**Summary of Product Characteristics**

**LONART 20/120 DISPERSIBLE**
**Artemether 20 and Lumefantrine120 Dispersible Tablets**

## 1. NAME OF THE MEDICINAL PRODUCT

LONART 20/120 Dispersible

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 20 mg artemether and 120 mg lumefantrine.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Dispersible tablets.

Yellow, circular, flat, beveled edges tablets having debossed "LT" on one side and "21" on the other side

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for pediatric use only.

LONART 20/120 Dispersible is indicated for the treatment of children and infants with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum.Lonart20/120 Dispersible may be used for self-administration, as stand-by emergency treatment in cases of suspected malarial infection, when no doctor can be reached within 24 hours or the medicinal product is not locally available.

LONART 20/120 Dispersible is effective against both drug-sensitive and drug-resistant P. falciparum, and it is therefore also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

Consideration should be given to official guidelines and to local recommendations based on the prevalence of resistance to antimalarial agents. Official guidelines are those issued by the WHO and by health authorities.

### 4.2 Posology and method of administration

LONART 20/120 Dispersible is not recommended for use in children below 5 kg body weight due to a lack of data on safety and efficacy.

Dispersible tablets for oral administration. The dispersible tablet(s) for one dose should be stirred in a small amount of water (approximately 10 ml per tablet) so that the active substance can be better dispersed before the suspension is drunk. Stir gently and administer immediately to

the patient. Pour some more water (approximately 10 ml) into the glass and give immediately to the patient.

Food or drinks (such as milk) that are rich in fat should be consumed following ingestion of the dose even though patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as possible, since this improves absorption of artemether and lumefantrine.

In the event of vomiting within one hour of administration, a repeat dose should be taken. The dispersible tablet is indicated only for infants and children. A separate tablet formulation is available for adolescents and adults.

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

Dosage for treatment and stand-by emergency treatment

A standard 3 day treatment schedule, with a total of 6 doses, is recommended as follows:

Dosage in infants and children ≤ 12 years of age weighing between 5 kg and < 35 kg

**5 to < 15 kg body weight**

One dispersible tablet at the time of initial diagnosis or as soon as symptoms appear, one dispersible tablet again after 8 hours and then one dispersible tablet twice daily (in the morning and evening) on each of the following two days (total course comprises 6 dispersible tablets).

**15 to < 25 kg body weight**

Two dispersible tablets as a single dose at the time of initial diagnosis or as soon as symptoms appear, two dispersible tablets again after 8 hours and then two dispersible tablets twice daily (in the morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).

**25 to < 35 kg body weight**

Three dispersible tablets as a single dose at the time of initial diagnosis or as soon as symptoms appear, three dispersible tablets again after 8 hours and then three dispersible tablets twice daily (in the morning and evening) on each of the following two days (total course comprises 18 dispersible tablets).

**Dosage in patients with impaired renal or hepatic function**

No specific studies have been performed in these patient populations. No specific dose adjustment recommendations can be made for these patients (see sections 4.3 and 4.4). Most patients with acute malaria present with some degree of hepatic impairment. In clinical trials the adverse event profile did not differ in patients with and those without hepatic impairment (see also section 4.4).

Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment withLonart20/120 DISPERSIBLE.

**New and recrudescent infections**

Data for a limited number of patients show that new and recrudescent infections can be treated with a second course ofLonart20/120 DISPERSIBLE.

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients. Severe hepatic or renal impairment (see also section 4.4).

Patients with severe malaria according to the WHO definition.

First trimester of pregnancy in situations where other suitable and effective antimalarials are available (see also section 4.6).

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, clinically relevant bradycardia or severe heart disease.

Patients taking drugs that prolong the QTc interval, such as class IA and III antiarrhythmics, neuroleptics, antidepressants, certain antibiotics (including some agents in the following classes: macrolides, fluoroquinolones, imidazoles and triazoles), antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride.

Patients with known disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.

Patients taking drugs metabolized by cytochrome CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

**4.4 Special warnings and precautions for use**

LONART 20/120DISPERSIBLE has not been evaluated for prophylaxis and is therefore not indicated for this use.

