Riamet® Dispersible und Riamet® Baby

Novartis Pharma Schweiz AG

Zusammensetzung

Wirkstoffe

Artemetherum, Lumefantrinum.

Auxiliary supplies

Riamet Dispersible

Cellulosum microcristallinum, Hypromellosum, Silica colloidalis anhydrica, Polysorbatum 80, Carmellosum natricum conexum, Magnesii stearas, Crospovidonum, Saccharinum natricum, Aromatica (Kirsche, enthält Ethylis benzoas), Maltodextrinum.

Total sodium content per tablet: 1.59 mg.

Riamet Baby

Cellulosum microcristallinum, Hypromellosum, Silica colloidalis anhydrica, Polysorbatum 80, Carmellosum natricum conexum, Magnesii stearas, Crospovidonum, Saccharinum natricum, Aromatica (Kirsche; enthält Ethylis benzoas), Maltodextrinum.

Total sodium content per tablet: 0.44mg.

Dosage form and amount of active ingredient per unit

Riamet Dispersible

Tablets for the preparation of an oral suspension containing 20 mg of artemetherum and 120 mg of lumefantrinum.

Riamet Baby

Tablets for oral suspension containing 2.5 mg of artemetherum and 30 mg of lumefantrinum.

Indications/Possible applications

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

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

Riamet Dispersible can be used as a stand-by-emergency treatment for self-treatment in the event that no doctor can be reached within 24 hours in the event of a suspected malaria infection or the medicine is not available on the spot.

Because Riamet Dispersible and Riamet Baby are effective against sensitive and resistant *P. falciparum*, they are also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.

Official guidelines as well as local recommendations of the prevalence of resistance to antimalarials should be taken into account. Official guidelines are those of the WHO and the health authorities.

Dosage/Application

Riamet Dispersible

Dispersible tablets for oral administration. Stir the dispersible tablet(s) that make up a dose in a little water (about 10 ml per tablet) to better distribute the active ingredient before drinking the suspension. Stir lightly and administer to the patient immediately. Add a little more water (approx. 10 ml) to the glass and administer it to the patient immediately.

Although patients with acute malaria often show an aversion to food, high-fat foods or beverages such as milk should be taken after the dose. An intake of 30-60 g of fat per day or breast milk is adequate for this.

Patients should be encouraged to resume eating as soon as possible, as this improves the absorption of artemether and lumefantrine.

If vomiting occurs within one hour of taking the medication, the dose should be taken again. Riamet Dispersible tablets are indicated only for infants and children weighing ≥5 kg. For infants and newborns with a body weight between 2 kg and less than 5 kg, Riamet Baby, dispersible tablets are indicated, and for adolescents and adults, Riamet tablets are indicated.

Therapy should be administered at the time of initial diagnosis or at the onset of symptoms.

Dosage for treatment and for emergency treatment

Basically, a 3-day treatment cycle with a total of 6 doses is recommended as follows:

Dosage for infants and children from 5 to <35 kg body weight up to the age of 12 years:

5-<15 kg body weight: 1 dispersible tablet at the time of diagnosis or immediately upon the onset of symptoms, 1 dispersible tablet again after 8 hours and then 1 dispersible tablet twice a day (morning and evening) on each of the two following days (the entire cycle includes 6 dispersible tablets).

15-<25 kg body weight: 2 dispersible tablets as one dose at the time of diagnosis or immediately when symptoms appear, after 8 hours another 2 dispersible tablets and then 2 dispersible tablets twice a day (morning and evening) on each of the two following days (the entire cycle includes 12 dispersible tablets).

25-<35 kg body weight: 3 dispersible tablets as one dose at the time of diagnosis or immediately when symptoms appear, after 8 hours another 3 dispersible tablets and then 3 dispersible tablets twice a day (morning and evening) on each of the two following days (the entire cycle includes 18 dispersible tablets).

If vomiting occurs within one hour of taking the medication, the dose should be taken again.

Riamet Baby

Dispersible tablets for oral administration. Two dispersible tablets yielding one dose should be completely dispersed in a small amount of water (approximately 3 ml) in a small drinking cup or application syringe. Stir gently and immediately give to the patient with the same drinking cup or application syringe. Again add some water (approx. 3 ml) to the drinking cup or application syringe and give it to the patient immediately.

Following the administration of Riamet Baby, the child should be breastfed or given formula immediately. Patients with acute malaria often show an aversion to food. If food cannot be ingested, the dose should still be given and parents or caregivers should be encouraged to return to normal feeding

routine as soon as possible as soon as the child can tolerate food, as this improves the absorption of artemether and lumefantrine.

If vomiting occurs within one hour of taking the medication, the dose should be taken again. Treatment with Riamet should begin immediately upon diagnosis or when symptoms appear.

