## 1. NAME OF THE MEDICINAL PRODUCT

VEGATEM 80mg/480mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Artemether 80mg

Lumefantrine .....480mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VEGATEM®/ ® is a fixed-dose combination of artemether and lumefantrine, which acts as a blood schizontocide. It is indicated for:

Treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Because VEGATEM/ is effective against both drug-sensitive and drugresistant
*P. falciparum* it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

Stand-by emergency treatment:

Most tourists and travellers, considered to be non-immune, will be able to obtain prompt medical attention if malaria is suspected. However, a minority at risk of infection may be unable to obtain such care within 24 hours of the onset of symptoms, particularly if they are in an isolated location far from medical services. In such cases, prescribers are advised to issue VEGATEM/ to be carried by the traveller for self-administration or by the parent or caregiver for administration to the traveling child ("standby emergency treatment").

Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

### 4.2 Posology and method of administration

**80 mg/480 mg tablets**

One tablet of 80 mg/480 mg at the time of initial diagnosis, again 1 tablet after 8 hours and then 1 tablet twice daily (morning and evening) on each of the following two days (total course comprises 6

tablets of 80 mg/480 mg)

**Dosage in infants and children weighing 5 kg to less than 35 kg and 12 years of age or less** A six-dose regimen is recommended with 1 to 3 dispersible tablets per dose, depending on bodyweight.

5 to <15 kg bodyweight: One dispersible tablet at the time of initial diagnosis, 1 dispersible tablet again after 8 hours and then 1 dispersible tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 dispersible tablets).

15 to <25 kg bodyweight: Two dispersible tablets as a single dose at the time of initial diagnosis, 2 dispersible tablets again after 8 hours and then 2 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).

25 to □35 kg bodyweight: Three dispersible tablets as a single dose at the time of initial diagnosis, 3 dispersible tablets again after 8 hours and then 3 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 18 dispersible tablets).

**Method of administration Tablets for oral administration**

The dose should be taken with food or drinks rich in fat such as milk. A standard African diet with fat content ranging between 30 and 60 g/day or breast milk were shown to be adequate in Africa . Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

In the event of vomiting within 1 hour of administration, a repeat dose should be taken.

## 4.3 Contraindications

VEGATEM is contraindicated in:

- Known hypersensitivity to artemether, lumefantrine or to any of the excipients of VEGATEM.
- Patients with severe malaria according to WHO definition*
- 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.
- Patients with known disturbances of electrolyte balance e.g. hypokalemia or hypomagnesaemia.
  • Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum)* .

## 4.4 Special warnings and precautions for use

VEGATEM has not been evaluated for prophylaxis and is therefore not indicated for prophylaxis.

VEGATEM has not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure.

VEGATEM is not indicated for, and has not been evaluated in, 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. VEGATEM is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

VEGATEM should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 9 Pregnancy, lactation, females and males of reproductive potential).

Like other antimalarials (e.g. halofantrine, quinine, quinidine), VEGATEM has the potential to cause QTc prolongation .

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

If a patient deteriorates whilst taking VEGATEM, 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 VEGATEM.

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

**Caution in case of concomitant administration of medicines**

**With other antimalarials**: Data on safety and efficacy are limited, and VEGATEM 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 VEGATEM

**Patients previously treated with other antimalarials:** If VEGATEM is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. In patients previously treated with halofantrine, VEGATEM should not be administered earlier than one month after the last halofantrine dose .

**With other drugs**: Caution is recommended when combining VEGATEM with substrates, inhibitors or weak to moderate inducers of CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking VEGATEM (see sections 8 Interactions and 11 Clinical pharmacology - Pharmacokinetics).

**With hormonal contraceptives**: VEGATEM 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 (see sections 8 Interactions and 9 Pregnancy, lactation, females and males of reproductive potential).

## 4.6 Pregnancy and lactation Pregnancy Risk Summary

Based on animal data, VEGATEM/ is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 6 Warnings and precautions and 13 Non-clinical

safety data).

VEGATEM/ should 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 lifethreatening situations where no other suitable and effective antimalarials are available (see section 6 Warnings and precautions). During the second and the third trimester, treatment should be considered if the expected benefit to the mother outweighs the risk to the fetus.

Reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats. Other artemisinin derivatives have in addition demonstrated teratogenic potential with an increased risk during early gestation.

**Human Data**

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded .

