AUSTRALIAN PRODUCT INFORMATION – RIAMET® TABLETS AND RIAMET® DISPERSIBLE TABLETS (ARTEMETHER/LUMEFANTRINE) 20MG/120MG

1 NAME OF THE MEDICINE

Artemether and lumefantrine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Riamet Tablets and Riamet Dispersible tablets contain the active ingredient Artemether and lumefantrine

Riamet Tablets: excipients with known effect: sugars and latex (in trace amounts)

Riamet Dispersible tablets: excipients with known effect: sugars and latex (in trace amounts).

For the full list of excipients. Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Riamet Tablets (20 mg/120mg)

Tablets

Riamet Dispersible tablets (20 mg/120mg)

Dispersible tablets

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Riamet tablet is indicated for the treatment of acute, uncomplicated malaria due to *Plasmodium falciparum* in adults, children and infants of 5kg and above.
Riamet Dispersible tablet is indicated for the treatment of acute, uncomplicated malaria due to *Plasmodium falciparum* in children and infants weighing between 5kg and less than 35kg.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage Regimen

Riamet Dispersible tablets for infants and children weighing 5 kg to < 35 kg, and aged ≥ 3 months up to 12 years:
Six doses of 1 to 3 dispersible tablets per dose, depending on bodyweight (i.e. total course of either 6, 12, or 18 tablets), given over a period of 60 hours.

5 to < 15 kg bodyweight, & ≥ 3 months: One dispersible tablet at the time of initial diagnosis, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 tablets).

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

25 to < 35 kg bodyweight & < 12 years: Three dispersible tablets as a single dose at the time of initial diagnosis, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) on each of the following two days (total course comprises 18 tablets).

Riamet tablets for adults, adolescents, and children weighing ≥ 35 kg or > 12 years of age:

Six doses of four tablets (i.e. total course of 24 tablets), given over a period of 60 hours.

Elderly:

Although no studies have been carried out in the elderly, no special precautions or dosage adjustments are considered necessary in such patients.

Renal or hepatic impairment:

Although no specific studies have been carried out, no dosage adjustments are considered necessary for these conditions.

No specific dose adjustment recommendations can also be made for patients with hepatic impairment *(see section 4.4 Special warnings and precautions for use)*. Most patients with acute malaria present with some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment.

New and recrudescent infections:

Data for a limited number of patients show that new and recrudescent infections can be treated with a second course of Riamet. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Riamet cannot be recommended.

Method of Administration

The first dose, given at the time of initial diagnosis, should be followed by five further doses given at 8, 24, 36, 48 and 60 hours thereafter. Whenever possible, the dose should be taken immediately after food. 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 *(see section 5.2 Pharmacokinetic Properties –Absorption).* In the event of vomiting within 1 hour of administration, a repeat dose should be taken.

Riamet Dispersible tablets for Infants and children weighing 5 kg to < 35 kg, and aged ≥ 3 months up to 12 years

The dispersible tablet(s) composing 1 dose should be completely dispersed in a small amount of water (approximately 10 mL per tablet). Stir gently and administer immediately to the patient. Rinse the glass with an additional small amount of water (approximately 10 mL) and give immediately to the patient.

Riamet tablets for adults, adolescents, and children weighing ≧ 35 kg or > 12 years of age
Swallow the tablets whole. The tablets may be taken with fluids.

4.3 CONTRAINDICATIONS

Riamet and Riamet Dispersible tablets are contraindicated in:

- Patients with known hypersensitivity to artemether or lumefantrine or any of the excipients.
- Patients with severe malaria according to the World Health Organisation definition*
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine)
- Patients who are taking any drug metabolised by strong inducers of CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, St John's wort (*Hypericum perforatum) (see section 4.5 Interaction with other medicines and other forms of interactions)*
- Patients with known pre-existing prolongation of the QTc interval *(see section 4.4 Special Warnings and Precautions for use and section 4.5 Interaction with other medicines and other forms of interactions)*
- Patients with a family history of congenital prolongation of the QTc interval on electrocardiograms or of 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, antidepressant agents
    - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents
    - certain non-sedating antihistamines (terfenadine, astemizole)
    - cisapride.
- patients with known disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.

Where * indicates the presence of one or more of the following clinical or laboratory features:

Clinical manifestations: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary oedema (radiological); abnormal bleeding; clinical jaundice; haemoglobinuria
Laboratory tests: Severe normocytic anaemia; haemoglobinuria; hypoglycaemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Riamet and Riamet Dispersible tablets have not been evaluated for the treatment of complicated malaria, including cases of cerebral malaria or other severe manifestations

such as pulmonary oedema or renal failure.