LONART 20/120DISPERSIBLE has not been investigated in the treatment of cerebral malaria or other severe manifestations of severe malaria, including pulmonary oedema or renal failure. Severe malaria.

In addition to the lack of clinical experience, use ofLonart20/120 DISPERSIBLE in such cases is also inadvisable on pharmacokinetic grounds (the bioavailability of artemether and, in particular, of lumefantrine is uncertain in patients with high parasitaemia and little or no food intake).Lonart20/120 DISPERSIBLE has not been evaluated in, and is not indicated for, the

treatment of malaria due to P. vivax, P. malariae or P. ovale, although some patients in clinical studies had co-infection with P. falciparum and P. vivax at baseline.Lonart20/120 DISPERSIBLE is active against blood stages of P. vivax, but not against hypnozoites (= dormant form / dormant stage in hepatocytes).

Like other antimalarials (e.g. halofantrine, quinine, quinidine), Lonart20/120 DISPERSIBLE may prolong the QTc interval, although no clinical adverse effect attributable to QTc prolongation (e.g. syncope, sudden death) has been reported (see section 5.1).

LONART 20/120Dispersible has not been studied for efficacy and safety in patients with severe hepatic or renal impairment, and therefore no recommendations can be made for these patient populations.

Patients who remain averse to food during treatment should be closely monitored. The risk of recurrence of disease may be greater.

If the patient's condition worsens during treatment withLonart20/120 DISPERSIBLE, alternative antimalarial treatment should be started without delay. In such cases, ECG monitoring is recommended and steps should be taken to correct any electrolyte disturbances.

Following treatment of mixed infections including P. vivax, follow-up treatment must be given in order to eradicate the exoerythrocytic forms of P. vivax.

Caution is required if other medicinal products are given concomitantly.

**Patients treated concomitantly with other antimalarials**

Data on safety and efficacy are limited, andLonart20/120 DISPERSIBLE 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 withLonart20/120 DISPERSIBLE. The ECG should be closely monitored in this case, as well as when Lonart20/120 DISPERSIBLE is administered following treatment with quinine, due to a possible additive prolongation of the QTc interval that has been observed in healthy subjects.

**Patients previously treated with other antimalarials**

Should Lonart20/120 DISPERSIBLE be administered following treatment with mefloquine, it is particularly important to ensure thatLonart20/120 DISPERSIBLE is taken together with food as lumefantrine levels may otherwise be insufficient.

In patients previously treated with halofantrine,Lonart20/120 DISPERSIBLE should be administered no earlier than one month after the last halofantrine dose (see section 4.5).

**Patients treated concomitantly with other medicinal products**

LONART 20/120Dispersible should not be used concomitantly with drugs metabolized by CYP2D6 (see section 4.3). Additionally, caution is required when combiningLonart20/120 DISPERSIBLE with substrates, inhibitors or inducers of CYP3A4 as the therapeutic effects of some drugs might be altered (see sections 4.5 and 5.2).

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

The mechanisms of the pharmacological and pharmacokinetic interactions are not all known. Artemether and lumefantrine are substrates of CYP3A4. Administration of inducers or inhibitors of CYP3A4 may therefore lead to an increase or a reduction in exposure to lumefantrine and artemether.

**Further interactions with CYP450 isoenzymes**

Lumefantrine was found to inhibit CYP2D6 in vitro. This might be of particular clinical relevance for substances with a narrow therapeutic index. Co-administration of Lonart20/120 Dispersible with drugs known to be metabolized by this isoenzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated (see section 4.3).

**Induction of CYP450 enzymes**

Whereas in vitro studies with artemether at therapeutic concentrations revealed no significant inhibition with CYP450 enzymes, artemether and dihydroartemisinin (DHA) were reported to have a mild inducing effect on CYP3A4 activity. Although the changes have generally been slight and are unlikely to pose any problems in the general patient population, CYP3A4 induction might alter the therapeutic effects of drugs that are predominantly metabolized by this enzyme class.

