Riamet® Dispersible and Riamet® Baby

Composition

Active substances

Artemether, lumefantrine

Excipients

Riamet Dispersible
Microcrystalline cellulose, hypromellose, colloidal anhydrous silica, polysorbate 80, croscarmellose sodium, magnesium stearate, crospovidone, saccharin sodium, flavouring agent (cherry; contains ethyl benzoate), maltodextrin.
Total sodium content per tablet: 1.59 mg.
Riamet Baby
Microcrystalline cellulose, hypromellose, colloidal anhydrous silica, polysorbate 80, croscarmellose sodium, magnesium stearate, crospovidone, saccharin sodium, flavouring agent (cherry; contains ethyl benzoate), maltodextrin.
Total sodium content per tablet: 0.44 mg.

Pharmaceutical form and quantity of active substance per unit

Riamet Dispersible
Dispersible tablets containing 20 mg artemether and 120 mg lumefantrine.
Riamet Baby
Dispersible tablets containing 2.5 mg artemether and 30 mg lumefantrine.

Indications/Potential uses

Riamet Dispersible is indicated for the treatment of children and infants (body weight ≥5 kg) with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

Riamet Baby is indicated for the treatment of infants and neonates weighing between 2 kg and less than 5 kg with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

Riamet Dispersible may be used as standby emergency treatment for self-administration in cases of suspected malaria infection when no doctor can be reached within 24 hours or the medicinal product is not locally available.

As Riamet Dispersible and Riamet Baby are effective against both drug-sensitive and drug-resistant *P. falciparum*, they are also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.
Consideration should be given to official guidelines and local recommendations regarding the prevalence of resistance to antimalarials. Official guidelines are those issued by the WHO and by health authorities.

Dosage/Administration

Riamet Dispersible
Dispersible tablets for oral administration. The dispersible tablet(s) comprising one dose should be stirred in a small amount of water (approx. 10 ml per tablet) so that the active substance is better dispersed before the suspension is drunk. Stir gently and administer immediately to the patient. Pour in some more water (approx. 10 ml) and give immediately to the patient.
Although patients with acute malaria are often averse to food, high-fat foods or drinks such as milk should be taken following the dose. Consumption of 30-60 g of fat per day or breast milk is adequate for this purpose.
Patients should be encouraged to resume eating as soon as possible since this improves absorption of artemether and lumefantrine.
In the event of vomiting within one hour of administration, a repeat dose should be given.
Riamet dispersible tablets are indicated for infants and children weighing ≥5 kg only. Riamet Baby dispersible tablets are indicated for infants and neonates weighing between 2 kg and less than 5 kg and Riamet tablets are indicated for adolescents and adults.
Treatment should be administered at the time of initial diagnosis or at the onset of symptoms.

Dosage for treatment and standby emergency treatment

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

Dosage in infants and children weighing 5 to <35 kg up to 12 years of age:

5 to <15 kg body weight: 1 dispersible tablet at the time of diagnosis or as soon as symptoms appear, 1 dispersible tablet again after 8 h and then 1 dispersible tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 dispersible tablets).
15 to <25 kg body weight: 2 dispersible tablets as a single dose at the time of diagnosis or as soon as symptoms appear, 2 dispersible tablets again after 8 h and then 2 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).
25 to <35 kg body weight: 3 dispersible tablets as a single dose at the time of diagnosis or as soon as symptoms appear, 3 dispersible tablets again after 8 h and then 3 dispersible tablets twice daily (morning and evening) on each of the following two days (total course comprises 18 dispersible tablets).

In the event of vomiting within one hour of administration, a repeat dose should be given.

Riamet Baby

Dispersible tablets for oral administration. Two dispersible tablets comprising one dose should be completely dispersed in a small amount of water (approx. 3 ml) in a small drinking cup or an oral syringe. Stir gently and administer immediately to the patient using the same drinking cup or oral syringe. Pour some more water (approx. 3 ml) into the drinking cup or oral syringe and give immediately to the patient.

The dose of Riamet Baby should be followed immediately by breast milk or formula milk. Patients with acute malaria are frequently averse to food. If no food can be ingested, the dose should still be given and the parents or caregivers encouraged to return as quickly as possible to the normal feeding routine as soon as the child can tolerate food since this improves the absorption of artemether and lumefantrine.

In the event of vomiting within one hour of administration, a repeat dose should be given. Riamet treatment should be started at the time of initial diagnosis or at the onset of symptoms.

Dosage for treatment:

Riamet Baby is only intended for use in infants and neonates weighing between 2 kg to less than 5 kg. It has not been studied in infants and neonates weighing less than 2 kg; therefore, no dosing recommendations can be made (see “Properties/Action”). A standard 3-day treatment schedule of Riamet Baby comprises a total of 6 doses, given as follows: Two Riamet Baby dispersible tablets as a single dose at the time of initial diagnosis, 2 dispersible tablets again after 8 hours and then 2 dispersible tablets twice daily (at 12-hour intervals, e.g. morning and evening) on each of the following two days (total course comprises 12 dispersible tablets).

Riamet Baby should not be used in adults and children weighing 5 kg or more. Separate Riamet tablets and Riamet dispersible tablets are available for adults and children weighing more than 5 kg.

Dosage in special populations

Renal impairment

No specific studies have been carried out in this group of patients. However, no significant renal excretion of lumefantrine, artemether or their metabolites (e.g. dihydroartemisinin (DHA)) was determined in studies in humans. Therefore, no dose adjustment is recommended when using Riamet Dispersible and Riamet Baby in patients with renal impairment (for patients with severe renal impairment, see “Contraindications” and “Warnings and precautions”).

Hepatic impairment

No specific studies have been carried out in this group of patients. No specific dose adjustments can be recommended for patients with hepatic impairment (for patients with severe hepatic impairment, see "Contraindications" and "Warnings and precautions").
Most patients with acute malaria have some degree of hepatic impairment. In clinical studies, the adverse effect profile did not differ in patients with hepatic impairment and those without (see "Warnings and precautions").
Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with Riamet.