Riamet and Riamet Dispersible tablets are not indicated for, and have 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. Riamet and Riamet Dispersible tablets are active against blood stages of *P. vivax*, but is not active against hypnozoites. Riamet and Riamet Dispersible tablets are not indicated and have not been evaluated for prophylaxis.
Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.
The exposure to artemether in Riamet Dispersible tablets and Riamet tablets are not bioequivalent *(see section 5.2 Pharmacokinectic Properties).*

Riamet should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6 Fertility, Pregnancy and Lactation)

QTc interval prolongation:
Halofantrine, quinine and quinidine are known to cause QTc interval prolongation. Like other antimalarials (e.g. halofantrine, quinine and quinidine), Riamet and Riamet Dispersible tablets have the potential to cause QTc interval prolongation with standard dosing, although no clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) has been reported. Asymptomatic prolongation of QTc intervals by > 30 ms, with an actual QTc > 450 ms in males and > 470 ms in females, was observed in approximately 7 % of patients treated with various dose regimens of Riamet in clinical trials. It is possible that these changes were disease related. No correlation has been found between QTc interval prolongation and plasma concentrations of artemether, dihydroartemisinin or lumefantrine.

Due to the lack of clinical data and due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering Riamet or Riamet Dispersible tablets to patients in whom there may be detectable concentrations of these drugs in the plasma following prior treatments *(see section 4.5 Interaction with other medicines and other forms of interactions)*

Due to the lack of data on safety and efficacy, Riamet or Riamet Dispersible tablets should not be given concurrently with any other antimalarial agents. However, if a patient deteriorates whilst taking Riamet or Riamet Dispersible tablets and requires alternative treatment, this should be commenced without delay, but with caution. ECG and blood potassium monitoring are recommended.

Use in hepatic impairment

Neither Riamet nor Riamet Dispersible tablets have been studied for efficacy and safety in patients with severe hepatic insufficiency and therefore no recommendations can be made for 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 Pharmacokinetic Properties).*

Use in renal impairment

Neither Riamet nor Riamet Dispersible tablets have been studied for efficacy and safety in patients with severe renal insufficiency and therefore no recommendations can be made for this group of patients.

Use in patient with cardiac impairment

Caution is advised when administering Riamet or Riamet Dispersible tablets to patients with severe cardiac disease. In these patients, ECG and blood potassium monitoring is advised.

Use in the elderly

There is no information suggesting that the dosage in patients under 65 years of age should be different to younger adults *(see section 5.2 Pharmacokinetic Properties and section 4.2 Dose and method of administration).*

Paediatric use

The efficacy of Riamet Dispersible tablet was based on a study population including 1 infant < 3 months of age and the safety data was based on a population including 4 patients less than 3 months of age only one of whom was treated with Riamet Dispersible tablets. *(See section 5.1 Phamacodynamic Properties – Clinical Trials).* The safety and efficacy of Riamet or Riamet Dispersible tablets in children aged less than 3 months have not been adequately assessed.

Carcinogenicity, mutagenicity and impairment of fertility

Carcinogenicity studies with Riamet or Riamet Dispersible tablets were not conducted. Neither artemether, lumefantrine or the combination were mutagenic in bacteria, nor were they mutagenic or clastogenic in V79 Chinese hamster ovary cells *in vitro*, and they did not induce micronuclei in bone marrow erythrocytes of rats following an oral dose of Riamet up to 2000 mg/kg.

Use with other drugs

Caution is recommended when combining Riamet 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 Riamet *(see 4.5 Interactions with other medicines and other forms of interactions and section 5.2 Pharmacokinectic Properties).*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

INTERACTIONS RESULTING IN A CONTRAINDICATION

Drugs that are known to prolong the QTc interval

Riamet 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 antihistamines (terfenadine, astemizole), and cisapride *(see section 4.3 Contraindications)*

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 Riamet with drugs which are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) (*see section 4.3 Contraindications* and *section 5.2 Pharmacokinectic Properties*).

Interaction with strong inducers of CYP3A4 such as rifampicin

Oral administration of 600 mg rifampicin daily, a strong CYP3A4 inducer, with Riamet Tablets (6-dose regimen over 3 days) resulted in significant decreases in exposure to artemether, DHA and lumefantrine when compared to exposure values after Riamet alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with Riamet *(see section 4.3 Contraindications).*

INTERACTIONS RESULTING IN CONCOMITANT USE NOT BEING RECOMMENDED

Other antimalarials:

Data on safety and efficacy are limited, and Riamet should therefore not be given concurrently with other antimalarials unless there is no other treatment option (*section 4.4 Special Warnings and Precautions for use*). If Riamet 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 Riamet.