Dosage for treatment:

Riamet Baby is intended for use only in infants and newborns weighing between 2 kg and less than 5 kg. In infants and newborns weighing less than 2 kg, Riamet Baby has not been studied, so no dosage recommendations can be made (see "Properties/Effects"). A standard treatment of Riamet Baby over 3 days includes a total of 6 doses, which should be given as follows: two Riamet Baby dispersible tablets as a single dose at the time of diagnosis, 2 dispersible tablets after 8 hours, and then 2 dispersible tablets twice a day (12 hours apart, e.g. morning and evening) on each of the following two days (the treatment includes a total of 12 dispersible tablets).

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

Dosing of special patient groups

Impaired kidney function

Special studies in this collective were not carried out. However, no significant renal excretion of lumefantrine, artemether or their metabolites (e.g. dihydroartemisinin (DHA)) has been detected in human studies; 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")

Impaired liver function

Special studies in this collective were not carried out. No specific dose adjustments can be recommended in patients with hepatic impairment (for patients with severe hepatic insufficiency, see "Contraindications", "Warnings and precautions").

Most patients with acute malaria have some functional impairment of the liver. The side effect profile in the clinical trials did not differ between patients with hepatic impairment and those without (see "Warnings and precautions").
In addition, deviations from baseline values in liver function tests improved in almost all patients after treatment with Riamet.

Contraindications

Riamet Dispersible and Riamet Baby

- Hypersensitivity to any of the active ingredients or any of the excipients.
- Severe hepatic and renal insufficiency ("Warnings and precautions").
- Patients with severe malaria, based on the WHO definition.
- Patients with a family history of congenital prolongation of the QTc interval or sudden death, or with another clinical cause that prolongs the QTc interval, such as patients with symptomatic cardiac arrhythmia, clinically relevant bradycardia, or a history of severe heart disease.
- Patients taking medications that prolong the QTc interval, such as class IA and III antiarrhythmic drugs, neuroleptics, antidepressants, certain antibiotics including some drugs in the following classes: macrolides, fluoroquinolones, imidazoles and triazole, antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), cisapride.
- Patients with known electrolyte balance disorders such as hypokalemia or hypomagnesemia.
- Patients taking medications metabolized by cytochrome CYP2D6 (e.g., flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking medications such as rifampicin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum) that strongly induce CYP3A4.

Warnings and precautions

Riamet Dispersible and Riamet Baby have not been studied for prophylaxis and are therefore not indicated for this purpose.

Riamet Dispersible and Riamet Baby have not been evaluated for the treatment of cerebral malaria or other severe manifestations of severe malaria, including pulmonary edema or renal failure.

Severe malaria: In addition to the lack of clinical experience, pharmacokinetics also militate against the use of Riamet Dispersible or Riamet Baby (the bioavailability of Artemether and especially lumefantrine is uncertain in high parasitemia and in the case 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 caused by *P. vivax*, *P. malariae* or *P. ovale*, although some patients in clinical trials have a mixed infection with *P. falciparum* and *P. vivax* as a basic infection. Riamet Dispersible and Riamet Baby are active against blood forms of *P. vivax*, but not against its hypnozoites (= resting form/stage in the hepatocytes).

Riamet Dispersible should not be used in the 1st trimester of pregnancy in situations where other appropriate and effective medicines for malaria are available (see "Pregnancy/breastfeeding")

Like other antimalarials (e.g. halofantrine, quinine, quinidine), Riamet Dispersible and Riamet Baby can prolong the QTc interval (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 insufficiency, and therefore no recommendations can be made for these patient groups (see "Contraindications").

Patients who retain an aversion to food under therapy should be closely monitored. The risk of recurrence of the disease may be increased.

If a patient's condition worsens while taking Riamet Dispersible or Riamet Baby, alternative malaria treatment should be started immediately. In such cases, ECG monitoring is recommended and steps should be taken to correct any electrolyte imbalances.

After treatment of mixed infections containing *P. vivax*, follow-up treatment must be given to eradicate the exoerythrocytic forms of *P. vivax*.

There is no information regarding the effect of Riamet on human fertility: In animals, on the other hand, reduced fertility occurred (see "Preclinical data").

Caution with concomitant drug therapy

With other antimalarials: Because safety and efficacy data are limited, Riamet Dispersible and Riamet Baby should not be given concomitantly with other antimalarials unless there are other treatment options. The long elimination half-life of lumefantrine must be taken into account when quinine is administered to patients who had previously been treated with Riamet Dispersible or Riamet Baby. Both in this sequence and in the case of treatment with Riamet Dispersible or Riamet Baby following quinine therapy, close monitoring of the ECG should be carried out due to possible additive extensions of the QTc interval, which have also been proven in healthy volunteers.

Patients who have previously been treated with other antimalarial drugs: If Riamet Dispersible or Riamet Baby are administered after mefloquine, taking the dose with concomitant food intake is particularly important and should be safeguarded, otherwise insufficient lumefantrine levels are possible.

In patients who have previously been treated with halofantrine, Riamet Dispersible or Riamet Baby should not be administered until 1 month after the last dose of halofantrine at the earliest (see "Interactions/interactions with antimalarial preparations").

