects

This fixed dose combination contains fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site of antiparasitic 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.
The anti-malarial activity of the combination of artemether and lumefantrine is greater than that of either substance alone. In a double-blind comparative study in China (n=157),the 28-day cure rate of Artemether and lumifantrine when given at 4 doses was 94% compared with 90% for lumefantrine and 46% for artemether based on intent-to-treat (ITT) population, when given as monotherapy. For the evaluable population, 28-day cure rates were 100% for Artemether and lumifantrine, compared with 92% for lumefantrine and 55% for artemether when given as monotherapy.

In areas where multi-drug-resistant strains of P. falciparum malaria are common and in the resident population, 28-day cure rates with the 6-dose regimen (given over 60-96 h) were 81% and 90% for Artemether and lumifantrine versus 94% and 96% for mefloquine/artesunate, based on the ITT population. For the evaluable population, 28-day cure rates were 97% and 95% for Artemether and lumifantrine and 100% for mefloquine/artesunate.

In an open, multicenter clinical study conducted in Africa in 310 children weighing 5kg - 25kg and receiving a 6-dose Artemether and lumifantrine according to their body weight range, the mean 28- day parasitological cure rate (PCR corrected) was 93.9% for the ITT population and 96.7% for the evaluable population. In non- immune patients living in malaria free regions but with malaria acquired when traveling in endemic regions, a similar efficacy and safety profile was shown.

In an open study (n=165) in adults the 28-day cure rate for Artemether and lumifantrine given as the 6-dose regimen was 96% (119/124) for the evaluable and 74.1% (120/162) for the ITT population. The main difference between the evaluable and ITT cure rates was owing to 38 patients who were excluded from the evaluable population for the following reasons: 33 patients were lost to follow up (19 of whom were not evaluated at Day 7 and 14 of whom had had parasitic clearance at Day 7 but their efficacy status at Day 28 was unknown) and 5 patients took concomitant medications that were not permitted by the protocol. All these patients were considered as treatment failures in the ITT analysis.

Patients of European origin were not included in the trial with 6-dose regime. However the safety and efficacy of the 4 dose regimen were similar in European and Thai patients, similar safety and efficacy would be expected for the 6-dose regime in both populations.

Pharmacokinetics

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 20/120 tablets [Uncoated] 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 is also bound to human serum proteins (47% to 76%). Protein binding to human plasma protein is linear.

Biotransformation

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. Arthemether 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 Special Warnings And Precautions For Use And Interactions).

During repeated administration of Artemether & Lumefantrine 20/120 tablets [Uncoated], 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 vitro* data 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 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 (see sections Contraindications and Interactions).

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 to 3 days in healthy volunteers and 4 to 6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether & Lumefantrine 20/120 tablets [Uncoated].

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 numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing to rats and dogs, metabolites (glucuronides of lumefantrine and of the des-butyl metabolite) were excreted with bile. Most of the dose was recovered in the form of the parent drug in faeces (including unabsorbed drug and drug released from glucuronide).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Material Name	Functions
Microcrystalline Cellulose	Diluent
Croscarmellose Sodium	Disintegrant
Colloidal Silicon Dioxide	Glidant
Povidone (K-30)	Binder
Purified Water	Granulating agent
Polysorbate 80	Wetting agent
Sodium Lauryl Sulfate	Surfactant
Magnesium Stearate	Lubricant

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24months

6.4 Storage Condition

Store in a cool, dry place below 30°C. Protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

6 tablets in a blister.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma Science Limited
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