SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LONART 20/120 Oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml suspension after reconstitution contains:

Artemether 20 mg

Lumefantrine 120 mg.

Excipients: q.s

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dosage Form: Powder for Oral Suspension.
Description: Yellow coloured granular powder, after reconstitution orange coloured viscous suspension having pleasant orange flavour packed in HDPE bottle.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for pediatric use only.

LONART 20/120 is indicated for the treatment of malaria in children, caused by all forms of Plasmodium including severe malaria caused by multiple drug resistant strains of P. falciparum. LONART 20/120 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

For ORAL use only LONART 20/120 oral suspension has especially been designed for use in children. The dose depends on the severity of the case and the clinical situation of the patient.
In general: 4 ml artemether/kg body weight in combination with lumefantrine per day. This dose should be repeated during three consecutive days.

The daily dose should be administered in one single administration.

NOTE: A full course therapy of three days is essential in order to avoid recrudescence. Vomiting within one hour requires repeating the dose.

Making up the LONART 20/120 oral suspension:

After opening the vial (breaking the seal), drinking water is added and carefully brought to the mark point indicating 60 ml level. When adding water the mixture turns yellow. After adding the water the mixture is vigorously shaken until all powder has disappeared from the bottom and an oral suspension is being formed. The composition of the powders is such that this process takes only a few seconds. It may be necessary to readjust the volume to the 60 ml mark. This oral suspension is stable for several days. It is advisable to shake the vial before use.
A subunit of 5 ml contains 15 mg artemether and 90 mg lumefantrine.
For each patient it will be calculated how many millilitres should be administered. It is recommended to round off the dosage to the nearest subdivision.
Practical scheme for administering the correct dose of LONART 20/120 oral suspension:

Body weight	Number of millilitres		
	Day 1	Day 2	Day 3
5 to <15 kg	5 ml	5 ml	5 ml
15 to < 25 kg	10 ml	10 ml	10 ml
25 to < 35 kg	15 ml	15 ml	15 ml

This is an average dosing scheme but when considered necessary the dose may be increased depending on the severity of the case and the clinical situation of the patient.

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 with LONART 20/120.

New and recrudescent infections

Data for a limited number of patients show that new and recrudescent infections can be treated with a second course of LONART 20/120 Oral suspension.

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 20/120 has not been evaluated for prophylaxis and is therefore not indicated for this use.
LONART 20/120 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 of LONART 20/120 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).
LONART 20/120 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. LONART 20/120 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), LONART 20/120 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 20/120 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 with LONART 20/120, 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, and LONART 20/120 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 with LONART 20/120. The ECG should be closely monitored in this case, as well as when LONART 20/120 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 LONART 20/120 be administered following treatment with mefloquine, it is particularly important to ensure that LONART 20/120 is taken together with food as lumefantrine levels may otherwise be insufficient.
In patients previously treated with halofantrine, LONART 20/120 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 20/120 should not be used concomitantly with drugs metabolized by CYP2D6 (see section 4.3). Additionally, caution is required when combining LONART 20/120 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 LONART 20/120 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.

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 with LONART 20/120 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 LONART 20/120 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 between LONART 20/120 and antiretroviral drugs. Caution is required when using LONART 20/120 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 of LONART 20/120 during pregnancy.
Data from animal studies suggest that LONART 20/120 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 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 20/120 is contraindicated during the first trimester of pregnancy, and women therefore should not conceive while undergoing malaria treatment with LONART 20/120. This includes women who are travelling, for whom LONART 20/120 has been prescribed as stand-by emergency treatment of malaria, should such treatment be required.
Women of childbearing potential undergoing treatment with LONART 20/120, 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 that LONART 20/120 passes into the breast milk but no data are available in humans. Women who are breastfeeding

should not take LONART 20/120. 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 with LONART 20/120.

4.7 Effects on ability to drive and use machines

LONART 20/120 has moderate influence on the ability to drive and use machines.

Patients receiving LONART 20/120 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

With artemether virtually no side effects have been seen. Laboratory abnormalities such as a 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 diarrhoea have been described but a causal relationship in 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. Sometimes it could be possible that rash, a common side effect, occurs. Check this with your doctor. Sometimes the following common side effects can occur: trouble of sleeping, nausea, vomiting, diarrhoea, coughing. They need medical attention when persisting.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

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

Both compounds, artemether and lumefantrine, have their own action

site in the malarial parasite. The presence of the endoperoxide bridge in artemether, generating singlet oxygen and free radicals which are very cytotoxic to the plasmodia, appears to be essential for antimalarial activity. Morphological changes of the parasitic membranes induced by artemether have been described as being the result of free-radical action. Lumefantrine interferes more in the polymerisation processes.
Other in vitro tests suggest that both cause a marked diminution of nucleic acid synthesis. Inhibition of protein synthesis as the basic mechanism of action is suggested in studies which showed morphological changes in ribosomes as well as in the endoplasmic reticulum. Although, Artemether acts essentially as a blood schizonticide, artemether/lumefantrine oral suspension did clear gametocytes in comparative clinical trials.

5.2 Pharmacokinetic properties

Orally administered artemether is rapidly absorbed reaching therapeutic levels within 60-90 minutes. Artemether is metabolized in the liver to the demethylated derivative dihydroartemisinin (DHA). The elimination is rapid, with a T1/2 of 2-4 hours.
DHA, being a potent anitmalarial itself, has a T1/2 of about 2-4 hours. The degree of binding to plasma proteins varied markedly according to the species studied. The binding of artemether with plasma protein in man is about 50%. Radioacivity distribution of artemether was found to be equal between cells and plasma.
The absorption of lumefantrine is highly influenced by lipids and food intake (from 10% by fasten to 100% at normal diet). Therefore parents should be encouraged to give the medication with some fatty food as soon as it can be tolerated.
Lumefantrine is N-debutylated in human liver microsomes. This metabolite has 5 to 8 fold higher antiparasitic effects than lumefantrine. Lumefantrine is found to be highly protein 32 bound (95%). The elimination half-life in malaria-attaint patients will be 4 to 6 days. Lumefantrine and his metabolites are found in bile and faeces.
Breastfeeding: Data on excretion in breast milk are not available for humans.

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 of LONART 20/120 (see sections 4.3, 4.4 and 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sucrose,
- Methyl Paraben,

- Propyl Paraben,
- Colloidal Anhydrous Silica (Aerosil),
- Citric Acid (Anhydrous),
- Xanthan Gum,
- Saccharin Sodium,
- Sunset Yellow Supra,
- Powderome Orange 4153.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 Months.

6.4 Special precautions for storage

Store in dry place, below 30˚C. Protect from light.
Keep out of the reach and sight of children.
After reconstitution orange coloured, viscous suspension having pleasant orange flavour packed in HDPE bottle.

6.5 Nature and contents of container

Powder for Oral Suspension

6.6 Special precautions for disposal

No special requirements.

7. Marketing Authorization Holder & Manufacturing Site Address

Marketing Authorization Holder

Bliss GVS Pharma Ltd.

102, Hyde Park, Saki Vihar Road, Andheri

(E) Mumbai – 400 072, India.

Manufacturing Site Addresses

Bliss GVS Pharma Limited
Plot 10, 11A, 12; Survey No. 38/1,
Dewan Udyog nagar Aliyali,
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8. Marketing authorization number(s)
H2011/22052/087/R1

9. Date of first authorization/renewal of the authorization
2025 September 22

10. Date of revision of the text
2025 September 22