With other medicines: Riamet Dispersible or Riamet Baby should not be used with medicines metabolised by CYP2D6 (see "Contraindications"). Caution should be exercised when using Riamet Dispersible Dispersible and Riamet Baby in combination with substrates, inhibitors or inducers of CYP3A4, as the therapeutic effect of some medicinal products may be altered (see "Interactions" and "Pharmacokinetics").

With hormonal contraceptives

Riamet Dispersible may reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal or other systemic hormonal contraceptives should therefore be advised to use a non-hormonal method of contraception in addition (see "Interactions" and "Pregnancy/breastfeeding").

In case of severe renal or hepatic insufficiency

In patients with severe impairment of hepatic function, 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 impairment of liver function (see "Clinical pharmacology").

Excipients of particular interest

The flavouring contained in Riamet Dispersible and Riamet Baby contains ethyl benzoate. An increase in bilirubin levels in the blood after displacement of albumin can intensify neonatal jaundice and lead to kernicterus (non-conjugated bilirubin deposits in brain tissue).

Riamet Dispersible and Riamet Baby contain less than 1 mmol of sodium (23 mg) per tablet, which means they are almost "sodium-free".

Interactions

Not all mechanisms of pharmacological or pharmacokinetic interactions are known so far.

Riamet Dispersible or Riamet Baby are contraindicated with the concomitant use of drugs that may cause prolongation of the QTc interval and torsade de pointes, such as class IA and III antiarrhythmic drugs, neuroleptics and antidepressants, certain antibiotics including some active substances in the macrolides classes, fluoroquinolones, imidazoles and triazole antifungals, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride (see . "Contraindications").

Artemether and lumefantrine are substrates of CYP3A4. Therefore, the administration of inducers or inhibitors of CYP3A4 may lead to an increase or decrease in lumefantrine and artemether exposure.

Further interaction with CYP450 isoenzymes

In vitro, inhibition of CYP2D6 by lumefantrine has been demonstrated. This could be of particular clinical relevance for substances with a narrow therapeutic index. Concomitant administration of Riamet Dispersible or Riamet Baby with drugs known to be metabolized by this isoenzyme (such as neuroleptics and tricyclic antidepressants) is contraindicated (see "Contraindications").

Induction of CYP450 enzymes

While in vitro studies with Artemether showed no significant inhibition of CYP450 enzymes at therapeutic concentrations, a slight inducing effect on CYP3A4 activity was reported for Artemether and dihydroartemisinin (DHA). Although the changes were generally minor and should not be a problem in the general patient population, it is possible that induction of CYP3A4 could alter the therapeutic effect of drugs that are predominantly metabolized by this class of enzymes.

Three specific pharmacokinetic and pharmacodynamic interaction studies were conducted in healthy volunteers with ketoconazole (potent CYP3A4 inhibitor), mefloquine and quinine.

Interactions with antimalarial drugs

Patients who are to receive Riamet Dispersible or Riamet Baby may have previously been treated with other antimalarial drugs. Therefore, interactions with mefloquine and quinine were investigated in a study with healthy volunteers.

If Riamet Dispersible or Riamet Baby is administered after administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or ECG (for quinine) is recommended. Due to the long elimination half-life of lumefantrine, this must be taken into account when administering quinine. In patients previously treated with halofantrine, Riamet Dispersible or Riamet Baby should not be administered until one month has elapsed after the last dose of halofantrine (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 on the artemether/DHA ratio, but there was a significant (approximately 30 to 40%) reduction in plasma levels of lumefantrine (C_{max} and AUC) due to lower absorption, possibly as a result of a mefloquine-induced decrease in bile production.

A combined administration of Riamet Dispersible or Riamet Baby and mefloquine should therefore be avoided as a rule.

In a drug interaction study in healthy volunteers, administration of Riamet alone to 14 subjects had no effect on the QTc interval, while IV infusion of quinine alone resulted in a transient prolongation of the QTc interval in 14 other subjects, consistent with the cardiotoxicity known for quinine. In another 14 subjects, this effect was slight but significantly stronger when quinine was infused after Riamet. Thus, the risk of QTc prolongation associated with IV administration of quinine appears to be increased by previously administered Riamet.

Concomitant IV administration of quinine (10 mg/kg/bw) with Riamet had no effect on the plasma concentration of lumefantrine or quinine. The plasma concentration of artemether and DHA seems to be lower.

In a clinical trial (conducted in Thailand), some adult patients who had not responded to mefloquine or quinine were given Riamet. 121 patients received Riamet without prior malaria treatment, and 34 and 9 patients respectively had quinine and mefloquine blood levels measurable at baseline. These patients showed similar safety and pharmacokinetic profiles for Riamet to those without measurable levels of other antimalarial drugs.

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are predominantly metabolized via CYP3A4 and do not inhibit this enzyme at therapeutic concentrations. Concomitant oral administration of ketoconazole with Riamet results in a maximum 2.4-fold increase in exposure in healthy adult subjects: artemether (+2.39-fold increase for AUC and 2.24-fold increase for C_{max}), DHA (+1.66-fold increase and 1.40-fold increase, respectively), and lumefantrine (+1.65-fold increase and 1.26-fold increase, respectively). This increase in exposure to the antimalarial combination was not accompanied by more frequent adverse effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Riamet Dispersible or Riamet Baby in *P. falciparum* malaria patients is considered unnecessary when concomitant administration of ketoconazole or other potent CYP3A4 inhibitors.