In-vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine and quinine (also see interaction study with quinine in healthy volunteers above).

Due to the lack of clinical data, and due also to the propensity of some antimalarials to prolong the QTc interval, caution is advised when administering Riamet or Riamet Dispersible tablets to patients in whom there may be detectable concentrations of these drugs in the plasma following prior treatments.

In particular, Riamet or Riamet Dispersible tablets must not be co-administered with halofantrine *(see section 4.3 Contraindications and section 4.4 Special Warnings and*

Precautions for use). In patients previously treated with halofantrine, Riamet should be dosed at least one month after the last halofantrine dose.

Drug-drug interaction studies

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

Ketoconazole:

Sixteen healthy adults were randomised in an open-label, two period crossover design study. Subjects received a single Riamet dose (4 tablets, i.e. 80 mg artemether / 480 mg lumefantrine) either alone or in combination with multiple oral doses of ketoconazole (400 mg on day 1 followed by 200 mg daily for 4 additional days). The concurrent administration of ketoconazole with Riamet led to an increase (maximum 2.3-fold) in artemether, dihydroartemisinin (the main metabolite) and lumefantrine exposure. The mean percent increase in AUC_{∞} for artemether, dihydroartemisinin and lumefantrine was 131%, 51% and 61%, respectively. 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 Riamet is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors. The addition of a CYP3A4 inhibitor to a multiple dose course of Riamet has not been studied.

Quinine:

The concurrent intravenous administration of quinine (10 mg/kg body weight) with Riamet had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and the main metabolite, dihydroartemisinin, appeared to be lower. In this study, administration of Riamet to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of the QTc interval, with the peak QTc interval post dose increasing by 5.5 msec, which is consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Riamet in 14 additional subjects, with the peak QTc interval post quinine dose increasing by 15.6 msec. It would thus appear that the inherent risk of QTc interval prolongation associated with intravenous quinine was enhanced by prior administration of Riamet.

Mefloquine:

A drug interaction study with Riamet 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 Riamet were not affected compared with a group who 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.

INTERACTIONS TO BE CONSIDERED

Interactions affecting the use of Riamet and Riamet Dispersible

CYP450 enzymes:

Both artemether and lumefantrine are metabolised by the cytochrome enzyme CYP3A4 but do not inhibit this enzyme at therapeutic concentrations. Due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Riamet should be used cautiously with drugs that inhibit CYP3A4. Grapefruit juice should be avoided during Riamet treatment *(see section 4.4 Special Warnings and Precautions for use).*

Anti-retroviral drugs:

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with Riamet requires caution. Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Riamet should be used cautiously in patients on anti-retroviral drugs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Riamet, and increased lumefantrine concentrations may cause QT prolongation *(see section 4.4 Special Warnings and Precautions for use).*

Interaction with weak to moderate inducers of CYP3A4

When Riamet is co-administered with weak to moderate inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy *(see section 4.4 Special Warnings and Precautions for use)*.

INTERACTIONS RESULTING IN EFFECTS OF RIAMET ON OTHER DRUGS

Interaction with drugs metabolized by CYP450 enzymes

When Riamet is co-administered with substrates of CYP3A4, it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Whereas *in-vitro* studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisinins have some capacity to induce the production of the cytochrome enzyme CYP2C19, and perhaps also CYP3A4. It is possible that iso-enzyme induction could alter the therapeutic effects of drugs which are predominantly metabolised by these enzymes *(see section 4.4 Special Warnings and Precautions for use and section 5.2 Pharmacokinectic Properties*).

Hormonal contraceptives:
Riamet 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 section 4.4 Special Warnings and Precautions for use).*

Drug-food/drink interactions

Riamet 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 Dose and Method of Administration)*

Grapefruit juice should be avoided during Riamet and/or Riamet Dispersible treatment.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data addressing the effects of Riamet or Riamet Dispersible tablets on fertility. In a reproductive toxicity study in rats, Riamet had no effects on male or female fertility at an oral dose up to 300 mg/kg/day, corresponding to an estimated systemic exposure to lumefantrine (based on AUC) of 4.7 – 47x and an artemether dose of 43 mg/kg/day (artemether exposures could not be estimated due to an extensive first-pass effect). At 1000 mg/kg/day, Riamet reduced the pregnancy rate by decreasing male fertility (reduced sperm motility and epididymal sperm count, increased percentage of morphologically abnormal sperm).

Use in pregnancy

Pregnancy Category D

Artemisinins are known to be embryotoxic and teratogenic in animals, causing cardiovascular and skeletal deformities.

Based on animal data, Riamet is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections section 4.4 Special Warnings and Precautions for use)

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.