Data from observational and open label studies in over 1200 pregnant women exposed to artemether-lumefantrine in their second- or third trimester, and pharmacovigilance data have not demonstrated an increase in adverse pregnancy outcomes or teratogenic effects [110].

**Animal data**

Reproductive oral toxicity studies in rats with the artemether-lumefantrine combination showed both 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 3.6 mg/kg artemether). In rabbits given orally the artemether-lumefantrine combination, maternal toxicity and increased post-implantation loss were seen at 175 mg/kg (corresponding to 25 mg/kg artemether), while the next lower dose level of 105 mg/kg (corresponding to 15 mg/kg artemether) was entirely free of treatment-induced effects. The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemesinin exposures similar to those achieved in humans.

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 [75] and 19.4 mg/kg artemether [74]. In rats, 3 mg/kg artemether was established as the non-toxic dose [26]. In rabbits, artemether produced maternal toxicity and increased post-implantation loss at 30 mg/kg but no materno/embryo/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.

Lumefantrine doses as high as 1,000 mg/kg showed no evidence to suggest materno-, embryo- or fetotoxicity or teratogenicity in rats and rabbits

**Lactation Risk Summary**

Animal data suggest excretion into breast milk but no data are available in humans. Breast-feeding women should not take VEGATEM/. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume before day 28 unless potential benefits to mother and child outweigh the risks of VEGATEM/ treatment.

**Females and males of reproductive potential**

As VEGATEM should not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available, women should not conceive while on VEGATEM/ treatment for malaria. This includes women prescribed VEGATEM/ for standby emergency treatment of malaria during their travel, in case they may require treatment for malaria.

**Contraception**

Women of child-bearing potential should be advised to practice contraception during travel with stand-by emergency treatment, while on VEGATEM/ and until the start of the next menstruation after the treatment.

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

**Infertility**

There is no information on the effects of VEGATEM/ on human fertility.

## 4.7 Effects on ability to drive and use machines

Not Relevant

## 4.8 Undesirable effects Summary of the safety profile

Most of the reported events were of mild to moderate severity and duration, and likely related to the underlying malaria and/or to an unsatisfactory response to the treatment rather than to VEGATEM/ although a causal relationship with the use of VEGATEM/ could not be excluded for some reports. For other reports, alternative factors were identified as the more likely cause of the events (e.g. concomitant drugs, concomitant infections) or the information provided was too scarce to draw any conclusion .

**Tabulated summary of adverse drug reactions from clinical trials**

Adverse drug reactions from clinical trials (Table 7-1 and Table 7-2) are ranked under heading 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. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

*Table 4-1 Adverse drug reactions compiled from a pooled safety analysis in clinical trials in*

| | |
|---|---|
| **Metabolism and nutrition disorders** | |
| Very common | Decreased appetite |
| **Psychiatric disorders** | |
| Very common | Sleep disorder |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common | Clonus |
| Uncommon: | Somnolence, hypoaesthesia, ataxia **Cardiac** |
| **disorders** | |
| Very common: | Palpitations |



| | |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough |
| **Gastrointestinal disorders** | |

*adults and adolescents >12 years of age using the recommended 6-dose regimen [89,102]*

| | |
|---|---|
| Very common: | Vomiting, abdominal pain, nausea |
| Common: | Diarrhoea |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Rash, pruritus |
| Uncommon: | Urticaria |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Arthralgia, myalgia |
| **General disorders and administration site conditions** | |
| Very common: | Asthenia, fatigue |
| Uncommon: | Gait disturbance |
| **Investigations** | |
| Uncommon | Electrocardiogram QT prolonged, liver function test increased |

*Table 4-2 Adverse drug reactions compiled from a pooled safety analysis of 4 studies in infants and children ≤12 years of age receiving a 6-dose regimen of VEGATEM/ or VEGATEM/ Dispersible [84a,89,102]*

| | | |
|---|---|---|
| **Immune system disorders** | | |
| | Rare: | Hypersensitivity |
| **Metabolism and nutrition disorders** | | |
| | Very common | Decreased appetite |
| **Psychiatric disorders** | | |
| | Uncommon | Sleep disorder |
| **Nervous system disorders** | | |
| | Common: | Headache, dizziness |
| | Uncommon: | Clonus, somnolence |
| **Cardiac disorders** | | |
| | Uncommon: | Palpitations |
| **Respiratory, thoracic and mediastinal disorders** | | |
| | Very common: | Cough |
| **Gastrointestinal disorders** | | |
| | Very common: | Vomiting |
| | Common: | Abdominal pain, diarrhoea, nausea |
| **Skin and subcutaneous tissue disorders** | | |
| | Common: | Rash |
| | Uncommon | Urticaria, pruritus |
| **Musculoskeletal and connective tissue disorders** | | |
| | Common: | Arthralgia, myalgia |
| **General disorders and administration site conditions** | | |
| | Common: | Asthenia, fatigue |
| **Investigations** | | |
| | Common | Liver function test increased |
| | Rare | Electrocardiogram QT prolonged |

Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (3.3% of adolescents and adults, no cases in children).