However, due to the possible increase in the concentration of lumefantrine, which may cause QT prolongation, Riamet Dispersible and Riamet Baby should be used with caution when concomitantly administering drugs that inhibit CYP3A4.

Interaction with strong inducers of CYP3A4 such as rifampicin

Concomitant oral administration of rifampicin (600 mg daily), a potent inducer of CYP3A4, and Riamet Tablets (6-dose treatment plan in three days) in six HIV-1 and tuberculosis co-infected adults without malaria resulted in large reductions in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) compared to exposure levels following administration of Riamet Dispersible alone. The concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin or St. John's wort and Riamet Dispersible or Riamet Baby are contraindicated (see "Contraindications").

Interaction with antiretroviral drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Antiretroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors are known to exhibit variable patterns of inhibition, induction of, or competition for CYP3A4. In a clinical trial in healthy volunteers, lopinavir/ritonavir decreased systemic exposure to artemether and DHA by about 40%, but increased exposure to lumefantrine to about 2.3-fold, while efavirenz decreased exposure to artemether by about 50%, to DHA by about 45%, and to lumefantrine by about 20%. Exposure to lopinavir/ritonavir and to efavirenz was not significantly affected by concomitant administration of Riamet. Published clinical studies on interaction with anti-retroviral treatments based on nevirapine indicate that concomitant use can lead to up to 70% reduced artemether exposure and up to 37% reduced DHA exposure. In these studies, a reduction or increase in lumefantrine exposure of up to around 50% has been reported.

Riamet Dispersible or Riamet Baby should be used with caution in patients treated with antiretroviral drugs, as decreased concentrations of artemether, DHA, and/or lumefantrine result in decreased anti-malarial efficacy of Riamet Dispersible or Riamet Baby, and increased lumefantrine concentrations may cause QT prolongation.

See also the section "Warnings and precautions".

Interaction with hormonal contraceptives

The metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA or lumefantrine in vitro. However, artemether has been reported to be a weak inducer of the activity of CYP2C19, CYP2B6 and CYP3A in humans. For this reason, Riamet Dispersible may reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal or other systemic hormonal contraceptives should be advised to use a non-hormonal method of contraception in addition (see "Warnings and precautions" and "Pregnancy/breastfeeding").

Interactions with food/beverages

Patients should be particularly instructed to eat at the same time as taking Riamet Dispersible, as this significantly improves the absorption of artemether and lumefantrine, thereby compensating for the decrease in bioavailability.

Following the administration of Riamet Baby, the child should be breastfed immediately or given formula to improve the absorption of artemether and lumefantrine.

Administration of Artemether together with double-concentrated grapefruit juice to healthy adult subjects resulted in an increase in systemic exposure to the parent substance to approximately twofold. Grapefruit juice should be avoided during treatment with Riamet.

Pregnancy, breastfeeding

Pregnancy

There are no controlled clinical studies on 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 1st trimester of pregnancy (see "Warnings and precautions" and "Preclinical data").

Animal studies of reproductive toxicity with Artemether have shown evidence of post-implantation loss and teratogenicity.

Other artemisinin derivatives have also shown teratogenic potential with increasing risk during the early phase of pregnancy (see "Preclinical data").

In a meta-analysis of observational studies with over 500 women who received Riamet during the first trimester of pregnancy, unfavorable pregnancy outcomes were analyzed. The data showed that compared to quinine, arteminisin treatment, including artemether/lumefantrine, is not associated with an increased risk of miscarriage, stillbirth or congenital malformations. However, due to the limitations of these studies, the risk of unfavorable pregnancy outcomes cannot be ruled out.

Safety data from observational studies and open-label studies during the second or third trimester of pregnancy in over 1,200 women receiving artemether/lumefantrine showed no increase in adverse pregnancy outcomes or teratogenic effects compared to other antimalarial drugs.

Riamet Dispersible should not be administered during the 1st trimester of pregnancy if other appropriate and effective medicines for malaria are available. However, in life-threatening situations where no other effective antimalarial medicine is available, Riamet Dispersible should not be withheld (see "Warnings and precautions").

During the 2nd and 3rd trimesters, the preparation should only be considered if the expected benefit to the mother (or pregnant woman) outweighs the risk to the foetus.

Women of childbearing age

Since Riamet Dispersible should not be taken during the 1st trimester of pregnancy in situations where other appropriate and effective antimalarial medicines are available, women should not become pregnant during malaria treatment with Riamet Dispersible. This includes women who have been prescribed Riamet Dispersible during their trip as an immediate emergency treatment for malaria in case they need treatment for malaria.