For congenital abnormalities, the results of the meta-analysis comparing the effect of artemisinin and quinine with the group unexposed to antimalarial were as follows:

	First trimester Treatment group	Embryo sensitive period treatment group	First trimester Adjusted HR 95% CI	Embryo Sensitive period Adjusted HR 95% CI
Congenital abnormalities				
Artemisinin	5/551	4/387	1.5% (0.6-3.5)*	2.4%(9-6.1)
Quinine	8/741	8/569	1.2%(0.6-2.4)*	1.5%(0.8-3.0)
Unexposed to antimalarials	187/23104	187/23104	0.7%(0.4-1.2)*	0.7%(0.4-1.2)

**Highlighted results are results from the primary and secondary analyses as the embryo sensitive period results are coming from a sensitivity analysis)*

Due to limitations of this analysis, the risk of adverse pregnancy outcomes for Artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from an observational pregnancy study including over 300 pregnant women who were exposed to Riamet during the second or third trimester, and published data of another approximately 500 pregnant women who were exposed to artemether-lumefantrine, 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.

In addition, there was no apparent increase in adverse pregnancy outcomes based on data from one open label randomized study of over 800 patients treated with Riamet in the second or third trimester.

Epidemiological studies have important methodological limitations, which hinder interpretation of data, including inability to control for confounders, such as underlying maternaldisease, and maternal use of concomitant medications and missing information on the dose and duration of use.

Riamet should not be used during the first trimester of pregnancy in situations where other suitable and 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 fetus.

Use in lactation

Riamet or Riamet Dispersible tablets should not be taken by breast-feeding women as no data on excretion in milk are available. Due to the long elimination half life of lumefantrine (4 to 6 days), it is recommended that breastfeeding should not resume until at least four weeks after the last dose, unless the potential benefits to the mother and child outweigh the risks of treatment.

There were no data on excretion of artemether, lumefantrine and/or their metabolites in the milk of animals; however distribution studies in pregnant rats suggested retention of the drugs and/or their metabolites in the mammary glands. A peri-postnatal study showed no development changes in rat pups whose mothers received 50 mg/kg/day of Riamet (7.1 mg/kg artemether, 42.9 mg/kg lumefantrine) up to day 21 of lactation.

Women of child-bearing potential

As Riamet or Riamet Dispersible tablets are contraindicated during the first trimester of pregnancy, women should not conceive while on this treatment for malaria. This includes women prescribed Riamet, for stand-by emergency treatment of malaria during their travel, in which case an effective form of contraception should be used during travel 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 (see section 4.5).

Embryofoetal development studies were performed in rats and rabbits with oral lumefantrine, artemether, and the combination. Transfer of the drug(s) and/or metabolites to the foetus was demonstrated in both species.

Administration of lumefantrine alone during gestation showed no evidence of maternal or embryofoetal toxicity, nor teratogenicity, at doses up to 1000 mg/kg/day (rats and rabbits), corresponding to approximate systemic exposure ratios (based on AUCs) of 5.3–55 times those measured at the maximum recommended clinical dose.

Administration of artemether alone to gestating rats showed no embryofoetal effects at doses up to 3 mg/kg/day. Increased post-implantation loss and decreased foetal bodyweights, but no maternotoxicity, were seen at 10 mg/kg/day. Artemisinins are known to be embryotoxic in animals, causing cardiovascular and skeletal malformations. These effects have been observed in some studies with artemether. In rabbits, there were no maternal or foetal effects at doses up to 25 mg/kg/day, but abortions and increased post-implantation loss occurred at 30 mg/kg/day. Systemic exposures to artemether could not be determined due to an extensive first-pass effect.

Administration of the combination showed no embryofoetal effects in rats at doses up to 30 mg/kg/day (4.3 mg/kg/day artemether), but increased post-implantation losses were seen at 60 mg/kg/day and above. In rabbits, there were no embryofoetal effects at doses up to 105 mg/kg/day (15 mg/kg/day artemether), but increased post-implantation losses and abortions were observed at 175 mg/kg/day (25 mg/kg/day artemether).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients receiving Riamet or Riamet Dispersible tablets should be warned that dizziness or fatigue/asthenia may occur, in which case they should not drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Events in Clinical Trials

Infants and Children weighing 5 kg to less than 35 kg and 12 years of age or less:

The pooled safety population included 1262 infants and children ≤12 years of age and ≥ 5 kg to < 35 kg body weight enrolled in 4 studies who received at least one dose of the assigned 6-dose regimen of Riamet tablets (815) or Riamet Dispersible tablets (447). 96% of the patients were black (studies conducted in Africa) and the remainder were

enrolled in studies conducted in Thailand. Only 4 of the 1262 participants were less than 3 months of age.