The following adverse reactions were reported in adults with a frequency of uncommon but were not reported in infants or children: hypoesthesia, ataxia, and gait disturbance.

**Adverse drug reactions from spontaneous reports and literature cases (frequency not known)**

The following adverse drug reactions have been derived from post-marketing experience with VEGATEM/ via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Hypersensitivity reactions including urticaria and angioedema

## 4.9 Overdose

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes (e.g. potassium) should be monitored.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group, ATC**

Pharmacotherapeutic group: Antimalarials, artemisinins and derivatives. ATC code: P01BF01

**Mechanism of action (MOA)**

VEGATEM/ contains a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. Artemether is a semisynthetic chiral acetal derived from the naturally occurring substance artemisinin. 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 malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic 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. VEGATEM/ has been reported to have potent activity in terms of clearing gametocytes **.**

Data from *in vitro* and *in vivo* studies show that VEGATEM/ did not induce resistance.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with VEGATEM/ 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. In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed .

**Pharmacodynamics (PD)**

**QT/QTc Prolongation**

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of VEGATEM/ was associated with prolongation of QTcF. The mean changes compared to placebo from baseline at 68, 72, 96, and 108 h post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 h after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 h after the single dose with a maximal change at 1h after dose of 14.1 msec .

In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients .

## 5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of VEGATEM/ 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, $C_{max}$).

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

**Biotransformation/Metabolism**

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. Artemether 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

Glucuronidation of dihydroartemisinin is predominately catalyzed by UGT1A9 and UGT2B7.

During repeated administration of VEGATEM/ , 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 8 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

**Elimination**

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours, while 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 VEGATEM/.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of VEGATEM/ , and urinary excretion of DHA 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. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of both drug components were eliminated in bile/faeces and urine.

**Dose proportionality**

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the VEGATEM/ dose. No conclusive data is available for artemether.

**Bioavailability/bioequivalence studies**

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of VEGATEM/ as dispersible tablets and crushed tablets of 20 mg/120 mg in healthy adults.

Systemic exposure to lumefantrine was similar following administration of VEGATEM/ dispersible tablets and intact tablets of 20 mg/120 mg in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet of 20 mg/120 mg. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the pediatric population since adequate efficacy of VEGATEM/ dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

The 80 mg/480 mg tablet was shown to be bioequivalent to 4 tablets of 20 mg/120 mg in healthy adults .

**Special populations**

**Geriatric patients (65 years or above)**

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.

**Pediatric patients (below 18 years)**

Systemic exposure to artemether, DHA, and lumefantrine when dosed on a mg/kg body weight basis in pediatric malaria patients (≥5 to <35 kg body weight) is comparable to that of the recommended dosing regimen in adult malaria patients .

**Infants weighing <5 kg**

Study B2306 showed that exposure to artemether and DHA in infants with uncomplicated *P.*

*falciparum* malaria weighing <5 kg and older than 28 days of age, was on average 2- to 3-fold higher than that in pediatric patients with a body weight ≥5 kg treated with the same dose of VEGATEM/ (i.e. 1 tablet of 20 mg/120 mg per dose) (see section 12 Clinical studies). However, exposure to 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.

**Renal impairment**

No specific pharmacokinetic studies have been performed in patients with renal impairment. However based on the pharmacokinetic data in healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and DHA, no dose adjustment for the use of VEGATEM/ in patients with renal impairment is advised.

**Hepatic impairment**

No specific pharmacokinetic studies have been performed in patients with hepatic impairment. Metabolism is the primary clearance mechanism of both artemether and lumefantrine and 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 (see section 6 Warnings and precautions).