Contraindications

Riamet Dispersible and Riamet Baby

- Hypersensitivity to any of the active substances or excipients.
- Severe hepatic and renal impairment (see "Warnings and precautions").
- Patients with severe malaria according to the WHO definition.
- Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition that prolongs the QTc interval such as a history of symptomatic cardiac arrhythmia, clinically relevant bradycardia or severe cardiac disease.
- Patients taking medicinal products that prolong the QTc interval such as class IA and III antiarrhythmics, neuroleptics, antidepressants, certain antibiotics (including some agents of the following classes: macrolides, fluoroquinolones, imidazoles and triazoles), antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride.
- Patients with known disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.
- Patients taking medicinal products metabolised by cytochrome CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking medicinal products that are strong inducers of CYP3A4, such as rifampicin, carbamazepine, phenytoin and St. John's wort (*Hypericum perforatum*).

Warnings and precautions

Riamet Dispersible and Riamet Baby have not been evaluated for prophylaxis and are therefore not indicated for this use.
Riamet Dispersible and Riamet Baby have not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria, including pulmonary oedema or renal failure.
Severe malaria: In addition to the lack of clinical experience, the use of Riamet Dispersible or Riamet Baby in such cases is also inadvisable on pharmacokinetic grounds (the bioavailability of

artemether and, in particular, of lumefantrine is uncertain in cases of high parasitaemia and cases of insufficient or no food intake).
Riamet Dispersible and Riamet Baby have not been evaluated in, and are not indicated for, the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical studies had co-infection with *P. falciparum* and *P. vivax* at baseline. Riamet Dispersible and Riamet Baby are active against blood stages of *P. vivax*, but not against its hypnozoites (= dormant form/dormant stage in hepatocytes).
Riamet Dispersible should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see “Pregnancy/Breast-feeding”).
Like other antimalarials (e.g. halofantrine, quinine, quinidine), Riamet Dispersible and Riamet Baby may cause QTc interval prolongation (see “Clinical pharmacology” and QT/QTc prolongation).
There are no study data on the efficacy and safety of Riamet Dispersible and Riamet Baby in patients with severe hepatic or renal impairment; therefore, no recommendations can be made for these patient populations (see “Contraindications”).
Patients who remain averse to food during treatment should be closely monitored. The risk of recrudescence of disease may be increased.
If a patient’s condition deteriorates whilst taking Riamet Dispersible or Riamet Baby, alternative antimalarial treatment should be started without delay. In such cases, ECG monitoring is recommended and steps should be taken to correct any electrolyte disturbances.
Following treatment of mixed infections including *P. vivax*, follow-up treatment must be given to eradicate the exoerythrocytic forms of *P. vivax*.
There is no information on the effect of Riamet on human fertility. However, fertility was reduced in animals (see “Preclinical data”).

Caution in case of co-administration of medicines

With other antimalarials: As data on safety and efficacy are limited, Riamet Dispersible and Riamet Baby should not be co-administered with other antimalarials unless there is no other treatment option. The long elimination half-life of lumefantrine must be taken into account when administering quinine to patients previously treated with Riamet Dispersible or Riamet Baby. The ECG should be closely monitored both when treatment is given in this order and when Riamet Dispersible or Riamet Baby is administered following treatment with quinine due to a possible additive prolongation of the QTc interval that has been observed in healthy subjects.
Patients previously treated with other antimalarials: If Riamet Dispersible or Riamet Baby is administered following treatment with mefloquine, it is particularly important to ensure that the dose is taken together with food as lumefantrine levels may otherwise be insufficient.

In patients previously treated with halofantrine Riamet Dispersible or Riamet Baby should not be administered earlier than 1 month after the last halofantrine dose (see “Interactions with antimalarials” under “Interactions”).
With other medicinal products: Riamet Dispersible or Riamet Baby should not be used concomitantly with medicinal products metabolised by CYP2D6 (see “Contraindications”) and caution is required when combining Riamet Dispersible and Riamet Baby with substrates, inhibitors or inducers of CYP3A4, as the therapeutic effects of some medicinal products could be altered (see “Interactions” and “Pharmacokinetics”).

With hormonal contraceptives

Riamet Dispersible may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal or other systemic hormonal contraceptives should be advised to use an additional, non-hormonal method of contraception (see “Interactions” and “Pregnancy/Breast-feeding”).

In severe renal or hepatic impairment

In patients with severe hepatic impairment a clinically relevant increase in exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore, caution should be exercised when administering to patients with severe hepatic impairment (see “Clinical pharmacology”).

Excipients of particular interest
The flavouring agent contained in Riamet Dispersible and Riamet Baby contains ethyl benzoate. An increase in blood bilirubin content after displacement of albumin may potentiate neonatal jaundice and lead to kernicterus (non-conjugated bilirubin deposits in brain tissue).
Riamet Dispersible and Riamet Baby contain less than 1 mmol (23 mg) of sodium per tablet, making them practically “sodium-free”.

Interactions

Not all mechanisms of pharmacological and pharmacokinetic interactions are known.
Concomitant use of Riamet Dispersible or Riamet Baby is contraindicated with medicinal products that may cause prolongation of the QTc interval and torsade de pointes such as class IA and III antiarrhythmics, neuroleptics and antidepressants, certain antibiotics, including some agents of the macrolide, fluoroquinolone and imidazole classes, triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride (see “Contraindications”).
Artemether and lumefantrine are substrates of CYP3A4. Therefore, administration of inducers or inhibitors of CYP3A4 may lead to an increase or decrease in exposure to lumefantrine and artemether.

Further interactions with CYP450 isoenzymes

Lumefantrine was found to inhibit CYP2D6 *in vitro*. This may be of particular clinical relevance for substances with a narrow therapeutic index. Co-administration of Riamet Dispersible or Riamet Baby with medicinal products known to be metabolised by this isoenzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated (see “Contraindications”).