Three specific pharmacokinetic and pharmacodynamic interaction studies with ketoconazole (a potent inhibitor of CYP3A4), mefloquine and quinine have been carried out in healthy volunteers.

**Interactions with antimalarial drugs**

Patients who are to receiveLonart20/120 Dispersible may previously have been treated with other antimalarials. Interactions with mefloquine and quinine were therefore studied in healthy volunteers.

Sequential oral administration of mefloquine prior toLonart20/120 Dispersible had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin (DHA) ratio, but there was a significant (approximately 30–40%) reduction in plasma levels (Cmax and AUC) of lumefantrine due to lower absorption, possibly secondary to a mefloquine-induced decrease in bile production.

Patients should be particularly advised to compensate for this decrease in bioavailability by eating something when takingLonart20/120 DISPERSIBLE. As a rule, therefore, combined administration ofLonart20/120 DISPERSIBLE and mefloquine should be avoided.

In a drug interaction study in healthy subjects, administration ofLonart20/120 DISPERSIBLE alone to 14 subjects had no effect on the QTc interval, while i.v. infusion of quinine alone in 14 other subjects caused a transient prolongation of the QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused afterLonart20/120 DISPERSIBLE in 14 additional subjects. Prior administration ofLonart20/120 DISPERSIBLE thus appears to increase the risk of QTc-prolongation associated with intravenous administration of quinine.

Concurrent intravenous administration of quinine (10 mg/kg body weight) with Lonart20/120 DISPERSIBLE had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and DHA appear to be lower.

In a clinical study (carried out in Thailand),Lonart20/120 DISPERSIBLE was given to some adult patients who had not responded to mefloquine or quinine. 121 patients receivedLonart20/120 DISPERSIBLE without any previous antimalarial treatment, whereas in 34 and 9 patients, respectively, blood levels of quinine or mefloquine were measurable at the start of the study. These patients showed safety and pharmacokinetic profiles forLonart20/120 DISPERSIBLE similar to those in patients who had no detectable levels of other antimalarials.

**Interaction with a CYP450 3A4 inhibitor (ketoconazole)**

Both artemether and lumefantrine are metabolized predominantly by CYP3A4, and at therapeutic concentrations do not inhibit this enzyme. In healthy adult subjects, concomitant oral administration of ketoconazole withLonart20/120 DISPERSIBLE leads to a modest increase (≤ 2-fold) in exposure: artemether (+130% in AUC and +116% in Cmax), DHA (+51% and +37%, respectively), and lumefantrine (+61% and +28%, respectively). This increase in exposure to the antimalarial combination was not associated with increased adverse effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Lonart20/120 Dispersible is not considered necessary in P. falciparum malaria patients given ketoconazole or other potent CYP3A4 inhibitors concomitantly.

**Interaction with antiretroviral drugs**

There have been no formal studies of interactions betweenLonart20/120 DISPERSIBLE and antiretroviral drugs. Caution is required when usingLonart20/120 Dispersible concomitantly with

protease inhibitor antiretroviral drugs, especially fixed combinations thereof, due to variable patterns of inhibition, induction or competition for CYP3A4 with such drugs (see section 4.4 and 5.2).

## 4.6 Pregnancy and lactation

### Pregnancy

There have been no controlled clinical studies of the safety ofLonart20/120 Dispersible during pregnancy.

Data from animal studies suggest thatLonart20/120 Dispersible may cause severe birth defects when administered during the first trimester of pregnancy (see sections 4.3 and 5.3). In animals, reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity.

Other artemisinin derivatives have in addition demonstrated teratogenic potential, with increased risk during early gestation (see section 5.3).

LONART 20/120 Dispersible is contraindicated during the first trimester of pregnancy if other effective antimalarials are available. However, it should not be withheld in life-threatening situations where no other effective antimalarials are available (see section 4.3).

During the second and the third trimesters, treatment should only be given if absolutely necessary.

### Women of childbearing potential

LONART 20/120DISPERSIBLE is contraindicated during the first trimester of pregnancy, and women therefore should not conceive while undergoing malaria treatment with Lonart20/120 DISPERSIBLE. This includes women who are travelling, for whomLonart20/120 DISPERSIBLE has been prescribed as stand-by emergency treatment of malaria, should such treatment be required.

