1. NAME OF THE MEDICINAL PRODUCT

GIMETHER TABLET (ARTEMETHER 20 MG & LUMEFANTRINE 120 MG TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated tablet contains:

Artemether.....20 mg

Lumefantrine ……120 mg

Excipients ..... qs

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Tablets for oral administration: Yellow coloured, biconvex uncoated tablet having breakline on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

GIMETHER TABLETS 20/120 is indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults, children and infants of 5 kg and above.

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

4.2 Posology and method of administration

Posology

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:

5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.

25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Method of administration

Tablets for oral administration.

To increase absorption, GIMETHER TABLETS 20/120 should be taken with food or a milky drink (see section 5.2). If patients are unable to tolerate food, GIMETHER TABLETS 20/120 should be administered with water, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For administration to small children and infants, the tablet/s may be crushed.

4.3 Contraindications

GIMETHER TABLETS 20/120 is contraindicated in:

- Patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Patients with severe malaria according to WHO definition*.
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitryptyline, clomipramine).
- Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- Patients taking drugs that are known to prolong the QTc interval (proarrythmic). These drugs include:

- antiarrhythmics of classes IA and III,
- Neuroleptics, antidepressive agents,
- Certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,

- Certain non-sedating antihistamines (terfenadine, astemizole),

- cisapride.

- flecainide

• Patients with a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

• Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

• Patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*).

(*Presence of one or more of the following clinical or laboratory features:

Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

GIMETHER TABLETS 20/120 must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

GIMETHER TABLETS 20/120 has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Due to limited data on safety and efficacy, GIMETHER TABLETS 20/120 should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment option.

If a patient deteriorates whilst taking GIMETHER TABLETS 20/120, 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 GIMETHER TABLETS 20/120.

If quinine is given after GIMETHER TABLETS 20/120, close monitoring of the ECG is advised (see section 4.5).

If GIMETHER TABLETS 20/120 is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, GIMETHER TABLETS 20/120 should not be administered earlier than one month after the last halofantrine dose.

GIMETHER TABLETS 20/120 is not indicated and has not been evaluated for prophylaxis of malaria.

GIMETHER TABLETS 20/120 should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of GIMETHER TABLETS 20/120 , (see section 4.5).

Like other antimalarials (e.g. halofantrine, quinine and quinidine) GIMETHER TABLETS 20/120 has the potential to cause QT prolongation (see section 5.1).

Caution is recommended when combining GIMETHER TABLETS 20/120 with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking GIMETHER TABLETS 20/120 (see sections 4.5 and 5.2).

Caution is recommended when combining GIMETHER TABLETS 20/120 with hormonal contraceptives. GIMETHER TABLETS 20/120 may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see sections 4.5).

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

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of GIMETHER TABLETS 20/120 in patients with renal impairment is recommended. Caution is advised when administering GIMETHER TABLETS 20/120 to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment (see section 5.2). In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

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

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of GIMETHER TABLETS 20/120. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of GIMETHER TABLETS 20/120 cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

GIMETHER TABLETS 20/120 is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) 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, flecainide (see section 4.3).

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of GIMETHER TABLETS 20/120 with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated (see sections 4.3 and 5.2).

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with GIMETHER TABLETS 20/120 Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after GIMETHER TABLETS 20/120 alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with GIMETHER TABLETS 20/120 (see section 4.3).

Inducers should not be administered at least one month after GIMETHER TABLETS 20/120 administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs (see section 4.4)

Data on safety and efficacy are limited, and GIMETHER TABLETS 20/120 should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section 4.4).

If GIMETHER TABLETS 20/120 is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with GIMETHER TABLETS 20/120 In patients previously treated with halofantrine, GIMETHER TABLETS 20/120 should not be administered earlier than one month after the last halofantrine dose (see section 4.4).

Mefloquine

A drug interaction study with GIMETHER TABLETS 20/120 in man involved administration of a 6- dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of GIMETHER TABLETS 20/120 were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of GIMETHER TABLETS 20/120 (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of GIMETHER TABLETS 20/120 to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after GIMETHER TABLETS 20/120 in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of GIMETHER TABLETS 20/120.