Induction of CYP450 enzymes

Whereas *in vitro* studies with artemether at therapeutic concentrations revealed no significant inhibition of CYP450 enzymes, artemether and dihydroartemisinin (DHA) were reported to have a mild inducing effect on CYP3A4 activity. Although the changes were generally minor and should pose no problems in the general patient population, it is possible that CYP3A4 induction could alter the therapeutic effects of medicinal products that are predominantly metabolised by this enzyme class.
Three specific pharmacokinetic and pharmacodynamic interaction studies with ketoconazole (a potent CYP3A4 inhibitor), mefloquine and quinine have been carried out in healthy volunteers.

Interactions with antimalarials

Patients who are to receive Riamet Dispersible or Riamet Baby may previously have been treated with other antimalarials. Therefore, interactions with mefloquine and quinine were investigated in a study in healthy volunteers.
If Riamet Dispersible or Riamet Baby 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 halofantrine, Riamet Dispersible or Riamet Baby should not be administered earlier than one month after the last halofantrine dose (see “Warnings and precautions”).
Sequential oral administration of mefloquine prior to Riamet Dispersible or Riamet Baby had no effect on plasma concentrations of artemether or the artemether/DHA ratio; however, there was a significant (around 30% to 40%) reduction in plasma levels (C_{max} and AUC) of lumefantrine due to lower absorption, possibly secondary to a mefloquine-induced decrease in bile production.
As a rule, combined administration of Riamet Dispersible or Riamet Baby and mefloquine should therefore be avoided.
In a drug interaction study in healthy subjects, administration of Riamet alone to 14 subjects had no effect on the QTc interval, while IV infusion of quinine alone in 14 other subjects caused a transient prolongation of the QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Riamet in 14 additional subjects. It would thus appear that the risk of QTc prolongation associated with IV administration of quinine is increased by prior administration of Riamet.

Concurrent IV administration of quinine (10 mg/kg BW) with Riamet had no effect on plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and DHA appeared to be lower.
In a clinical study (performed in Thailand), Riamet was given to some adult patients who had not responded to mefloquine or quinine. 121 patients received Riamet without any previous antimalarial treatment, whereas 34 and 9 patients, respectively, had measurable blood levels of quinine or mefloquine at the start of the study. These patients showed similar safety and pharmacokinetic profiles for Riamet to patients who had no detectable levels of other antimalarials.

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by CYP3A4 and do not inhibit this enzyme at therapeutic concentrations. In healthy adult subjects, oral co-administration of ketoconazole with Riamet led to a maximum 2.4-fold increase in exposure: AUC and C_{max} increased 2.39- and 2.24-fold, respectively, for artemether, 1.66- and 1.40-fold for DHA, and 1.65- and 1.26-fold for lumefantrine. This increase in exposure to the antimalarial combination was not associated with increased adverse effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Riamet Dispersible or Riamet Baby is considered unnecessary in *P. falciparum* malaria patients when co-administered with ketoconazole or other potent CYP3A4 inhibitors.
However, due to the potential increase in concentrations of lumefantrine, which could cause QT prolongation, Riamet Dispersible and Riamet Baby should be used with caution when co-administered with medicinal products that inhibit CYP3A4.

Interaction with strong CYP3A4 inducers such as rifampicin

Oral co-administration of rifampicin (600 mg daily), a strong CYP3A4 inducer, and Riamet tablets (6-dose regimen over 3 days) in 6 HIV-1 and tuberculosis co-infected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) compared to exposure values after administration of Riamet Dispersible alone. Concomitant use of strong CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin or St. John’s wort and Riamet Dispersible or Riamet Baby is contraindicated (see “Contraindications”).

Interaction with antiretrovirals

Both artemether and lumefantrine are metabolised by CYP3A4. Antiretrovirals such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors are known to have variable patterns of inhibition, induction or competition for CYP3A4. In a clinical study in healthy subjects, lopinavir/ritonavir decreased systemic exposure to artemether and DHA by approximately 40% but increased exposure to lumefantrine by approximately 2.3-fold, while efavirenz decreased exposure to artemether, DHA and lumefantrine by approximately 50%, 45% and 20%, respectively. Exposure to lopinavir/ritonavir and

efavirenz was not significantly affected by concomitant use of Riamet. Published clinical studies on interactions with nevirapine-based antiretroviral treatments suggest that concomitant use may result in up to 70% reduced artemether exposure and up to 37% reduced DHA exposure. A decrease or increase in lumefantrine exposure of up to approximately 50% was reported in these studies.
Riamet Dispersible or Riamet Baby should be used with caution in patients treated with antiretrovirals since decreased artemether, DHA and/or lumefantrine concentrations may result in decreased antimalarial efficacy of Riamet Dispersible or Riamet Baby and increased lumefantrine concentrations may cause QT prolongation.
See also “Warnings and precautions”.

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl oestradiol and levonorgestrel was not induced by artemether, DHA or lumefantrine. However, artemether has been reported to be a weak inducer of the activity of CYP2C19, CYP2B6 and CYP3A in humans. Therefore, Riamet Dispersible may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal or other systemic hormonal contraceptives should be advised to use an additional, non-hormonal method of contraception (see “Warnings and precautions” and “Pregnancy/Breast-feeding”).

Drug-food/drink interactions

Patients should be instructed to eat something with each dose of Riamet Dispersible as this decisively improves absorption of artemether and lumefantrine, thus compensating for the decrease in bioavailability.
The dose of Riamet Baby should be followed immediately by breast milk or formula milk to improve the absorption of artemether and lumefantrine.

Administration of artemether with double-concentrated grapefruit juice to healthy adult subjects resulted in an approximately two-fold increase in systemic exposure to the parent drug. Grapefruit juice should be avoided during Riamet treatment.

Pregnancy/Breast-feeding

Pregnancy

There have been no controlled clinical studies of the safe use of Riamet Dispersible during pregnancy. Data from animal studies suggest that Riamet Dispersible may cause severe birth defects when administered during the first trimester of pregnancy (see “Warnings and precautions” and “Preclinical data”).
Reproductive toxicity studies with artemether in animals have shown evidence of post-implantation losses and teratogenicity.