Women of childbearing potential should be instructed to use contraceptive measures during a trip on which Riamet is taken as emergency treatment, as well as during the use of Riamet Dispersible and until the onset of the next menstrual period following treatment with Riamet Dispersible. Women using hormonal contraceptives (oral, transdermal or other systemic) should be instructed to use a non-hormonal method of contraception in addition (see "Warnings and precautions").

Nursing period

Data in animals indicate that Riamet Dispersible passes into human milk, human data are not available. Breastfeeding women should not take Riamet Dispersible. Because of the long elimination half-life of lumefantrine (4 to 6 days), it is recommended not to resume breastfeeding until day 28 unless the potential benefits to mother and child exceed the risks of treatment with Riamet Dispersible.

Effect on driving ability and on the operation of machines

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

Undesirable effects

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

Frequency definition: 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.

List 1 summarizes the results of a pooled safety analysis of 4 studies in infants and children aged ≤12 years and ≥5 kg to <35 kg body weight, who were given 6 doses of Riamet or Riamet Dispersible.

List 1

Diseases of the immune system

Rare: hypersensitivity reactions.

Metabolic and nutritional disorders

Very common: anorexia, decreased appetite.

Psychiatric disorders

Uncommon: sleep disorders.

Diseases of the nervous system

Common: headaches, dizziness.

Uncommon: drowsiness, clonus.

Heart disease

Common: Electrocardiogram QT prolonged (incl. QTc extensions >60 msec and/or QTc absolute value >500 msec).

Uncommon: palpitations.

Diseases of the respiratory, thoracic cavity and mediastinum

Very common: cough (23.5%).

Diseases of the gastrointestinal tract

Very common: vomiting (17.5%).

Common: abdominal pain, diarrhea, nausea.

Liver and Biliary Disorders

Common: Liver function values increased.

Diseases of the skin and subcutaneous tissue

Often: rash.

Uncommon: pruritus, urticaria.

Skeletal muscle, connective tissue and bone diseases

Common: joint pain, muscle pain.

General illnesses

Common: weakness, fatigue.

In this pooled safety analysis, less than 1.2% of pediatric patients treated with Riamet reported mood changes, but the study physicians did not believe they were drug-related.

Adverse effects identified in non-recommended treatment regimens that are not included in this pooled safety analysis: paresthesia (3% of adolescents and adults, no cases in children); Non-specific personality disorders reported in 1.1% of children under 5 years of age treated with Riamet in clinical trials. This frequency is 2 to 3 times lower than in children of the same age who were treated with the reference antimalarials used in these studies (mefloquine/artesunate, quinine or sulfadoxine/pyrimethamine).

The following adverse effects have been reported occasionally in adults but not in infants or children: hypoesthesia, ataxia, gait disturbances.

Infants and newborns weighing <5 kg

The safety of Riamet Baby (Artemether: lumefantrine (2.5 mg: 30 mg)) was evaluated in an open-label study of 28 infants and neonates weighing between 2 kg and less than 5 kg and acute uncomplicated malaria caused by *P. falciparum*. Limited data show that the Riamet Baby dispersible tablets were well tolerated (see "Properties/effects"). The safety profile for infants and newborns weighing between 2 kg and less than 5 kg was comparable to that of infants and children weighing 5 kg or more (List 1). Further studies by the Shoklo Malaria Research Unit (SMRU) in children as young as one year of age found no negative effects on the neurodevelopmental status of infants and newborns weighing <5 kg.

Post-market adverse effects

The following additional adverse effects were identified on the basis of spontaneous reports in the post-marketing phase. Since these effects are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency.

Hypersensitivity reactions including urticaria and angioedema.

Reporting suspected side effects after approval is of great importance. It enables continuous monitoring of the benefit-risk ratio of the drug. Healthcare professionals are encouraged to report any suspicion of a new or serious adverse reaction via the EIViS (Electronic Vigilance System) online portal. You can find information about this under www.swissmedic.ch.

Overdosing

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

Properties/Effects

ATC-Code

P01BF01

Action

Riamet Dispersible contains a fixed combination of Artemether and Lumefantrine in a ratio of 1:6, which acts as an antimalarial against schizonts. Riamet Baby contains a fixed combination of Artemether and Lumefantrine in a 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 antimalarial drugs (quinine, mefloquine, halofantrine), lumefantrine belongs to the arylamino alcohol family.

Pharmacodynamics

The site of the antiparasitic effect of both components is the food vacuum of the malaria parasite. Lumefantrine is thought to interfere with the polymerization process there, which causes the conversion of haemin, a toxic intermediate product of haemoglobin degradation, into the non-toxic malaria pigment haemozine. Artemether, on the other hand, can generate toxic, reactive metabolites as a result of the interaction of its endoperoxide bridge and Haem iron. Both artemether and lumefantrine have a secondary inhibitory effect on nucleic acid and protein synthesis. Riamet Dispersible has been reported to exhibit activity in relation to the elimination of gametocytes.

Klinische Wirksamkeit

Daten aus *in vitro*- und *in vivo*-Studien zeigen bisher, dass Riamet keine Resistenz induzierte.