## 5.3 Preclinical safety data

**Non-clinical safety data**

Based on conventional studies, repeated dose toxicity, and genotoxicity, preclinical data reveal no special hazard for humans administered artemether/lumefantrine in adults and children weighing at least 5 kg for the treatment of malaria when used in accordance with the Core Data Sheet/Product Information.

Adverse drug reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use, were as follows: postimplantation losses and teratogenicity of artemisinin derivatives .

**General toxicity**

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary hematopoiesis.

**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 with artemether at 25 mg/kg for 7 or 14 days and dogs dosed at 20 mg/kg for 8 days or longer,

but lesions were not observed after shorter courses of drug or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7-fold greater than the estimated artemether 24 h AUC in humans

on day 1 of the standard 3-day oral treatment regimen; oral exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent to 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 6dose regimen were mild in intensity and resolved by the end of the study.

**Mutagenicity**

No evidence of mutagenicity was detected in *in vitro* or *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, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

**Carcinogenicity**

Due to the short time of treatment, carcinogenicity studies with the artemether-lumefantrine combination were not conducted.

**Reproductive toxicity studies**

See section 9 Pregnancy, lactation and females and males of reproductive potential.

**Fertility**

Reduced fertility occurred at 1000 mg/kg/day where altered sperm motility, reduced epididymal sperm count, increased testes weight, and embryotoxicity and other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. General toxicity was observed in males and females at doses ≥ 300 mg/kg/day. 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 specific study to investigate the neurotoxicity of artemether in juvenile rats involved oral administration of artemether during four different dosing intervals, at doses of 30 or 80 mg/kg/day on post partum days 7 to 13, and at doses of 30 or 120 mg/kg/day on post partum days 14 to 21, 22 to 28, or 29 to 36. Mortality, clinical signs and reductions in body weight parameters occurred most notably during the first two dosing intervals. 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 of orally administered artemether on the brain of juvenile rats.

Juvenile studies in the rat indicate that very young animals (aged 7-21 days) are more sensitive to artemether than adult animals. There is no difference in sensitivity in slightly older (3-5 weeks of age) animals following 13 weeks of artemether/lumefantrine administration. Consistent with the later data, 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, only at higher doses than intended for use in man (600 mg/kg/day), there was some evidence of prolongation of the QTc interval (safety margin of 1.3- to 2.2-fold for artemether using calculated free $C_{max}$) . In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the currents responsible for cardiac repolarization. This potency was lower than that of the other antimalarial drugs tested. From the $IC_{50}$ values, the order of potency of HERG current block was halofantrine ($IC_{50}$ = 0.04 micromolar) >chloroquine (2.5 micromolar)

>mefloquine (2.6 micromolar) >desbutyl-lumefantrine (5.5 micromolar) >lumefantrine (8.1 micromolar)

Additional studies were performed to evaluate the *in vitro* effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at $C_{max}$ or greater than 1000 if they are estimated using the calculated free $C_{max}$. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted .

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Excipients**

Cellulose microcrystalline, croscarmellose sodium, hypromellose, magnesium stearate, polysorbate 80 and silica colloidal anhydrous.

### 6.2 Incompatibilities

None Known

### 6.3 Shelf life

36 Months

### 6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.

Store in the original package in order to protect from moisture. VEGATEM must be kept out of the reach and sight of children. Do not use past the expiration date indicated on the package.

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

Not available

### 6.6 Special precautions for disposal and other handling

For the treatment of children and infants, the 24-tablet pack of 20 mg/120 mg tablets may be prescribed. The prescriber and pharmacist should instruct the parent or caregiver on the posology for their child and that a specific number of tablets should be given to the child based upon the child's body weight for the full treatment. Therefore, some tablets may remain in the pack at the end of the full treatment course. After successful treatment the remaining tablets should be discarded or

returned to the pharmacist (see section 4 Dosage regimen and administration).

## 7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

M/s. Vega Biotec Pvt. Ltd - At: 156/157A, Siddhi Industrial Infrastructure Park Waghodia, Vadodara - 391 760,Gujarat, India

M/s. VEGAGEN UK LIMITED - THE LITTON SUITE SHEEPBRIDGE BUSINESS CENTRE, 655 SHEFFIELD ROAD, CHESTERFIELD, S41 9ED,, United Kingdom

## 8. MARKETING AUTHORISATION NUMBER

FDA/SD.245-122471

## 9. DATE OF FIRST AUTHORISATION OR RENEWAL

12/20/2024

## 10. DATE OF REVISION OF THE TEXT

09/2025