Women of childbearing potential undergoing treatment withLonart20/120 DISPERSIBLE, including stand-by emergency treatment during travel, should be advised to practice contraception until the start of the next menstruation following the end of treatment.

### Lactation

Animal data suggest thatLonart20/120 Dispersible passes into the breast milk but no data are available in humans. Women who are breastfeeding should not takeLonart20/120 DISPERSIBLE. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is

recommended that breastfeeding should not resume before day 28 unless the potential benefits to both mother and child outweigh the risks of treatment withLonart20/120 DISPERSIBLE.

### 4.7 Effects on ability to drive and use machines

LONART 20/120DISPERSIBLE has moderate influence on the ability to drive and use machines. Patients receivingLonart20/120 DISPERSIBLE should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or use machines may be impaired.

### 4.8 Undesirable effects

Most of the reported events were mild to moderate in severity and of short to moderate duration. They were probably related more to the underlying malaria and/or to an inadequate response to treatment rather than toLonart20/120 DISPERSIBLE treatment, although a causal relationship withLonart20/120 DISPERSIBLE cannot be ruled out in some of the reported cases. In other reports, other factors (e.g. concomitant drug therapy, concurrent infections) were presumed to be the more likely cause of the events, or the available information was too meagre to allow any conclusions to be drawn.

Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1 Adverse reactions reported in patients**

| | |
|---|---|
| **Immune system disorders** | |
| Rare | Hypersensitivity reactions |
| **Metabolism and nutrition disorders** | |
| Very common | Loss of appetite (10.8%) |
| **Psychiatric disorders** | |
| Uncommon | Sleep disturbances |

**Nervous system disorders** Common
Headache Common
Dizziness Uncommon
Drowsiness
**Cardiac disorders**
Common QT interval prolonged in electrocardiogram (including QTc prolongations >60 msec and/or absolute QTc intervals >500 msec)
Uncommon Palpitations
**Respiratory, thoracic and mediastinal disorders**
Very common Cough (23.5%)
**Gastrointestinal disorders**
Very common Vomiting (17.5%)
Common Abdominal pain
Common Diarrhoea Common
Nausea
**Hepatobiliary disorders**
Common Elevated liver function values
**Skin and subcutaneous tissue disorders**
Common Rash
Uncommon Pruritus

**Musculoskeletal and connective tissue disorders**
Common Arthralgia, myalgia
**General disorders and administration site conditions**
Common Asthenia, fatigue

In this pooled safety analysis, mood swings were reported in fewer than 1.2% of the paediatric patients treated withLonart20/120 DISPERSIBLE, but they were not considered drug-related by the investigators.

Adverse effects found in non-recommended regimens not included in this pooled safety analysis are: paraesthesia (1.2% of adolescents and adults, no cases in children); involuntary muscle contractions (1.3% of children); non-specific personality disorders which have been reported in 1.1% of children under 5 years of age who were treated withLonart20/120 DISPERSIBLE during clinical studies. This incidence is 2–3 times lower than that observed in children of the same age who were treated with the reference antimalarials used in these studies (mefloquine/artesunate, quinine or sulphadoxine/pyrimethamine).

There were uncommon reports of the following adverse effects in adults, but not in infants or children: hypoaesthesia, ataxia, and abnormal gait.

## 4.9 Overdose

No case of overdose has been reported.

If overdosage is suspected, symptomatic and supportive therapy should be initiated based on the clinical picture. The ECG and electrolytes (e.g. potassium) should be monitored.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Artemisinin and derivatives, ATC code: P01BE52.

LONART 20/120Dispersible contains a fixed combination of artemether and lumefantrine, in the ratio of 1:6, which acts as an antimalarial agent against schizonts. Artemether is a semisynthetic chiral acetal derivative of artemisinin isolated from the plant Artemisia annua. Lumefantrine is a racemic mixture of a synthetic fluorene derivative. Like other antimalarials (quinine, mefloquine, halofantrine), lumefantrine belongs to the aryl-amino-alcohol family.