Seit 2015 gibt es in Südostasien Fälle einer Resistenz gegen Artemisinine. Studien mit Riamet in dieser Region zeigten eine verzögerte Parasiten-Clearance (erkennbar an einem höheren Anteil an Patienten mit Parasitämie an Tag 3 nach Behandlungsbeginn), wenngleich die Gesamtwirksamkeit bei Messung der Heilungsraten nach 28 Tagen immer noch hoch war (WHO 2014). Aus Afrika liegen lediglich vereinzelte Meldungen über eine verzögerte Parasiten-Clearance vor, und es war keine eindeutige Tendenz in Richtung einer Resistenzentwicklung erkennbar.

Behandlung der akuten, unkomplizierten, durch P. falciparum hervorgerufenen Malaria

The efficacy of Riamet tablets has been assessed in the treatment of acute, uncomplicated malaria caused by *P. falciparum*. Uncomplicated malaria is defined as symptomatic *P. falciparum-related* malaria with no signs and symptoms of severe malaria or evidence of dysfunction of vital organs. In the majority of patients, the parasite density at baseline was between 500/µl and 200,000/µl (parasitemia of 0.01% to 0.4%). The 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 impairment of heart, kidney or liver function were excluded.

Five studies were conducted using the six-dose regimen and one study comparing the six-dose regimen with a four-dose regimen

Riamet tablets were administered at 0, 8, 24, 36, 48 and 60 hours in the six-dose regimen and at 0, 8, 24 and 48 hours in the four-dose regimen. The efficacy endpoints included:

- 28-day cure rate, defined as the proportion of patients with clearance of the asexual parasites (erythrocytic stage) within 7 days without recurrence until day 28.
- Parasite clearance time (PCT), defined as the time from the first dose to the first complete disappearance of the asexual parasites, which lasts for the following 48 hours.
- Fever clearance time (FCT), defined as the time from the first dose to the first drop in body temperature below 37.5 °C, which lasts for at least 48 hours (only in patients with a baseline temperature of >37.5 °C).

The modified intent-to-treat (mITT) population includes all patients with a confirmed diagnosis of malaria who received at least one dose of the study drug. Patients who can be evaluated are basically all patients in whom a parasitological examination was carried out on days 7 and 28 or in whom there was a therapy failure on day 28.

Table 1: Summary of clinical efficacy studies

Studynumber	Study design	Number of patients		Population	Year/ Place of Study
		Riamet/Riamet Baby	Comparison		
A025	Double-blind, randomized (1:1:1), comparative parallel-group study on the efficacy and safety of two 6-dose regimens vs. 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
A026	Open-label, randomized (3:1), confirmatory parallel-group study on the efficacy and safety of the 6-dose regimen compared to mefloquine artesunate (MAS)	150	Mefloquin-Artesunat: 50	Adults/Children (2-12 years,n = 34)	1997-98 Thailand
A028	Open-label, randomized (3:1), confirmatory parallel-group study on the efficacy and safety of the 6-dose regimen compared to mefloquine artesunate (MAS)	164	Mefloquin-Artesunat: 55	Erwachsene	1998-99 Thailand

A2401	Open-label, randomized (3:1), non-comparative study of 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, randomized (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 PK, safety, tolerability and efficacy	Riamet Baby Dispersible Tablet (Artemether: Lumefantrine: 2.5 mg:30 mg): 28		Babies/ Newborn (2-<5 kg)	2020-23 (2 countries in Africa)

Table 2: Clinical efficacy results

Studynumber	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate[1] n/N (%) in evaluable patients	Medianwert FCT[2] [25., 75. Perzentil]	Median PCT[2] [25., 75. Perzentil]
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]	ON
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 d	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	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 based on cure rate, based on microscopic examination of blood smears In certain studies, the effectiveness of treatment was assessed by evaluating the 29-day cure rate 28 days after treatment.

[2] mITT population (mITT: Modified-Intent-to-Treat) (total group in B2307)

[3] For patients who had a body temperature of >37.5 °C at baseline only.4 Group data will be presented only for the 6-dose regimen over 60 hours.

*Only patients weighing between 2 kg and less than 5 kg were enrolled in the study

[CT] Crushed Riamet tablets

[DT] Riamet Dispersible Tablets

Table 3: Clinical efficacy studies depending on the body weight of pediatric patients

Study number Weight category	Median PCT[1] [25., 75. Perzentil]	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 (mITT: Modified-Intent-to-Treat) In certain studies, the 29-day cure rate was assessed 28 days after treatment

[2] Efficacy based on cure rate, based on microscopic examination of blood smears

[CT] Crushed Riamet tablets

[DT] Riamet Dispersible Tablet

Study A025 was a randomized, double-blind, two-center study in Thailand in adults and children (≥2 years of age) that compared the four-dose regimen of Riamet tablets (administered over a 48-hour period) with a six-dose regimen (administered over a 60-hour period). The PCR-corrected 28-day cure rate of evaluable patients was 96.9% (93/96) in the six-dose treatment arm with Riamet tablets compared to 83.3% (85/102) in the four-dose regimen treatment arm.