Other artemisinin derivatives have also demonstrated teratogenic potential, with an increased risk during early gestation (see “Preclinical data”).
A meta-analysis of observational studies with over 500 women who received Riamet in the first trimester of pregnancy analysed adverse pregnancy outcomes. The data showed that, compared to quinine, artemisinin treatment, including artemether/lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes cannot be excluded.
Safety data from observational studies and unblinded studies during the second or third trimester of pregnancy in over 1,200 women who received artemether/lumefantrine did not show any increase in adverse pregnancy outcomes or teratogenic effects compared to other antimalarials.
Riamet Dispersible should not be administered during the first trimester of pregnancy if other suitable and effective antimalarials are available. However, Riamet Dispersible should not be withheld in life-threatening situations where no other effective antimalarials are available (see “Warnings and precautions”).
During the second and third trimesters, the medicinal product should only be considered if the expected benefit to the mother (or pregnant woman) outweighs the risk to the fetus.

Women of childbearing potential

As Riamet Dispersible should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available, women should not become pregnant during antimalarial treatment with Riamet Dispersible. This includes women prescribed Riamet Dispersible for standby emergency treatment of malaria while travelling in case they may require treatment for malaria.
Women of childbearing potential should be instructed to use contraception while carrying Riamet Dispersible as standby emergency treatment during travel, while using Riamet Dispersible and until the start of the next menstruation after treatment with Riamet Dispersible. Women using hormonal contraceptives (oral, transdermal or other systemic contraceptives) should be advised to use an additional, non-hormonal method of contraception (see “Warnings and precautions”).

Breast-feeding

Animal data suggest that Riamet Dispersible passes into breast milk; however, human data are not available. Breast-feeding women should not take Riamet Dispersible. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume before day 28 unless the potential benefits to the mother and child outweigh the risks of Riamet Dispersible treatment.

Effects on ability to drive and to use machines

Patients receiving Riamet Dispersible should be made aware that dizziness or fatigue/asthenia may occur and that their ability to drive or use machines may therefore be impaired.

Adverse effects

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

Definition of frequencies: 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), including isolated reports.

List 1 summarises the results of a pooled safety analysis of 4 studies in infants and children of ≤12 years of age with a body weight of ≥5 kg to <35 kg administered 6 doses of Riamet or Riamet Dispersible.

List 1

Immune system disorders

Rare: Hypersensitivity reactions

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

Common: Prolonged electrocardiogram QT (including QTc prolongations >60 ms and/or absolute QTc values >500 ms)
Uncommon: Palpitations

Respiratory, thoracic and mediastinal disorders

Very common: Cough (23.5%)

Gastrointestinal disorders

Very common: Vomiting (17.5%)
Common: Abdominal pain, diarrhoea, nausea

Hepatobiliary disorders

Common: Increased liver function values

Skin and subcutaneous tissue disorders

Common: Rash
Uncommon: Pruritus, urticaria

Musculoskeletal and connective tissue disorders

Common: Arthralgia, myalgia

General disorders

Common: Asthenia, fatigue
In this pooled safety analysis, mood swings were reported in fewer than 1.2% of paediatric patients treated with Riamet, but they were not considered medicinal product-related by the investigators. Adverse effects found in non-recommended regimens not included in this pooled safety analysis are: paraesthesia (3% of adolescents and adults, no cases in children); non-specific personality disorders, which were reported in 1.1% of children under 5 years of age who were treated with Riamet in clinical studies. This frequency is 2 to 3 times lower than that observed in children of the same age who were treated with the reference antimalarials used in these studies (mefloquine/artesunate, quinine or sulfadoxine/pyrimethamine).
There were uncommon reports of the following adverse effects in adults, but not in infants or children: hypoaesthesia, ataxia, and gait disturbance.

Infants and neonates weighing <5 kg

The safety of Riamet Baby (artemether:lumefantrine (2.5 mg:30 mg)) was evaluated in an open-label study in 28 infants and neonates weighing between 2 kg to less than 5 kg with acute uncomplicated *P. falciparum* malaria. Limited data show that Riamet Baby dispersible tablets were well tolerated (see “Properties/Actions”). The safety profile in infants and neonates weighing between 2 kg and <5 kg was comparable to that in infants and children weighing 5 kg or more (List 1). The follow-up studies of the Shoklo Malaria Research Unit (SMRU) in children aged one year did not reveal any adverse impact on the neurodevelopmental status of infants and neonates weighing <5 kg.

Post-marketing adverse effects

The following additional adverse effects have been identified based on spontaneous post-marketing reports. Because these effects are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequencies.
Hypersensitivity reactions, including urticaria and angioedema.
Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

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

Properties/Actions

ATC code

P01BF01

Mechanism of action

Riamet Dispersible contains a fixed combination of artemether and lumefantrine in the ratio of 1:6, which acts as an antimalarial against schizonts. Riamet Baby contains a fixed combination of artemether and lumefantrine in the ratio of 1:12, which acts as an antimalarial against schizonts. Artemether is a semisynthetic chiral acetal derivative of artemisinin isolated from the plant *Artemisia annua*. Lumefantrine is a racemic mixture of a synthetic fluorene derivative. Like other antimalarials (quinine, mefloquine, halofantrine), lumefantrine belongs to the aryl-amino-alcohol family.

Pharmacodynamics

The site of antiparasitic action of both components is the food vacuole of the malaria parasite. Lumefantrine is thought to interfere with the polymerisation process that brings about the conversion of haemin, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic malaria pigment haemozoin. Artemether, on the other hand, may generate toxic, reactive metabolites as a result of the interaction between its endoperoxide bridge and haem iron. Both artemether and lumefantrine have a secondary inhibitory action on nucleic acid and protein synthesis.
Riamet Dispersible has been reported to exhibit activity in terms of clearing gametocytes.

Clinical efficacy

To date, data from *in vitro* and *in vivo* studies show that Riamet did not induce resistance.

Since 2015, there have been cases of resistance to artemisinins in South East Asia. Studies with Riamet in this region showed delayed parasite clearance (observed as a higher proportion of patients with parasitaemia on day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed.