The site of antiparasitic action of both components is the food vacuole of the malaria parasite. Lumefantrine is thought to interfere with the polymerization process that brings about the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic haemozoin, malaria pigment. Artemether, on the other hand, may generate toxic, reactive metabolites as a result of the interaction between its endoperoxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis.

To date, data from in vitro and in vivo studies show thatLonart20/120 DISPERSIBLE has not induced resistance.

The efficacy of the combination of lumefantrine and artemether inLonart20/120 DISPERSIBLE is greater than that of either substance alone. In a double-blind, comparative study in adults in China (n = 157), the cure rate forLonart20/120 DISPERSIBLE – given in 4 doses over a 28 day period – was 94%; it was 90% for lumefantrine monotherapy and 46% for artemether monotherapy (based on the intent-to-treat [ITT] population). For the evaluable population, the 28 day cure rates were 100% for Lonart20/120 DISPERSIBLE, compared with 92% for lumefantrine monotherapy and 55% for artemether monotherapy.

In the resident population of areas where multi-drug-resistant strains of P. falciparum malaria are common, 28 day cure rates with the six-dose regimen (given over 60 or 96 hours) were 81% and 90% forLonart20/120 DISPERSIBLE versus 94% and 96% for mefloquine/artesunate (based on the ITT population). For the evaluable population, the 28 day cure rates were 97% and 95% forLonart20/120 DISPERSIBLE and 100% for mefloquine/artesunate.

In 319 adult patients in whom gametocytes were present, the average time to gametocyte clearance withLonart20/120 DISPERSIBLE was 96 hours.Lonart20/120 DISPERSIBLE showed more rapid gametocyte clearance than any comparator except mefloquine/artesunate.Lonart20/120 DISPERSIBLE is active against blood stages of P. vivax, but not against hypnozoites.

A similar efficacy and safety profile was shown in non-immune adult patients living in regions free of malaria but with malaria acquired when travelling in endemic regions. In an open-label

study in adults (n = 165), the 28 day cure rate forLonart20/120 DISPERSIBLE given in the 6 dose regimen was 96% (119/124) in the evaluable population and 74.1% (120/162) in the ITT population. The difference between evaluable and ITT population cure rates was due to 38 patients who were excluded from the evaluable population for the following reasons: 33 patients were lost to follow up, of whom 19 had no evaluation and 14 had parasitic clearance at day 7 (but unknown efficacy status at day 28); 5 patients took concomitant medications that were not permitted by the protocol. All these patients were considered as treatment failures in the ITT analysis.

**Efficacy data in infants and children**

In a randomized, investigator-blinded, multicentre trial in sub-Saharan Africa comparing the efficacy of 6 dose Lonart20/120 Dispersible tablets and (crushed)Lonart20/120 DISPERSIBLE administered according to body weight in 899 children 12 years of age or younger with between 5 kg and 35 kg body weight, the 28 day parasitological (PCR-corrected) cure rate was 97.8% and 98.5%, respectively, in the primary analysis population and 95% and 96.2%, respectively, in the ITT population.

The mean 28 day parasitological (polymerase-chain-reaction [PCR]-corrected) cure rate was 93.9% in the ITT population and 96.7% in the evaluable population in an open, multicentre clinical study conducted in Africa in 310 children, weighing between 5 kg and 25 kg, who received a 6 doseLonart20/120 DISPERSIBLE regimen that varied according to body weight. Children from non-endemic countries were not included in the clinical trials.

**QT/QTc prolongation**

The administration of the six dose regimen ofLonart20/120 DISPERSIBLE was associated with QTcF prolongation in a parallel study in healthy adults that included placebo and moxifloxacin control groups (n = 42 per group). The mean change from baseline at 68, 72, 96, and 108 hours after the first dose were 7.45, 7.29, 6.12 and 6.84 milliseconds, respectively. The change from baseline QTcF was zero at 156 and 168 hours after the first dose. No subject had an increase from baseline > 30 milliseconds, nor an absolute value > 500 milliseconds. As compared with the placebo group, the moxifloxacin control was associated with a QTcF prolongation for 12 hours after the single dose, with the maximum change 1 hour after the dose amounting to 14.1 milliseconds.