Concomitant use requiring caution

Interactions affecting the use of GIMETHER TABLETS 20/120

Interaction with CYP3A4 inhibitors

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with GIMETHER TABLETS 20/120 led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of GIMETHER TABLETS 20/120 is considered unnecessary in *Falciparum malaria* patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

GIMETHER TABLETS 20/120 should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc (see Section 4.3 Contraindications), due to potential for increased concentrations of lumefantrine which could lead to

QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When GIMETHER TABLETS 20/120 is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy (see section 4.4).

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. GIMETHER TABLETS 20/120 should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of GIMETHER TABLETS 20/120, and increased lumefantrine concentrations may cause QT prolongation (see Section 4.4).

Lopinavir/ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of GIMETHER TABLETS 20/120.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of GIMETHER TABLETS 20/120.

Interactions resulting in effects of GIMETHER TABLETS 20/120 on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When GIMETHER TABLETS 20/120 is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised by these enzymes (see sections 4.4 and 5.2).

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, GIMETHER TABLETS 20/120 may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control for about one month (see sections 4.4 and 4.6).

Drug-food/drink interactions

GIMETHER TABLETS 20/120 should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see Section 4.2).

Grapefruit juice should be used cautiously during GIMETHER TABLETS 20/120 treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Pregnancy and Lactation

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see section 4.4).

Pregnancy

Based on animal data, GIMETHER TABLETS 20/120 is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 4.4 and 5.3) Reproductive studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation (see section 5.3).

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to GIMETHER TABLETS 20/120 (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

GIMETHER TABLETS 20/120 treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking GIMETHER TABLETS 20/120 should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of GIMETHER TABLETS 20/120 unless potential benefits to the mother and child outweigh the risks of GIMETHER TABLETS 20/120 treatment.

Fertility

There is no information on the effects of GIMETHER TABLETS 20/120 on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients receiving GIMETHER TABLETS 20/120 should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

The safety of GIMETHER TABLETS 20/120 has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received GIMETHER TABLETS 20/120 in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention: Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000)

Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects

	Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below (incidence estimates)
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon

Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

*: These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard)

4.9 Overdose

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamics properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01. Pharmacodynamic effects

GIMETHER TABLETS 20/120 comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of GIMETHER TABLETS 20/120 was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic *P. falciparum* malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µL
- 200,000/µL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or
non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub- Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

- 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28
- parasite clearance time (PCT), defined as time from first dose until first total and continued

disappearance of asexual parasite which continues for a further 48 hours

- fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

Table 2 Clinical efficacy results

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients	Median FCT[2] [25th, 75th percentile]	Median PCT[2] [25th, 75th percentile]	Year/ Study location
A025[4]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

1 Efficacy cure rate based on blood smear microscopy

2 mITT population

3 For patients who had a body temperature >37.5°C at baseline only 4Only the

6-dose regimen over 60 hours group data is presented

CT –GIMETHER TABLETS 20/120 administered as crushed tablets

GIMETHER TABLETS 20/120 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. GIMETHER TABLETS 20/120 is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population

Two studies have been conducted

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5°C. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours. This study compared crushed tablets and dispersible tablets. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed tablets are reported in table 3 below:

Table 3 Clinical efficacy by weight for pediatric studies

Study No. **Weight category**	**Median PCT[1]** **[25th, 75th percentile]**	**PCR-corrected 28-day cure rate[2]** **n/N (%) in evaluable patients**
Study A2403		
5 - <10 kg	24 hours [24, 36]	145/149 (97.3)
10 - <15 kg	35 hours [24, 36]	103/107 (96.3)
15 -25 kg	24 hours [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 hours [24, 36]	65/69 (94.2)
10 - <15 kg	35 hours [24, 36]	174/179 (97.2)
15 -<25 kg	35 hours [24, 36]	134/140 (95.7)
25-35 kg	26 hours [24, 36]	30/31 (96.8)

1 mITT population

2 Efficacy cure rate based on blood smear microscopy

CT GIMETHER TABLETS 20/120 administered as crushed tablets

QT/QTc Prolongation:

Adults and children with malaria

For information on the risk of QT/QTc prolongation in patients see section 4.4

Healthy adults

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 GIMETHER TABLETS 20/120 was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours 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 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving GIMETHER TABLETS 20/120 experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

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.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of GIMETHER TABLETS 20/120 is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption

Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether,

appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0- 104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of GIMETHER TABLETS 20/120 , 20 mg artemether/120 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively.
Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/mL. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when GIMETHER TABLETS 20/120 was taken after a high-fat meal.

Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).

Biotransformation

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

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of GIMETHER TABLETS 20/120, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree.
The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the

metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the *in vitro* data described in section 4.5

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration of GIMETHER TABLETS 20/120 over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). Systemic exposure to the metabolite desbutyl- lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see sections 4.3 and 4.5).

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days.
Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of GIMETHER TABLETS 20/120.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of GIMETHER TABLETS 20/120, and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the GIMETHER TABLETS 20/120 dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following

administration of GIMETHER TABLETS 20/120 as crushed tablets in healthy adults.

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

Older people

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Paediatric population

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of GIMETHER TABLETS 20/120) were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of GIMETHER TABLETS 20/120) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

Hepatic and Renal impairment

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe

hepatic impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of GIMETHER TABLETS 20/120 in patients with renal impairment is advised.

5.3 Preclinical safety data

General toxicity

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

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most
nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing. Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether:lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

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

Juvenile toxicity studies

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

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

Cardiovascular Safety Pharmacology

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

Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted. For effects in the human see sections 4.3, 4.4 and 5.1.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cross Carmellose sodium

Microcrystalline cellulose

Maize Starch

Hydroxy propyl methyl cellulose (HPMC E5) Purified

Water

Magnesium stearate Colloidal

Anhydrous silica Sodium lauryl

sulphate Purified Talc

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

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

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

Alu-PVC Blister with 24'Tablets of ARTEMETHER 20 MG AND LUMEFANTRINE 120 MG TABLETS.

6.6 Special precautions for disposal

No special requirements.

7 APPLICANT/MANUFACTURER

MANUFACTURER:

ASTAMED HEALTHCARE (I) PVT LTD.

Plot No. 2 & 3 Phase II Genesis Ind. Complex, Kolgaon,

Palghar, Thane 401404

Maharashtra, India.

MARKETED BY:

GIMBA PHARMACY LIMITED

NO.10, Funtua Road, Brinin-gawri, Kaduna

State

National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again before, during or after use of this medicine.
- If you have any further questions, ask your health care provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please inform your health care provider.

In this leaflet:

1. WHAT GIMETHER TABLETS 20/120 IS AND WHAT IT IS USED FOR

GIMETHER TABLETS 20/120 contains two substances called artemether and lumefantrine. They belong to a group of medicines called anti-malarial.

GIMETHER TABLETS 20/120 is only used for the treatment of acute uncomplicated malaria infections caused by a parasite called "*Plasmodium falciparum*". This parasite is a tiny organism made up of one cell that is found inside red blood cells.

GIMETHER TABLETS 20/120 is used to treat adults, children and infants of 5 kg body weight and above.

GIMETHER TABLETS 20/120 is not used to prevent malaria or to treat severe malaria (where it has affected the brain, lungs or kidneys).

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE GIMETHER TABLETS 20/120

Do not take GIMETHER TABLETS 20/120 if you

- if you are allergic (hypersensitive) to artemether, lumefantrine, or any of the other ingredients of this medicine (listed in section 6).
- if you have a severe type of malaria infection where it has affected parts of your body such as the brain, lungs or kidneys.
- if you have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.
- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.
- if your doctor has told you that you have low levels of electrolytes such as potassium or magnesium in your blood.
- if you are taking the following medicines: flecainide, metoprolol, imipramine, amitriptyline, clomipramine, certain antibiotics (macrolides, fluoroquinolones, imidazole), triazole antifungal agents, terfenadine, astemizole, cisapride (see also "Other medicines and GIMETHER TABLETS 20/120 ").
- if you are taking certain medicines (see also "Other medicines and GIMETHER TABLETS 20/120 "). If any of the above apply to you, tell your doctor without taking GIMETHER TABLETS 20/120. Warnings and precautions

Talk to your doctor or pharmacist before taking GIMETHER TABLETS 20/120:

- if you have severe liver or kidney problems.