Studies A026, A028, A2401, A2403 and B2303: In these studies, Riamet tablets were administered according to 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 living in regions where malaria is not endemic (Europe and Colombia) who had contracted acute, uncomplicated *P. falciparum-related* malaria while traveling to endemic regions.

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years with a body weight of 5 to 25 kg and an axillary body temperature ≥37.5 °C.

Study B2303 was conducted in Africa in 899 infants and children aged 3 months to 12 years weighing 5 to <35 kg with fever (≥37.5 °C axillary or ≥38 °C rectal) or fever in the previous 24 hours. The primary objective was to demonstrate the non-inferiority of the tablets for oral suspension compared to the (crushed) tablets with regard to the PCR-corrected parasitological 28-day cure rate.The results of the PCR-corrected 28-day cure rate, the median parasite clearance time (PCT) and the fever clearance time (FCT) are presented in Table 3.

Study B2307 (CALINA) was a multicenter, 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 in the form of two dispersible tablets (2.5 mg: 30 mg each) in the treatment of infants and newborns weighing between 2 kg and less than 5 kg and acute, uncomplicated malaria caused by *P. falciparum*.

Two Riamet Baby Dispersible Tablets were administered twice a day with or after food for 3 days. A total of 28 patients were treated with Artemether: Lumefantrine 5 mg: 60 mg and followed up for 43 days. At the age of 12 months, a neurological developmental assessment was also carried out by the Shoklo Malaria Research Unit (SMRU).

Die beobachtete maximale Konzentration (C_{max}) von Artemether bei Säuglingen und Neugeborenen (mit einem Körpergewicht zwischen 2 kg und unter5 kg), die mit einer Dosis von 5 mg/60 mg (d.h. 2 Tabletten Riamet <5 kg Baby) behandelt wurden, lag innerhalb des Bereichs der bei pädiatrischen Patienten mit einem Gewicht von 5 kg bis unter 15 kg als sicher und wirksam angesehen wird. Diese Patientengruppe erhielt eine Dosis von 20 mg/120 mg (siehe «Pharmakokinetik»). Die wichtigsten sekundären Endpunkte der Tag-8-Konzentration (C168 h) von Lumefantrin, verbunden mit der 29-Tage-Heilungsrate, und die C_{max} von Lumefantrin lagen ebenfalls innerhalb der vordefinierten Zielbereiche. In der Gesamtgruppe betrug die PCR-korrigierte Heilungsrate für die gepoolte Kohorte an Tag 29 und Tag 43 96,4 % (95%-KI: 81,65, 99,91) bzw. 92,9 % (95%-KI: 76,5, 99,12) (Tabelle 2). Die mittlere Parasiten-Clearance-Zeit (PCT) für die gepoolte Kohorte betrug 35 Stunden, was vergleichbar mit der Clearance-Zeit bei älteren Kindern ist (≥5 kg und <15 kg), die mit Artemether: Lumefantrin 20 mg/120 mg behandelt wurden. E Begrenzte Daten zeigen, dass es gab keine Unterschiede in der Ansprechrate basierend auf dem Alter bei der Aufnahme in die Studie (Tabelle 2). Riamet Baby dispergierbare Tabletten wurden gut vertragen und das Sicherheitsprofil entsprach den Erwartungen von Riamet dispergierbaren Tabletten (siehe «Nebenwirkungen»).

Riamet Dispersible und Riamet Baby sind aktiv gegen Blutformen von *P. vivax*, jedoch nicht gegen Hypnozoiten.

QT/QTc-Verlängerung

In einer parallelen Studie an gesunden Erwachsenen mit je einer Placebo- und Moxifloxacinkontrollgruppe (n=42 pro Gruppe) wurde die Verabreichung von Riamet im 6-Dosis-Schema mit einer QTcF-Verlängerung in Zusammenhang gebracht. Die durchschnittliche Abweichung vom Ausgangswert betrug 68, 72, 96 und 108 h nach der ersten Dosis je 7.45, 7.29, 6.12 und 6.84 msec. 156 und 168 h nach der ersten Dosis war die Abweichung vom Ausgangswert für QTcF gleich null. Bei keinem Probanden betrug die Abweichung nach oben im Vergleich zum Ausgangswert >30 msec und bei keinem Probanden betrug der absolute Wert >500 msec. Die Moxifloxacinkontrolle wurde im Vergleich mit der Placebogruppe über einen Zeitraum von 12 h nach der Einzeldosis mit einer QTcF-Verlängerung in Verbindung gebracht, wobei die maximale Veränderung 1 h nach der Dosis 14.1 msec betrug.

In clinical trials in children on the 6-dose regimen, the QTcF interval >500 msec post-baseline was not reported in any of the patients, with an increase in the QTcF interval from baseline >30 msec in 29.4% of patients and >60 msec in 5.1%. In clinical trials in adults and adolescents on the 6-dose regimen, a QTcF prolongation of >500 msec was reported in 0.2% of patients, with the QTcF interval increasing from baseline >30 msec in 33.9% of patients and to >60 msec in 6.2% of patients.