Riamet and Riamet Dispersible tablets appeared to be well tolerated regardless of the administration form. 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 Riamet or Riamet Dispersible tablets although a causal relationship 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.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000), including isolated reports.

Table 5: Treatment Emergent adverse drug reactions compiled from a pooled safety analysis of 4 studies in infants and children ≤ 12 years of age receiving Riamet tablets or Riamet dispersible tablets

Immune system disorders		
	Rare:	Hypersensitivity
Metabolism and nutrition disorders		
	Very common	Anorexia, decreased appetite
Psychiatric disorders		
	Uncommon	Sleep disorders
Nervous system disorders		
	Common:	Headache, dizziness
	Uncommon:	Somnolence, clonus
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
Blood and lymphatic system disorders		
	Common:	Splenomegaly, Anemia

Investigations

Common	Liver function tests increased, white blood cell count decreased, platelet count decreased
Rare	Electrocardiogram QT prolonged

Adverse events found in non-recommended regimens not included in this pooled safety analysis: paraesthesia (1.2% of adolescents and adults, no cases in children); involuntary muscle contractions (1.3% of children).

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

Adolescents and Adults:
Treatment Emergent Signs and Symptoms occurring with an incidence of ≥ 1% in patients over 12 years of age given the 6-dose regimen (N = 495) are shown in Table 6. These events are not necessarily related to treatment with the drug and may be related to the underlying disease.

Table 6: Treatment Emergent Signs and Symptoms with an incidence of ≥ 1% in patients over 12 years of age given the 6-dose regimen (N = 495)

Body System	n	(%)	Body System	n	(%)
Nervous system			**Musculoskeletal**		
Headache	118	(23.8)	Myalgia	44	(8.9)
Dizziness	74	(14.9)	Arthralgia	41	(8.3)
Sleep disorder	47	(9.5)	Back pain	5	(1.0)
Cardiovascular			**Haematologic**		
Palpitation	37	(7.5)	Anaemia	11	(2.2)
Gastrointestinal			**Skin and appendages**		
Anorexia	55	(11.1)	Pruritus	13	(2.6)
Abdominal Pain	47	(9.5)	Rash	8	(1.6)
Nausea	33	(6.7)	**Body as a whole**		
Vomiting	15	(3.0)	Fever	78	(15.8)
Dyspepsia	11	(2.2)	Asthenia	62	(12.5)
Diarrhoea	7	(1.4)	Fatigue	11	(2.2)
Infections and infestations			Rigors	10	(2.0)
Infestation, parasitic	22	(4.4)	**Respiratory**		

Body System	n	(%)	Body System	n	(%)
Infection, viral	15	(3.0)	Pharyngitis	15	(3.0)
Abscess	14	(2.8)	Coughing	14	(2.8)

Serious adverse events that occurred in patients taking Riamet in clinical trials included isolated reports of haemolytic anaemia, hepatitis and QTc prolongation. Asymptomatic QTc prolongation was reported in adults, children and infants but no causal relationship with Riamet could be confirmed.

A causal relationship with the use of Riamet could not be excluded for the following adverse events.

The adverse events listed in Table 7 represent a pooled safety analysis of adverse reactions from clinical trials in adults and adolescents > 12 years of age or ≥ 35 kg body weight using the recommended 6-dose regimen:

Table 7: Adverse drug reactions in adults and adolescents > 12 years of age or ≥ 35 kg body weight

Metabolism and nutrition disorders

Very common: Anorexia, decreased appetite

Psychiatric disorders

Very common: Sleep disorders

Nervous system disorders

Very common: Headache, dizziness

Common: Clonus

Uncommon: Somnolence, involuntary muscle contractions, paraesthesia, hypoaesthesia, abnormal gait, ataxia

Cardiac disorders

Very common: Palpitations

Respiratory, thoracic and mediastinal disorders

Common: Cough

Gastrointestinal disorders

Very common: Abdominal pain, vomiting, nausea

Common: Diarrhoea

Skin and subcutaneous tissue disorders

Common: Pruritus, rash

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

Common:	Liver function tests increased
Uncommon:	Electocardiogram QT prolonged

Post-marketing Experience

Listing of adverse drug reactions from post-marketing spontaneous reports:

Riamet Dispersible - The following additional adverse drug reactions have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency, which is therefore categorised as not known.

Hypersensitivity reactions including urticaria and angioedema have been rarely reported.

Riamet - It is estimated that over 1,250,000 patients have been exposed to Riamet in other countries.