- if you have a heart disorder, such as an abnormal electrical signal called “prolongation of the QT interval”.
- if you are infected with both the “Plasmodium falciparum” and “*Plasmodium vivax*” parasites.
- if you are taking or have taken any other medicines for the treatment of malaria. Some of these medicines must not be given together with GIMETHER TABLETS 20/120.

if you are in the first 3 months of pregnancy or intend to become pregnant. Your doctor will try to give you an alternative medicine first.

- if you feel worse, or if you feel too unwell to eat and drink.

If any of these apply to you, talk to your doctor before you take GIMETHER TABLETS 20/120.

Other medicines and GIMETHER TABLETS 20/120

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

In particular, do not take this medicine and tell your doctor if you are taking any of the following:

- medicines used to treat heart rhythm problems such as flecainide or metoprolol.
- medicines used to treat depression such as imipramine, amitriptyline or clomipramine.
- medicines used to treat infections called:
- rifampin, an antibiotic to treat leprosy or tuberculosis
- antibiotics, including the following types: macrolides, fluoroquinolones or imidazole,
- triazole antifungal agents.
- medicines used to treat allergies or inflammation called “non-sedating antihistamics” such as terfenadine or astemizole.
- cisapride - a medicine used to treat stomach problems.
- certain medicines used to treat epilepsy (such as carbamazepine, phenytoin).
- St John's wort (Hypericum perforatum) a medicinal plant or extract of this medicinal plant used to treat for example depressed mood.

If you are taking any of the above medicines, do not take GIMEMETHER 20/120. Please tell your doctor if you are taking:

- any other medicines to treat malaria.
- medicines to treat HIV infections or AIDS.
- an hormonal birth control medicine (in this case you should follow an additional method of birth control).

GIMETHER TABLETS 20/120 with food and drink

GIMETHER TABLETS 20/120 should be taken with food or drinks rich in fat such as milk.

Grapefruit juice should be used cautiously. Please ask your doctor for advice on

the best food or drinks to take GIMETHER TABLETS 20/120 with.

Pregnancy and breast-feeding

GIMETHER TABLETS 20/120 must not be used during the first 3 months of pregnancy if it is possible for the doctor to give an alternative medicine first. In the later stages of pregnancy, you should take GIMETHER TABLETS 20/120 only if clearly necessary.
Your doctor will discuss with you the potential risk of taking GIMETHER TABLETS 20/120 during pregnancy. If you are taking hormonal birth control medicine, you should also use an additional method of birth control for about one month.
You should not breast-feed while you are taking GIMETHER TABLETS 20/120. Once you have stopped taking GIMETHER TABLETS 20/120, you should wait at least 1 week before starting to breast-feed again.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

GIMETHER TABLETS 20/120 may make you feel sleepy, dizzy or generally weak. If this happens to you, do not drive or use any tools or machines.

3. HOW TO TAKE GIMETHER TABLETS 20/120

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Taking GIMETHER TABLETS 20/120

- the tablets should be taken with food or drinks rich in fat such as milk. Please ask your doctor for advice on the best food or drinks to take GIMETHER TABLETS 20/120 with.
- if you feel worse or are too unwell to eat or drink, please talk to your doctor.
- if you are sick (vomit) within 1 hour of taking the tablets take another dose. If in doubt, talk to your doctor.

Use in children

- when given to small children or infants, the tablets may be crushed.

When treating your child, a 24-tablet pack will be provided. Follow your doctor´s instructions carefully and use only the number of tablets needed. Return the remaining tablets to your pharmacist. How much to take or give

- six doses are taken over 3 days.
- the first dose should be taken as soon as possible and should be followed by five further doses at 8, 24, 36, 48 and 60 hours after the first dose, as described in the next section.
- when you take your first dose, work out the times you will need to take the rest of the doses at and write them down.

- all doses must be taken, and at the right times, to gain the full benefits of this medicine.

Adults and children weighing 35 kg and above

Take four tablets at each time interval. So you take or give:

- 4 tablets as soon as possible, then
- 4 tablets 8 hours later, then
- 4 tablets 24 hours after the first dose, then
- 4 tablets 36 hours after the first dose, then
- 4 tablets 48 hours after the first dose and then
- the final 4 tablets 60 hours after the first dose. This will mean you take or give a total of 24 tablets.