Treatment of acute, uncomplicated malaria caused by P. falciparum

The efficacy of Riamet tablets was evaluated for the treatment of acute, uncomplicated malaria caused by *P. falciparum*. Uncomplicated malaria is defined as symptomatic *P. falciparum* malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction. Baseline parasite density was between 500/µl and 200,000/µl (0.01% to 0.4% parasitaemia) in the majority of patients. Studies were conducted in partially immune and non-immune adults and children (≥5 kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe and South America. Patients with clinical features of severe malaria or severe cardiac, renal or hepatic impairment were excluded.
Five 6-dose regimen studies were carried out and one study comparing the 6-dose regimen with a 4-dose regimen.
Riamet tablets were administered at 0, 8, 24, 36, 48 and 60 hours in the 6-dose regimen and at 0, 8, 24 and 48 hours in the 4-dose regimen. Efficacy endpoints consisted of:

- 28-day cure rate, defined as the proportion of patients with clearance of asexual parasites (the erythrocytic stage) within 7 days without recrudescence by day 28.
- Parasite clearance time (PCT), defined as the time from the first dose until the first total disappearance of asexual parasites which continues for a further 48 hours.
- Fever clearance time (FCT), defined as the time from the first dose until the first-time body temperature falls below 37.5°C and remains 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 a confirmed malaria diagnosis who received at least one dose of study drug. Evaluable patients generally are all patients who had a parasitological assessment on day 7 and day 28 or experienced treatment failure by day 28.

Table 1: Summary of clinical efficacy studies

Study no.	Study design	Number of patients		Population	Year/ study location
		Riamet/Riamet Baby	Comparison		
A025	Double-blind, randomised (1:1:1), parallel-group comparative study on the efficacy and safety of two 6-dose regimens vs a 4-dose regimen	6 doses over 60 hours: 118 6 doses over 96 hours: 121 4 doses over 48 hours: 120	-	Adults/children (≤12 years, n = 43)	1996-97 Thailand

Study no.	Study design	Number of patients		Population	Year/ study location
		Riamet/Riamet Baby	Comparison		
A026	Open-label, randomised (3:1), parallel-group confirmatory study on the efficacy and safety of the 6-dose regimen in comparison with mefloquine-artesunate (MAS)	150	Mefloquine-artesunate: 50	Adults/children (2-12 years, n = 34)	1997-98 Thailand
A028	Open-label, randomised (3:1), parallel-group confirmatory study on the efficacy and safety of the 6-dose regimen in comparison with mefloquine-artesunate (MAS)	164	Mefloquine-artesunate: 55	Adults	1998-99 Thailand
A2401	Open-label, randomised (3:1), non-comparative study on the efficacy and safety of the 6-dose regimen in non-immune patients	165	-	Adults	2001-05 Europe, Colombia
A2403	Open-label, non-comparative study on the efficacy and safety of the 6-dose regimen	310	-	Infants/children (5-25 kg)	2002-03 3 countries in Africa
B2303	Investigator-blinded, randomised (1:1), parallel-group study on the efficacy and safety of the 6-dose regimen	Riamet crushed tablet: 452 Riamet dispersible tablet: 447	-	Infants/children (5-35 kg)	2006-07 5 countries in Africa
B2307	Open-label, single-arm study to evaluate the PK, safety, tolerability and efficacy	Riamet Baby dispersible tablet (artemether: lumefantrine: 2.5 mg:30 mg): 28		Infants/ neonates (2-<5 kg)	2020-23 (2 countries in Africa)

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]
A025[4]	3-62 years	93/96 (96.9)	n[3] = 59 35 hours [20, 46]	n = 118 44 hours [22, 47]
A026	2-63 years	130/133 (97.7)	n[3] = 87 22 hours [19, 44]	N/A

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]
A028	12-71 years	148/154 (96.1)	n[3] = 76 29 hours [8, 51]	n = 164 29 hours [18, 40]
A2401	16-66 years	119/124 (96.0)	n[3] = 100 37 hours [18, 44]	n = 162 42 hours [34, 63]
A2403	2 months- 9 years	289/299 (96.7)	n[3] = 309 8 hours [8, 24]	n = 310 24 hours [24, 36]
B2303[CT]	3 months- 12 years	403/419 (96.2)	n[3] = 323 8 hours [8, 23]	n = 452 35 hours [24, 36]
B2303[DT]	3 months- 12 years	394/416 (94.7)	n[3] = 311 8 hours [8, 24]	n = 446 34 hours [24, 36]
B2307				
Age group >28 days	53-157 days	21/22 (95.5)	n = 4 15.7 hours (3.9, 29.7)	n = 22 35.0 hours (24, 36)
Age group <28 days	1-26 days	6/6 (100)	n = 1 7.6 hours (7.6, 7.6)	n = 6 30.6 hours (24, 48)
Pooled cohort	1 day- 157 days*	27/28 (96.4)	n = 5 7.6 hours (7.5-24.0)	n = 28 35.0 hours (24, 36)

[1] Efficacy (cure rate) based on blood smear microscopy. In certain studies, the efficacy of treatment was assessed by evaluating day 29 cure rate 28 days after treatment.

[2] mITT population (full analysis set population for B2307)

[3] For patients who had a body temperature of >37.5°C at baseline only

[4] Only the group data for the 6-dose regimen over 60 hours are presented. * Only patients weighing between 2 kg and less than 5 kg were enrolled in the study

[CT] Riamet tablets administered as crushed tablets

[DT] Riamet dispersible tablets

Table 3: Studies of clinical efficacy by body weight in paediatric patients

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)
Study B2303^{DT}		
5-<10 kg	36 hours [24, 43]	74/78 (94.9)
10-<15 kg	35 hours [24, 36]	156/168 (92.9)
15-<25 kg	25 hours [24, 36]	137/142 (96.5)
25-35 kg	26 hours [24, 36]	27/28 (96.4)
Study B2307		
2-<5 kg	35 hours [24, 36]	27/28 (96.4)

[1] mITT population. In certain studies, day 29 cure rate was evaluated 28 days after treatment

[2] Efficacy (cure rate) based on blood smear microscopy

^{CT} Riamet tablets administered as crushed tablets

^{DT} Riamet dispersible tablets

Study A025 was a randomised, double-blind, two-centre study conducted in Thailand in adults and children (aged ≥2 years), which compared the 4-dose regimen of Riamet tablets (administered over 48 hours) to a 6-dose regimen (administered over 60 hours). The PCR-corrected 28-day cure rate in

evaluable patients was 96.9% (93/96) in the Riamet tablets 6-dose arm compared to 83.3% (85/102) in the 4-dose arm.