The following additional adverse drug reactions have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

The most frequently reported adverse events since marketing include: anaemia NOS*, chromaturia, diarrhoea NOS, face oedema, haemoglobinuria, hypersensitivity NOS reactions including urticaria and angioedema have been rarely reported, hypertension NOS, jaundice NOS, peripheral oedema, pruritus NOS, pyrexia, erythematous rash, thrombocytopenia, vomiting NOS. On the basis of the above-mentioned patient population exposed to the drug, all these events could be classified as “very rare” (<0.01%).
(* NOS stands for "Not Otherwise Specified" and means that more specific information was not provided).

Many of these events are likely to be related to the underlying malaria and/or to an unsatisfactory response to the treatment. The remaining are isolated reports where other factors were identified as more likely cause of the events (e.g. concomitant drugs, concomitant infections) or where the information provided was too scarce to draw any conclusion.

Adverse events found in non-recommended regimens not included in the pooled safety analysis: paraesthesia (1.2% of adolescents and adults).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and electrolytes should be monitored.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Riamet and Riamet Dispersible tablets are blood schizontocides comprising 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 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 synthesis and protein synthesis within the malarial parasite.

The antimalarial activity of the combination of lumefantrine and artemether in Riamet is greater than that of either substance alone. In a double-blind comparative study in China, the 28-day cure rate of Riamet when given as 4 doses was 100%, compared with 92% for lumefantrine and 55% for artemether when given as monotherapy.

In comparative clinical trials, Riamet tablets cleared gametocytes in less than one week and more rapidly than non-artemisinin antimalarial comparators.

Clinical trials

<u>Efficacy data in infants and children</u>

Study B2303 was a phase III, randomised, investigator-blinded, multicentre, parallel-group trial comparing the efficacy, safety, and tolerability of Riamet Dispersible tablet to crushed Riamet tablets, administered according to body weight ranges, in 899 male and female infants and children, weighing between 5 kg and ≤ 35 kg and aged ≤ 12 years, with microscopically confirmed, acute, uncomplicated *P. falciparum* malaria or with mixed infection including *P. falciparum*. The study was conducted in eight study centres in Sub-Saharan Africa.

Riamet Dispersible tablet was compared to crushed Riamet tablet rather than another antimalarial, because Riamet is the approved reference treatment for the treatment of uncomplicated falciparum malaria in several endemic and non-endemic countries in this patient population.
The primary efficacy variable was the proportion of patients who were clinically free of parasitemia (PCR corrected if *P. falciparum* asexual forms present) at 28 days as measured by PCR-corrected parasitological cure rate (see Table 1). Baseline demographics characteristics are presented in Table 2.

Table 1: B2303 PCR-corrected 28-day cure rate, by treatment (Primary Analysis population)

Population	Statistic	Riamet Dispersible tablet	Crushed Riamet tablet
PA (primary)	N	403	409
	n (%) cured	394 (97.8)	403 (98.5)
	Asymptotic 95% CI	(96.3 - 99.2)	(97.4 - 99.7)

Table 2: Study B2303 baseline demographics (Safety Population)

Variable	Riamet Dispersible tablet (N=447)	Crushed Riamet tablet (N=452)	Total (N=899)
Age categories - n (%)			
< 3 months	1 (0.2)	1 (0.2)	2 (0.2)
3 -< 6 months	6 (1.3)	7 (1.5)	13 (1.4)
6 - < 12 months	23 (5.1)	28 (6.2)	51 (5.7)
12 - < 24 months	81 (18.1)	73 (16.2)	154 (17.1)
2- < 4 yrs	145 (32.4)	149 (33.0)	294 (32.7)
4- < 6 yrs	92 (20.6)	89 (19.7)	181 (20.1)
6 - 12 yrs	99 (22.1)	105 (23.2)	204 (22.7)
Sex - n (%)			
Male	232 (51.9)	247 (54.6)	479 (53.3)
Female	215 (48.1)	205 (45.4)	420 (46.7)
Body weight (kg)			
Mean ± SD	14.4 ± 5.51	14.5 ± 5.53	14.4 ± 5.52
Median	13.0	13.1	13.0
Range	5.0 - 34.0	6.0 - 34.0	5.0 - 34.0
Body weight categories - n (%)			

Variable	Riamet Dispersible tablet (N=447)	Crushed Riamet tablet (N=452)	Total (N=899)
5-<15 kg	274 (61.3)	273 (60.4)	547 (60.8)
15-<25 kg	144 (32.2)	145 (32.1)	289 (32.1)
25-<35 kg	29 (6.5)	34 (7.5)	63 (7.0)
Parasite density asexual forms (n/μL)			
Median	26,364	32,288	29,241
Range	196,840	1,581 – 628,571	0 – 628,571

In an open, multicentre clinical study conducted in Africa in 310 children weighing ≥ 5 kg to ≤ 25 kg and receiving a 6-dose Riamet according to body weight ranges, the mean 28-day parasitological cure rate (PCR corrected) was 93.9 % for the ITT population and 96.7 % for the evaluable population.
Children from non-endemic countries were not included in clinical trials.