QTcB prolongation > 500 milliseconds was reported in one patient (0.1%) in clinical trials in children. No patient had a QTcF interval > 500 milliseconds. In clinical studies in adults, QTcB prolongation > 500 milliseconds was reported in 0.9% of patients and QTcF prolongation > 500 milliseconds was reported in 0.3% of patients.

There have been no reports of clinical adverse effects attributable to QTc prolongation (e.g. syncope, sudden death).

**5.2 Pharmacokinetic properties**

Pharmacokinetic characterization ofLonart20/120 DISPERSIBLE 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, Cmax).

**Absorption**

Artemether is absorbed fairly rapidly, with peak plasma concentrations attained approx. 2 hours after administration. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6–8 hours after administration. Food enhances the absorption of both artemether and lumefantrine: In healthy volunteers given a high-fat meal, the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions. 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. Food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (probably less than 10% of the dose). Patients should therefore be strongly encouraged to take the medication with a normal diet as soon as food can be tolerated.

In healthy (adult) volunteers, systemic exposure to artemether, its metabolite dihydroartemisinin (DHA) and lumefantrine was similar with dispersible and crushed tablets (see table 2).

Table 2: Pharmacokinetic parameters following a single dose (4 tablets) – containing 80 mg artemether / 480 mg lumefantrine – administered as either dispersible or crushed tablets

| | Dispersible tablets | Crushed tablets |
|---|---|---|
| | Artemether | |
| | (n = 54) | (n = 50) |
| Cmax (ng/ml) | 73.3 ± 39.5 | 67.4 ± 35.5 |
| Tmax (hours) | 2.02 [0.50-4.02] | 2.05 [0.52-4.07] |
| AUClast (ngxhours/ml) | 263 ± 143 | 229 ± 136 |
| | DHA | |
| | (n = 54) | (n = 50) |
| Cmax (ng/ml) | 48.6 ±23.2 | 48.8 ± 26.0 |
| Tmax (hours) | 2.98 [0.75-5.98] | 2.54 [0.75-4.07] |

| | | |
|---|---|---|
| AUClast (ngxhours/ml) | 171 ± 59.5 | 160 ± 68.0 |
| | Lumefantrine | |
| | (n = 55) | (n = 52) |
| Cmax (ng/ml) | 10.2 ± 3.08 | 10.0 ± 2.57 |
| Tmax (hours) | 8.00 [4.98-24.02] | 8.00 [4.98-24.02] |
| AUClast (ngxhours/ml) | 295 ± 107 | 280 ± 93.2 |

Table shows mean ± standard deviation for Cmax und AUClast, median values and [min-max] ranges for tmax.

**Distribution**

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively).

DHA is also bound to human serum proteins (47%–76%). Protein binding to human plasma protein is linear.

**Biotransformation**

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism). In vitro data show that human liver microsomes metabolize artemether to the biologically active main metabolite DHA (demethylation), predominantly by way of CYP3A4/5.

The pharmacokinetics of this metabolite have also been described in humans in vivo.

The artemether/DHA AUC ratio is 1.2 after a single dose and 0.3 after the last of 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity that is not expected to pose a problem in the general patient population.

Plasma levels of artemether decreased markedly during repeated administration ofLonart20/120 DISPERSIBLE, while levels of the active metabolite (DHA) 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 in the section 4.5.

In vitro, 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, systemic exposure to the desbutyl-lumefantrine metabolite – which has an in vitro antiparasitic effect 5 to 8 times higher than that of lumefantrine – amounted to less than 1% of the exposure to the parent compound.

In vitro, therapeutic plasma concentrations of lumefantrine significantly inhibit the activity of CYP2D6 (see sections 4.4, 4.5 and 4.3).

**Elimination**

Artemether and DHA 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 2–3 days in healthy volunteers and 4–6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics ofLonart20/120 DISPERSIBLE.

