1. NAME OF THE MEDICINAL PRODUCT

COMALART PLUS (ARTEMETHER AND LUMEFANTRINE TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each uncoated tablet contains:
Artemether 80 mg
Lumefantrine 480 mg

3. PHARMACEUTICAL FORM

Yellow coloured, elongated, biconvex, uncoated tablets with breakline on one side and plain on the other side

4. Clinical particulars

4.1 Therapeutic indications

Artemether and lumefantrine combination therapy is indicated for the treatment of acute uncomplicated malaria caused by Plasmodium falciparum, including malaria acquired in chloroquine-resistant areas. May also be used to treat uncomplicated malaria when the Plasmodium species has not been identified. Indicated for use in adults and children greater than 5 kg.

4.2 Posology and method of administration

Posology

Tablets for oral administration. To increase absorption, Artemether and lumefantrine should be taken with food or a milky drink. If patients are unable to tolerate food, should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose. For administration to small children and infants, the tablet/s may be crushed. Adults and children weighing 35 kg and above For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter. Children and infants weighing 5 kg to less than 35 kg
A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight: 5 to less than 15 kg
bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further
doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter. 15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter. 25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Method of administration

For oral use

4.3 Contraindications

• patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
• patients with severe malaria according to WHO definition*.
• patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. 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 that are known to prolong the QTc interval (proarrythmic). These drugs include: -
antiarrhythmics of classes IA and III, - neuroleptics, antidepressive agents, - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents, - certain nonsedating antihistamines (terfenadine, astemizole), - cisapride. - flecainide
• patients with a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
• patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
• patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*). (*Presence of one or more of the following clinical or laboratory features: Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

4.4 Special warnings and precautions for use

SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) 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, SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) should not be given concurrently with any other antimalarial agent unless there is no other treatment option. If a patient deteriorates whilst taking SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS), 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 SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS). If quinine is given after SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS), close monitoring of the ECG is advised. If SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) is given after

mefloquine, close monitoring of food intake is advised.In patients previously treated with halofantrine
SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS)should not be administered earlier than one month after the last halofantrine dose. SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) is not indicated and has not been evaluated for prophylaxis of malaria. SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS), Like other antimalarials (e.g. halofantrine, quinine and quinidine) SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) has the potential to cause QT prolongation Caution is recommended when combining SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially antiretroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) Caution is recommended when combining SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) with hormonal contraceptives. MEFARTTABLETS (ARTEMETHER AND LUMEFANTRINE TABLETS 80 MG/480 MG) 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 for about one month.
Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Renal impairment
No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS)in patients with renal impairment is recommended. Caution is advised when administering SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS)to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment
No specific studies have been carried out in this group 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 In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

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

New infections
Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS). In the absence of carcinogenicity study data, and due to lack of clinical

experience, more than two courses of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other antimalarial drugs Data on safety and efficacy are limited, and Artemether and lumefantrine should therefore not be given concurrently with other antimalarials unless there is no other treatment option. If Artemether and lumefantrine is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether and lumefantrine. In patients previously treated with halofantrine, Artemether and lumefantrine should not be administered earlier than one month after the last halofantrine dose. Mefloquine A drug interaction study with Artemether and lumefantrine 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 lumefantrine 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.

Quinine
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 hours) was given sequentially 2 hours after the last (sixth) dose of Artemether and lumefantrine (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 lumefantrine 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 cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and lumefantrine 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 lumefantrine.

4.6 Pregnancy and Lactation

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Artemether and lumefantrine is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether and lumefantrine (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 artemetherlumefantrine (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. Artemether and lumefantrine treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. 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 only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Women of childbearing potential
Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an
additional non-hormonal method of birth control for about one month.

Lactation
Animal data suggest excretion into breast milk but no data are available in humans. Women taking SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breastfeeding should not resume until at least one week after the last dose of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) unless potential benefits to the mother and child outweigh the risks SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) treatment.

Fertility
There is no information on the effects of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) on human fertility

4.7 Effects on ability to drive and use machines

Patients receiving SOFTMAL (ARTEMETHER AND 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

With Artemether virtually no side effects have been seen. Laboratory abnormalities such as slight rise in transaminases and a decrease in reticulocyte count are rare and transient. A lowering of sinus frequency
without causing ECG changes has been noticed. At high doses transient abdominal pain, tinnitus and diarrhea have been described but a causal relationship is unclear. Some antimalarials as halofantrine and quinine can influence the ECG pattern Attention should be made to patients previously treated with those antimalarials. A reasonable period should be taken in account before to start a treatment with lumefantrine combinations. For those patients physicians will be prescribed Artemismin derivatives in mono therapy in cause of severe paludism. Sometimes it could be possible that the following common side effect occur; rash, check this with you doctor. Other common side effects may occur as trouble of sleeping, nausea, vomiting, diarrhea, coughing. They need medical attention when persisting.

4.9 Overdose
Although no case of overdosage has been documented, in case of accident, symptomatic treatment
is recommended under the instruction of doctors

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antimalarials,

ATC code: P01BE02

Pharmacodynamic effects

SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) comprises a 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. SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µl - 200,000/µl (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) 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 and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0–104 ng/ml and 146–338 ng·h/ml, respectively, in fed

healthy adults after a single dose of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS), 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7–104 ng/mL and 169-308 ng·h/ml, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10–9.80 µg/ml) about 6–8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/ml. 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 SOFTMAL (ARTEMETHER AND 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 is also bound to human serum proteins (47–76%).

Biotransformation

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*.

Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT2B7.

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS), plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. 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. The clinical evidence of induction is consistent with the *in vitro* data described in section 4.5

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 exposure to lumefantrine increases with repeated administration of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). Systemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not

available specifically for an African population. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see sections 4.3 and 4.5).

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. 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 SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS).

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS), and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin 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, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Older people

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.

Paediatric population

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS)) were 223 (139%), 198 (90%) and 174 ng/ml (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/ml (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101

ng/ml (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS)) were 577, 699 and 1150 µg•h/ml for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/ml (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

Infants weighing <5 kg

Study B2306 (see section 5.1) showed that the C_{max} of artemether and DHA in infants with uncomplicated *P. falciparum* malaria weighing <5 kg and older than 28 days of age who were treated with artemether/lumefantrine dispersible tablets, was on average 2- to 3-fold higher than that in pediatric patients with a body weight ≥5 kg and children up to 12 years of age treated with the same dose of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) tablets. The mean C_{max} of lumefantrine was similar to that observed in pediatric patients with a body weight ≥5 kg.

Race/Ethnicity

Pharmacokinetics of artemether, DHA and lumefantrine in the Japanese population was found to be consistent with other populations.

Hepatic and Renal impairment

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine 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. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS) in patients with renal impairment is advised.

5.3 Preclinical 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 embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses $\geq$600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC_{50} was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose BP, Maize Starch BP, Sodium lauryl Sulphate USP, Sodium Starch Glycolate USP, Colloidal Silicon Dioxide BP, Cross Carmellose sodium, Magnesium Stearate BP, Purified Water BP are used as excipients in the manufacturing process of SOFTMAL (ARTEMETHER AND LUMEFANTRINE TABLETS)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Month

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

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

1 X 6 TABLET ALUMINIUM/ CLEAR PVDC BLISTER PACK

6.6 Special precautions for disposal

No special requirements

7. APPLICANT/MANUFACTURER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.
C- 1101/1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway, Goregaon (East) Mumbai,
Maharashtra, India – 400063
Tel: +91-22-62748000
Fax: +91-22-26780784
E Mail: mail@cironpharma.com
Website: www.cironp