Efficacy data in adults

Active-controlled trials:

Three randomised, parallel group studies using the recommended 6-dose regimen were conducted in Thailand. One study (Study 025) compared the efficacy and safety of a 4-dose regimen of Riamet tablets with two 6-dose Riamet tablet regimens (6 doses over 3 days or 6 doses over 5 days). The other two studies (Studies 026 and 028) compared 6 doses of Riamet tablets over 3 days with mefloquine 15 mg/kg on Day 2 and 10 mg/kg on Day 3 + artesunate 4 mg/kg od for 3 days (MAS). In all three studies the primary efficacy criteria was the cure rate at Day 28. Time to parasite clearance was a secondary measure of efficacy. For the 385 evaluable patients given Riamet, the cure rate at Day 28 was 96.4% (95% CI 94.0, 98.0). Parasite clearance had occurred in 32.2% of patients by Day 2 and in 88.2% of patients by Day 3.

Another study conducted in Thailand (Study 008) compared the 4-dose regimen of Riamet tablets with MAS. For the 364 evaluable patients given MAS the cure rate at Day 28 was 98.1% (95% CI 96.1, 99.2). Parasite clearance had occurred in 55.2% of patients by Day 2 and in 84.0% of patients by Day 3. In the two studies where Riamet was compared with MAS, parasite clearance rates at Day 2 and Day 3 were comparable. Cure rates in patients given Riamet were negatively affected by high parasite density at baseline, high body weight and no food before the first 2 doses.

The 28-day cure rate and parasite clearance observed for Riamet given as a 6-dose regimen over 3 days vs. MAS are summarised below in Tables 3 and 4, respectively.

No studies using the proposed dose regimen have been conducted in non-immune travellers. However, two studies using the 4-dose regimen in travellers returning to Europe demonstrate the safety and efficacy of Riamet in this population. In addition, general results demonstrate that the 6-dose regimen is as safe as and more effective than the 4-dose regimen, thereby supporting the use of the 6-dose regimen in non-immune patients. Efficacy and safety of Riamet for use as a "stand by" treatment have not been assessed.

Table 3: 28-day cure rate for Riamet (6-dose regimen over 3 days) vs. MAS

Study	Riamet		MAS	
	No. of evaluable patients 28-day cure rate [95% CI]		No. of evaluable patients 28-day cure rate [95% CI]	
Study 008		(6-dose regimen not used in this study)	n=264	97.3% [94.6, 98.9]%
Study 025	N=96	96.9% [91.1, 99.4]%		(Not used in this study)
Study 026	N=134	97.0% [92.5, 99.2]%	n=47	100% [92.5, 100]%
Study 028	N=155	95.5% [90.9, 98.2]%	n=53	100% [93.3, 100]%
All	N=385	96.4% [94.0, 98.0]%	n=364	98.1% [96.1, 99.2]%

Table 4: Parasite reduction for Riamet (6-dose regimen over 3 days) vs. MAS

Study	Riamet		MAS	
	No. of evaluable patients with negative slide on Day 2 and 3		No. of evaluable patients with negative slide on Day 2 and 3	
		Day 2 Day 3		Day 2 Day 3
Study 008		(6-dose regimen not used in this study)	n=308	62.0% 81.5%
Study 025	N=118	26.3% 78.8%		(Not used in this study)
Study 026	N=150	21.3% 89.3%	n=50	26.0% 88.0%
Study 028	N=164	46.3% 93.9%	n=55	43.6%, 94.5%
ALL	N=432	32.2% 88.2%	n=413	55.2%, 84.0%

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic characterisation of Riamet and Riamet Dispersible tablets are 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 6-8 hours after dosing.
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 Riamet 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), 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* (97.9 % and 99.9 %, respectively). Protein binding to human plasma protein is linear.

Metabolism

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 enzyme CYP3A4/5. This metabolite has also been detected 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. *In-vivo* data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4 *(see section 4.3 Contraindications and section 4.5 Interaction with other medicines and other forms of interactions).*

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes; the N-debutylated metabolite of lumefantrine is active. *In vitro*, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations *(see section 4.3 Contraindications and section 4.5 Interaction with other medicines and other forms of interactions).*

Excretion

Artemether and dihydroartemisinin are rapidly cleared from plasma, with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly, with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Riamet.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Riamet, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.