No data are available on urinary excretion of artemether and lumefantrine in humans. In rats and dogs, unchanged artemether has not been detected in the faeces and the urine due to its rapid and high firstpass metabolism, but numerous metabolites (identified in part) have been detected in the faeces, the bile and the urine. Lumefantrine is eliminated into the bile in rats and dogs, with excretion primarily in the faeces. Metabolites (glucuronides of lumefantrine and of the desbutyl metabolite) were eliminated into the bile following oral administration in rats and dogs. Most of the dose was recovered in the faeces in the form of parent drug (this included unabsorbed drug components and drug components released from glucuronides).

**Pharmacokinetics in special patient populations**

No specific pharmacokinetic studies have been performed in patients with hepatic or renal impairment. Systemic exposure to artemether, DHA, and lumefantrine in paediatric malaria patients (≥ 5 to < 35 kg body weight) dosed on a mg/kg body weight basis is comparable to that measured in adult malaria patients on the recommended dosing regimen.

## 5.2 Preclinical safety data

**Mutagenicity**

There have been no reports of mutagenicity in in vitro and in vivo tests with an artemether:lumefantrine combination consisting of 1 part artemether : 6 parts lumefantrine. In the micronucleus test, myelotoxicity was seen at all dose levels (500, 1000 and 2000 mg/kg), but recovery was reported to be almost complete 48 hours after dosing.

**Carcinogenicity**

Due to the short period of treatment, carcinogenicity studies with the artemether:lumefantrine combination were not carried out.

**Reproductive toxicity**

Reproductive toxicity studies in rats given oral doses of the artemether:lumefantrine combination showed maternal toxicity and increased post-implantation loss at doses ≥ 50 mg/kg (corresponding to approximately 7 mg/kg artemether). The artemether:lumefantrine combination was not embryotoxic in rats at a dose of 25 mg/kg (corresponding to approximately 3.6 mg/kg

artemether). Following oral administration of the artemether:lumefantrine combination in rabbits, maternal toxicity and increased post- implantation loss were seen at a dose of 175 mg/kg (corresponding to 25 mg/kg artemether), while the next lowest dose level of 105 mg/kg (corresponding to 15 mg/kg artemether) was free of treatment-induced effects.

Artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at a dose of 6 mg/kg artesunate and 19.4 mg/kg artemether. In rats, 3 mg/kg artemether was established as the non-toxic dose. In rabbits, artemether produced maternal toxicity and an increase in post-implantation loss at a dose of 30 mg/kg, but no maternal toxicity, embryotoxicity or fetotoxicity at doses up to 25 mg/kg. The artemisinin derivative artesunate produced a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose used The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and DHA exposures similar to those in humans

**Cardiovascular pharmacology**

In toxicity studies in dogs, there was some evidence of QTc prolongation at doses higher than the therapeutic doses used in man (≥ 600 mg/kg/day). In an in vitro assay of HERG channels stably expressed in an HEK293 cell line, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the ion channels responsible for cardiac repolarization.

However, this potency was lower than that of the other antimalarial drugs tested. From the estimated IC50 values, the order of potency of HERG current block was: halofantrine (IC50 = 0.04 micromolar) > chloroquine (2.5 micromolar) > mefloquine (2.6 micromolar) > desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar). A study in healthy adults shows that the QTcF interval may be prolonged by standard dosing ofLonart20/120 DISPERSIBLE (see sections 4.3, 4.4 and 5.1).

## 6.PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose, Crospovidone, Croscarmellose, Saccharine sodium, Colloidal Anhydrous Silica, Magnesium stearate, Powdarome orange, Polysorbate 80, Hypromellose.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years.

**6.4 Special precautions for storage**

Keep in cool and dry place below 30°C. Keep out of reach of children.

**6.5 Nature and contents of container**

ALU/PVC foil blisters.

1 x 6 tablets packed in one mono carton along with pack insert.

**6.6 Special precautions for disposal**

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Bliss GVS Pharma Ltd., 102,Hyde park, Saki Vihar Road, Andheri (east), Mumbai - 400 072