Studies A026, A028, A2401, A2403 and B2303: In these studies, Riamet tablets were administered as the six-dose regimen.

In study A026, a total of 150 adults and children aged ≥2 years received Riamet tablets. In study A028, a total of 164 adults and children aged ≥12 years received Riamet tablets. Both studies were conducted in Thailand.

Study A2401 was a study of 165 non-immune adults residing in regions non-endemic for malaria (Europe and Colombia) who contracted acute, uncomplicated *P. falciparum* malaria when travelling in endemic regions.

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.

Study B2303 was conducted in Africa in 899 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. The primary objective was to demonstrate the non-inferiority of the dispersible tablets versus the tablet (administered crushed) in terms of the 28-day PCR-corrected parasitological cure rate. The results of the 28-day PCR-corrected cure rate, median parasite clearance time (PCT) and fever clearance time (FCT) are reported in Table 3.

Study B2307 (CALINA) was a multicentre, open-label, single-arm study conducted in sub-Saharan countries in regions where malaria is endemic. The study evaluated the pharmacokinetics, safety, tolerability and efficacy of the combination of artemether and lumefantrine (5 mg:60 mg), given as two dispersible tablets (each 2.5 mg:30 mg) for the treatment of infants and neonates weighing between 2 kg to less than 5 kg with acute, uncomplicated *P. falciparum* malaria.

Two Riamet Baby dispersible tablets were administered twice a day for 3 days with or after food. A total of 28 patients were treated with artemether:lumefantrine 5 mg:60 mg and were followed up for 43 days. A neurodevelopmental assessment by the Shoklo Malaria Research Unit (SMRU) was additionally conducted at the age of 12 months.

The observed maximum concentration (C_{max}) of artemether in infants and neonates (weighing between 2 kg to <5 kg) treated with a 5 mg/60 mg dose (i.e. 2 tablets of Riamet <5 kg Baby) was within the range of safe and efficacious concentrations observed in paediatric patients weighing 5 kg to less than 15 kg. This patient group received a dose of 20 mg/120 mg (see “Pharmacokinetics”). The key secondary endpoints of lumefantrine day-8 concentration (C168 h), associated with day-29 cure rate, and lumefantrine C_{max} were also within the pre-defined target ranges. In the full analysis set, PCR-corrected cure rate for the pooled cohort at days 29 and 43 were 96.4% (95% CI: 81.65, 99.91) and 92.9% (95% CI: 76.5, 99.12), respectively (Table 2). Mean parasite clearance time (PCT) for the pooled

cohort was 35 hours, which is comparable to clearance time in older children (≥5 kg and <15 kg) treated with artemether:lumefantrine 20 mg/120 mg. Limited data show that there was no difference in response based on age at enrolment (Table 2). Riamet Baby dispersible tablets were well tolerated and the safety profile was consistent with expectations for Riamet dispersible tablets (see “Adverse effects”).
Riamet Dispersible and Riamet Baby are active against blood stages of *P. vivax*, but not against hypnozoites.

QT/QTc prolongation

The administration of the 6-dose regimen of Riamet was associated with QTcF prolongation in a parallel study in healthy adults that included a placebo and moxifloxacin control group (n = 42 per group). The mean change from baseline at 68, 72, 96 and 108 h after the first dose was 7.45, 7.29, 6.12 and 6.84 ms, respectively. The change from baseline QTcF was zero at 156 and 168 h after the first dose. No subject had an increase from baseline >30 ms, nor an absolute value >500 ms. The moxifloxacin control was associated with QTcF prolongation compared to the placebo group over a period of 12 h after the single dose, with a maximal change at 1 h post-dose of 14.1 ms.
In clinical studies conducted in children with the 6-dose regimen, no patient had a post-baseline QTcF interval >500 ms; 29.4% exhibited a QTcF interval increase from baseline >30 ms and 5.1% >60 ms. In clinical studies conducted in adults and adolescents with the 6-dose regimen, QTcF prolongation of >500 ms was reported in 0.2% of patients; the QTcF interval increased from baseline to >30 ms in 33.9% of patients and to >60 ms in 6.2% of patients.

Pharmacokinetics

The pharmacokinetic characterisation of Riamet Dispersible or Riamet Baby is limited by the lack of an intravenous dosage form and the very high inter- and intrasubject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC and/or C_{max}).

Absorption

Artemether is absorbed fairly rapidly, with peak plasma concentrations attained approx. 2 h after administration. Absorption of lumefantrine, a highly lipophilic component, starts after a lag time of up to 2 h; peak plasma concentration is not reached until around 6-8 hours after administration. Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers given a meal containing fat, the relative bioavailability of artemether increased more than 2-fold, and that of lumefantrine 16-fold, compared with fasted conditions. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately 2-fold). This is most probably due to the lower fat content of the food of acutely ill patients. Food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (probably less than

10% of the dose). Patients should therefore be strongly encouraged to take the medication with a normal meal as soon as food can be tolerated.
In healthy (adult) volunteers, the dispersible and crushed tablets led to similar systemic exposures to artemether, its metabolite dihydroartemisinin (DHA) and lumefantrine (see Table 4).