Bioavailability of Riamet tablets and Riamet Dispersible tablets in adults:

A randomized, open-label, single-dose, three-period, two-sequence, crossover study (B2104) compared the relative bioavailability of Riamet Dispersible tablet to intact and crushed non-dispersible Riamet tablets for oral suspension in healthy adult volunteers. Results showed that the exposure to lumefantrine, artemether, and dihydroartemisinin was similar between Riamet Dispersible and Riamet tablet crushed. Bioequivalence of the two formulations was shown for the AUCs of all three compounds and for Cmax of lumefantrine and dihydroartemisinin. Results also showed that the exposure to lumefantrine was similar between Riamet Dispersible and Riamet tablet intact, and bioequivalence between the two formulations was shown for lumefantrine AUC and Cmax. Of note, the exposure (AUC, C_{max}) to artemether and dihydroartemisinin were significantly lower (by 20 – 35 %) following the administration of Riamet Dispersible tablets as compared to intact Riamet tablets.

Pharmacokinetics in special patient populations:

Paediatrics

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

Elderly patients

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 *(see section 4.4 Special warnings and Precaution for use and section 4.2 Dose and method of administration).*

Renal impairment

No specific pharmacokinetic studies have been performed in patients with renal impairment. 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 Riamet and Riamet Dispersible in patients with renal impairment is advised

(see section 4.4 Special warnings and Precaution for use and section 4.2 Dose and method of administration).

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 in 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 4.4 Special warnings and Precaution for use and section 4.2 Dose and method of administration).*

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Refer to section [4.4 Special warning and precautions for use - Carcinogenicity, mutagenicity and impairment of fertility]

Carcinogenicity

Refer to section [4.4 Special warning and precautions for use - Carcinogenicity, mutagenicity and impairment of fertility]

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Riamet Tablets and Riamet Dispersible tablets contain microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose, colloidal anhydrous silica and polysorbate 80.

Riamet Dispersible tablets also contain sodium saccharin and cherry flavour.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Protect from moisture (Dispersible tablets).
Keep out of the reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Riamet 20 mg/120 mg Dispersible tablets contain artemether 20 mg and lumefantrine 120 mg. They are flat, yellow, round, uncoated tablets with bevelled edges; imprinted with "CD" on one side and "NVR" on the other side. Blister packs containing 6*, 12*, 18, 180*, 360*, 540* dispersible tablets.

Riamet tablets (20 mg/120 mg) contain artemether 20 mg and lumefantrine 120 mg. They are pale yellow, flat, round, uncoated tablets with bevelled edges; marked with N/C and a score line on one side and CG on the other. Blister packs containing 16*, 24, or 400* tablets.

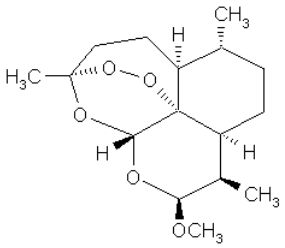
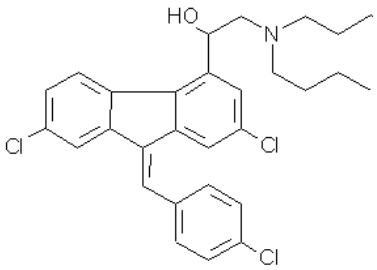
*Not all presentations may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Active ingredient	artemether	lumefantrine
Chemical name	(3*R*, 5a*S*, 6*R*, 8a*S*, 9*R*, 10*S*, 12*R*, 12a*R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-j]-1,2-benzodioxepin	(*1RS*)-*2*-Dibutylamino-1-{2,7-dichloro-9-[(*Z*)4-chlorobenzylidene]-9*H*-fluoren-4-yl}-ethanol
Molecular weight	298.38	528.95
Molecular formula	$C_{16}H_{26}O_5$	$C_{30}H_{32}Cl_3NO$
Chemical structure		

CAS number

Active ingredient	artemether	lumefantrine
CAS Number	**71963-77-4**	**82186-77-4**

Pharmacotherapeutic group: Antimalarials, artemisinins and derivatives

ATC code: P01BE52

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113
Website: www.novartis.com.au
® = Registered Trade name

9 DATE OF FIRST APPROVAL

24 July 2002: AUST R 90011 RIAMET artemether/lumefantrine 20 mg/120 mg tablet blister pack)

9 July 2010: AUST R 158523 RIAMET 20 mg/120 mg artemether/lumefantrine 20 mg/120 mg dispersible tablet blister pack

10 DATE OF REVISION

24 June 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Moved excipient information to section 6.1. Added allergen information.
4.7	Editorial revision of heading numbers
6.1	Addition of excipient information.

Internal use ria240620i based on CDS dated 02jul2018