No special precautions or dosage adjustments are considered to be necessary in elderly patients. Infants and children weighing 5 kg to less than 35 kg

The number of tablets you need to give to your child depends on their weight:

- children 5 kg to less than 15 kg bodyweight: give 1 tablet at each of the time intervals outlined above. This means your child will take a total of 6 tablets.
- children 15 kg to less than 25 kg bodyweight: give 2 tablets at each of the time intervals outlined above. This means your child will take a total of 12 tablets.
- Children 25 kg to less than 35 kg bodyweight: give 3 tablets at each of the time intervals outlined Above. This means your child will take a total of 18 tablets.

If the malaria infection returns

A second course of GIMETHER TABLETS 20/120 may be necessary if the malaria infection returns, or if you are re-infected

With the parasite "*Plasmodium falciparum*" after having been cured. If this happens to you please talk to your doctor.

If you take more GIMETHER TABLETS 20/120 than you should

If you have accidentally taken too many tablets, talk to your doctor straight away, or go to your nearest Emergency unit. You may require medical attention. Remember to take your medicine with you, and show it to your doctor or the staff of the emergency unit. If you have run out of tablets, take the empty Packaging along with you.

If you forget to take GIMETHER TABLETS 20/120

Try to make sure that you do not miss any doses. However, if you do forget a dose of GIMETHER TABLETS 20/120, take the missed dose as soon as you remember unless it is almost time for your next dose. Then take your next dose at the usual time. Ask your doctor for advice. Do not take a double dose to make up for a forgotten dose.

If you stop taking GIMETHER TABLETS 20/120

Do not stop taking your medicine unless your doctor tells you to. Always follow your doctor´s instructions carefully, and complete the course of medication.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and generally disappear after a few days to a few weeks after treatment. Some side effects are more commonly reported in children and others are more commonly reported in adults. In cases where there is a difference, the frequency listed below is the more common one.

Some side effects could be serious and need immediate medical attention.

Rare (may affect up to 1 in 1,000 people)

If you get a rash, swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing, tell your doctor straight away. These are signs of an allergic reaction. Other side effects are:

Very common (may affect more than 1 in 10 people)

Fast heartbeat, headache, dizziness, cough, being sick (vomiting), stomach pain, feeling sick (nausea), joints or muscles aching, loss of appetite, general weakness, tiredness, trouble with sleeping. Common (may affect up to 1 in 10 people)

Involuntary muscle contractions (sometimes in rapid spasms), heart rhythm disturbances (called QTc prolongation), Symptoms such as unexplained persistent nausea, stomach problems, loss of appetite or unusual tiredness or weakness (signs of liver problems), diarrhoea, abnormal walking-) , tingling or numbness of the hands and feet-) a rash or itching on the skin, insomnia.

Uncommon (may affect up to 1 in 100 patients)

inability to coordinate movements decreased skin sensitivity, sleepiness, itching rash.) These side effects have been reported in adults and adolescents above 12 years of age. 5

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GIMETHER TABLETS 20/120

Keep this medicine out of the sight and reach of children.

Do not use GIMETHER TABLETS 20/120 after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Do not store above 30°C.

Do not use GIMETHER TABLETS 20/120 if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What it looks like GIMETHER TABLETS 20/120 are Yellow colored circular flat uncoated tablets having break line on one side and plain on other side of each tablet. They are available in blister in carton of 24 tablets. Ingredients Each GIMETHER TABLETS 20/120 contains:

• 20 mg of ARTEMETHER and 120 mg LUMEFANTRINE as active ingredient.

• Cross Carmellose sodium, Microcrystalline cellulose, Maize Starch, Hydroxy propyl methyl cellulose (HPMC E5), Purified Water, Magnesium stearate, Colloidal Anhydrous silica, Sodium lauryl sulphate and Purified Talc are excipients

Manufacturer

ASTAMED HEALTHCARE (I) PVT LTD
Plot No. 2 & 3 Phase II , Genesis Ind. Complex, Kolgaon
Palghar Thane 401404, Maharashtra ,India.