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

	Dispersible tablet	Crushed tablet
Artemether		
	(n = 54)	(n = 50)
C_{max} (ng/ml)	73.3 ± 39.5	67.4 ± 35.5
t_{max} (h)	2.02 [0.50-4.02]	2.05 [0.52-4.07]
AUC_{last} (ng·h/ml)	263 ± 142	229 ± 136
DHA		
	(n = 54)	(n = 50)
C_{max} (ng/ml)	48.6 ± 23.2	48.8 ± 26.0
t_{max} (h)	2.98 [0.75-5.98]	2.54 [0.75-4.07]
AUC_{last} (ng·h/ml)	171 ± 59.5	160 ± 68.0
Lumefantrine		
	(n = 55)	(n = 52)
C_{max} (µg/ml)	10.2 ± 3.08	10.0 ± 2.57
t_{max} (h)	8.00 [4.98-24.02]	8.00 [4.98-24.02]
AUC_{last} (µg·h/ml)	295 ± 107	280 ± 93.2
Mean ± standard deviation is shown for C_{max} and AUC_{last} and median and [min-max] ranges are shown for t_{max}.		

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins *in vitro* (95.4% and 99.7%, respectively).
DHA is also bound to human serum protein (47% to 76%). Protein binding to human plasma protein is linear.

Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). *In vitro* data show that human liver microsomes metabolise artemether to the biologically active main metabolite DHA (demethylation) predominantly through CYP3A4/5.
The pharmacokinetics of this metabolite have also been described in humans *in vivo*.
The artemether/DHA AUC ratio is 1.2 after a single dose and 0.3 after the last of 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity that should not pose a problem in the general patient population. Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT2B7.
During repeated administration of Riamet, plasma artemether concentrations decreased significantly, while concentrations of the active metabolite (DHA) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for artemether metabolism. The clinical evidence of induction is consistent with the *in vitro* data in the “Interactions” section.
In vitro, lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, systemic exposure to the metabolite desbutyl-lumefantrine, whose *in vitro* antiparasitic effect is 5 to 8-fold higher than that of lumefantrine, was less than 1% of exposure to the parent compound.
In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see “Warnings and precautions”, “Interactions” and “Contraindications”).

Elimination

Artemether and DHA are rapidly cleared from plasma with an elimination half-life of about 2 h. Lumefantrine is eliminated very slowly with a terminal 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 Riamet.
In healthy volunteers, neither lumefantrine nor artemether were detected in the urine after administration of Riamet and urinary excretion of DHA amounted to less than 0.01% of the dose of artemether.
In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism. Lumefantrine was excreted unchanged in the faeces and only in trace amounts in the urine. Metabolites of both medicinal product components were eliminated in the bile/faeces and urine.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase in systemic exposure to lumefantrine after doubling the Riamet dose. No conclusive data are available for artemether.

Bioavailability/bioequivalence studies

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

Pharmacokinetics in special populations

No specific pharmacokinetic studies have been performed in patients with hepatic and renal impairment.

Hepatic impairment

Metabolism is the primary clearance mechanism of both artemether and lumefantrine and may be impaired 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 when administering to patients with severe hepatic impairment (see “Warnings and precautions”).

Renal impairment

Based on pharmacokinetic data in healthy subjects indicating no or insignificant renal excretion of lumefantrine, artemether and DHA, no dose adjustment is recommended for the use of Riamet Dispersible or Riamet Baby in patients with renal impairment.

Children (weighing ≥5 to <35 kg)

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

Infants and neonates weighing between 2 kg and <5 kg

Study B2306, a multicentre, open-label, single-arm study, was conducted with 20 infants in Africa. This study showed that exposure to artemether and DHA in infants with uncomplicated *P. falciparum* malaria weighing <5 kg and older than 28 days of age who received 1 dispersible tablet twice daily (20 mg artemether/120 mg lumefantrine) for 3 days was on average 2- to 3-fold higher than that in paediatric patients with a body weight ≥5 kg treated with the same dose of Riamet (i.e. 1 dispersible tablet of 20 mg/120 mg per dose). These exposures are higher than exposures associated with neurotoxicity in dogs. The relevance of these exposures in humans is not known (see “Preclinical data”). Lumefantrine exposure was similar to that in paediatric patients weighing ≥5 kg.

The results of Study B2307 showed that systemic exposure to artemether and lumefantrine in infants and neonates (weighing between 2 kg to less than 5 kg) with acute uncomplicated *P. falciparum* malaria treated with a 5 mg/60 mg dose (i.e. 2 tablets of Riamet Baby) twice daily for 3 days was within the range of safe and effective concentrations. These concentrations were also observed in paediatric patients

(weighing ≥5 kg and <15 kg) treated with a dose of 20 mg/120 mg (Table 5) (see “Properties/Actions”).

Table 5: Geometric mean (90% CI) values for infants and neonates weighing <5 kg receiving artemether/lumefantrine 5 mg/60 mg twice daily for 3 days in Study B2307.

Statistics	Age group >28 days **N = 22**	Age group <28 days **N = 6**	**Target concentration***
Artemether			
n	20	5	90% CI should contain C_{max} of 101 ng/ml
C_{max} (ng/ml)	68.0 (45.1, 103)	62.2 (33.6, 115)	
Lumefantrine			
n	22	6	
Concentration at day 8 (168h) (ng/ml)	353 (250, 498)	480 (265, 870)	Upper limit of 90% CI should not be less than 212 ng/ml
C_{max} (ng/ml)	3,180 (2,530; 4,000)	3,510 (1,880; 6,540)	90% CI should contain 3,900 ng/ml

* Target concentrations derived from Study B2303, conducted in paediatric patients weighing ≥5 and <15 kg who received Riamet dispersible tablets (20 mg/120 mg) in accordance with the prescribing information.

Ethnicity

The pharmacokinetics of artemether, DHA and lumefantrine in the Japanese population was found to be consistent with other populations.

Preclinical data

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. The lesions observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats that received 25 mg/kg artemether for 7 or 14 days and dogs that received 20 mg/kg for 8 days or longer. However, lesions were not observed after shorter courses of the medicinal product or after oral dosing. The estimated artemether 24-hour AUC after 7 days of dosing at the no observed effect level (10 mg/kg/day given intramuscularly) is approximately 7-fold greater than the estimated artemether 24-hour AUC in humans on day 1 of the standard 3-day oral treatment regimen; oral exposure in humans decreases on subsequent days, thus the exposure margin increases. Dogs that received 143 mg/kg artemether orally showed a statistically measurable effect on the hearing threshold at 20 dB. Exposures (AUC0-24h) to artemether and dihydroartemether, an active metabolite of similar structure, were 1,294 and 2,253 ng/ml, respectively, on day 1, corresponding in total to twice the adult exposures (AUC0-24h = 1,070 and 422 ng.h/ml). Exposures to these substances in dogs decreased to 52 and 363 ng/ml, respectively, on day 3, while exposures in humans –though they also fell– were higher on day 3 than in dogs (640 and 1,208 ng.h/ml for artemether and dihydroartemether, respectively). Exposures in animals were similar to (day 1) or lower than (day 3) clinical exposures.

Mutagenicity

There have been no reports of mutagenicity in *in vitro* and *in vivo* tests using a (1:6) combination of artemether and lumefantrine. In the micronucleus test, myelotoxicity was seen at all dosages (500, 1,000 and 2,000 mg/kg), but recovery was reported to be almost complete 48 hours after dosing.

Carcinogenicity

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

Reproductive toxicity

Reproductive toxicity studies in rats given oral doses of the artemether/lumefantrine combination showed maternal toxicity and increased post-implantation loss at doses ≥50 mg/kg (corresponding to approx. 7 mg/kg artemether). The artemether/lumefantrine combination was not embryotoxic in rats at a dosage of 25 mg/kg (corresponding to approx. 3.6 mg/kg artemether). Following oral administration of the artemether/lumefantrine combination to rabbits, maternal toxicity and increased post-implantation loss were seen at a dosage of 175 mg/kg (corresponding to 25 mg/kg artemether), while treatment-

induced effects were absent at the next lowest dosage of 105 mg/kg (corresponding to 15 mg/kg artemether).
Artemisinins are known to be embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives demonstrated increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at a dosage of 6 mg/kg artesunate and 19.4 mg/kg artemether. In rats, 3 mg/kg artemether was established as the non-toxic dose.
In rabbits, artemether produced maternal toxicity and an increase in post-implantation loss at a dosage of 30 mg/kg, but no maternal toxicity, embryotoxicity or fetotoxicity at doses up to 25 mg/kg. The artemisinin derivative artesunate produced a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose used.
The embryotoxic artemether dose, 20 mg/kg/day in rats, yields artemether and dihydroartemisinin exposures similar to those in humans.

Fertility

Reduced fertility occurred with the artemether/lumefantrine combination at doses of 1,000 mg/kg/day, where altered sperm motility, reduced epididymal sperm count, increased testes weight and embryotoxicity and other reproductive effects (decreased number of implantations and viable embryos, increased pre-implantation loss) were also observed. General toxicity was observed in males and females at doses ≥300 mg/kg/day. The no-adverse-effect level for fertility was 300 mg/kg/day. The relevance of this finding for humans is unknown.

Toxicity studies in juvenile animals

A specific study to investigate the neurotoxicity of artemether in juvenile rats involved oral administration of artemether during four different dosing intervals at doses of 30 or 80 mg/kg/day on post-partum days 7 to 13 and at doses of 30 or 120 mg/kg/day on post-partum days 14 to 21, 22 to 28, or 29 to 36. Mortality, clinical signs and reductions in body weight parameters occurred most notably during the first two dosing intervals. Despite the systemic toxicity noted, no effects of artemether were observed on any of the functional tests performed and there was no evidence of a direct neurotoxic effect of orally administered artemether on the brain of juvenile rats.
Studies in juvenile rats indicate that very young animals (aged 7-21 days) are more sensitive to artemether than adult animals. There is no difference in sensitivity in slightly older (3-5 weeks of age) animals following 13 weeks of artemether/lumefantrine administration.

Cardiovascular pharmacology

In toxicity studies in dogs, evidence of QTc prolongation was only observed from doses providing exposures slightly higher than during therapeutic use in humans (≥600 mg/kg/day artemether) (safety margin of 1.3-2.2-fold for artemether when C_{max} was calculated independently).

In an *in vitro* assay of HERG channels stably expressed from an HEK293 cell line, lumefantrine and its main metabolite desbutyl-lumefantrine showed some inhibitory potential on one of the ion channels responsible for cardiac repolarisation. However, this was lower than that of the other antimalarials tested. From the estimated IC_{50} values, the order of potency of HERG channel blockade was: halofantrine (IC_{50} = 0.04 micromolar) > chloroquine (2.5 micromolar) > mefloquine (2.6 micromolar) > desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar). Additional studies were performed to evaluate the effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at C_{max} or greater than 1,000 if they are estimated using the calculated free C_{max}. Based on the available non-clinical data, the potential for QTc prolongation in humans cannot be discounted.

Other information

Shelf life

Riamet Dispersible and Riamet Baby
Do not use after the date (= EXP) printed on the pack.

Special precautions for storage

Riamet Dispersible and Riamet Baby
Keep out of the reach of children.
Do not store above 30°C.
Store in the original pack and protect from heat and moisture.

Use and handling in children and infants

Riamet Dispersible
The pack containing 12 dispersible tablets may be prescribed for the treatment of children and infants weighing 5 kg or more. The physician or pharmacist should explain to parents or caregivers how to use the product in the child to be treated and should inform them that a variable number of tablets (depending on body weight) will be required for the full treatment. Depending on the required number of tablets, it may not be necessary to use the whole pack. After successful treatment, any extra tablets should be properly disposed of or returned to a pharmacy.
Riamet Baby
The pack of 12 dispersible tablets is prescribed for the treatment of infants and neonates weighing between 2 kg to less than 5 kg. The doctor or pharmacist should instruct the parents or caregivers how to administer the medicinal product to the child to be treated and inform them that all tablets must be taken for the full treatment course.

Authorisation number

58528, 67664 (Swissmedic).

Pack sizes

Riamet Dispersible

Packs containing 12 dispersible tablets [A]

Riamet Baby

Packs containing 12 dispersible tablets [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

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