Pharmacokinetics

The pharmacokinetic characterization of Riamet Dispersible or Riamet Baby is limited by the absence of an intravenous form of administration and the very high inter- and intra-individual variability of artemether and lumefantrine plasma concentrations and the pharmacokinetic parameters derived therefrom (AUC and/or C_{max}).

Absorption

Artemether is absorbed quite quickly, with the maximum plasma concentration being reached about 2 h after administration. The absorption of lumefantrine, a highly lipophilic component, begins after a latency period of up to 2 h, the plasma peak concentration is not reached until about 6-8 h after administration. Food increases the absorption of both artemether and lumefantrine. In healthy volunteers, the relative bioavailability of artemether was increased by more than 2 times and of lumefantrine by 16 times after a fatty meal compared to food abstinence. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, albeit to a lesser extent (about 2-fold). This can best be explained by a lower fat concentration in the food of acutely ill patients. Data on interactions with food suggest that the absorption of lumefantrine during fasting is very low, probably less than 10% of the dose. Patients should therefore be urged to take the medication with a normal meal as soon as food can be tolerated.

In healthy volunteers (adults), the dispersible and crushed tablets resulted in similar systemic exposures of artemether, its metabolite dihydroartemisinin (DHA) and lumefantrine (see Table 4).

Table 4: Pharmacokinetic parameters after 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
Lumefantrin		
	(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
Dargestellt sind Mittelwerte ± Standardabweichung für C_{max} und AUC_{last}, Medianwerte und Bereiche [min-max] für t_{max}		

Distribution

Artemether und Lumefantrin werden in vitro zu einem hohen Prozentsatz an humane Serumproteine gebunden (95.4% resp. 99. 7%).

DHA ist ebenso an menschliches Serumprotein (47% bis 76%) gebunden. Die Proteinbindung zu menschlichem Plasmaprotein ist linear.

Metabolismus

Artemether wird schnell und umfassend metabolisiert (substantieller First-pass-Metabolismus). In vitro-Daten zeigen, dass menschliche Lebermikrosomen Artemether vor allem unter Beteiligung des CYP3A4/5 zum biologisch aktiven Hauptmetaboliten DHA (Demethylisierung) metabolisieren.

Die Pharmakokinetik dieses Metabolits wurde ebenfalls in Menschen *in vivo* beschrieben.

Das AUC-Verhältnis von Artemether/DHA ist 1.2 nach einer Einzeldosierung und 0.3 nach der letzten der 6 verabreichten Dosen über 3 Tage hinweg. Für Artemether und DHA wurde eine leichte induzierende Wirkung auf die CYP3A4-Aktivität gemeldet, die in der allgemeinen Patientenpopulation kein Problem darstellen dürfte. Die Glucuronidierung von Dihydroartemisinin wird hauptsächlich von UGT1A9 und UGT2B7 katalysiert.

Bei wiederholter Verabreichung von Riamet verringerten sich die Plasmakonzentrationen von Artemether erheblich, während sich die Konzentrationen des aktiven Metabolits (DHA) erhöhten, wenngleich dieser Anstieg statistisch unerheblich war. Dies bestätigt, dass eine Induktion des Enzyms vorlag, welches für den Artemethermetabolismus verantwortlich ist. Die klinische Evidenz einer Induktion deckt sich mit den *in vitro*-Daten in Rubrik «Interaktionen».

Lumefantrine is N-debutylated in human liver microsomes, primarily by CYP3A4. *In vivo*, glucuronidation of lumefantrine takes place directly and after oxidative biotransformation in animals (dogs and rats). In humans, systemic exposure to the metabolite desbutyl-lumefantrine, whose antiparasitic activity *in vitro* is 5 to 8 times higher than that of lumefantrine, was less than 1% of exposure to the parent substance.

In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see also "Warnings and precautions", "Interactions" and "Contraindications").

Elimination

Artemether and DHA are rapidly removed from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2 to 6 days. Demographic characteristics such as sex and weight do not appear to have a clinically relevant influence on the pharmacokinetics of Riamet.

In healthy subjects, neither lumefantrine nor artemether was detected in the urine following administration of Riamet, and urinary excretion of DHA was 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 high first-pass metabolism. Lumefantrine was excreted unchanged via the faeces and only in trace amounts via the urine. Metabolites of both drug components were eliminated via bile/faeces and urine.

Dose proportionality

No specific dose-proportionality studies have been conducted. Limited data suggest a dose-proportional increase in systemic exposure to lumefantrine after doubling the dose of Riamet. No meaningful data is available for Artemether.

Bioavailability/Bioequivalence Studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was comparable to healthy adults following administration of Riamet in the form of tablets for oral suspension and in the form of crushed tablets.

Systemic exposure to lumefantrine was comparable to healthy adults following administration of Riamet in the form of tablets for oral suspension and in the form of intact tablets. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) after administration of the tablet for oral suspension than after administration of the intact tablets. These observations are not considered to be clinically relevant for the use of the oral suspension tablets in children and adolescents, as sufficient efficacy of Riamet in the form of oral suspension tablets has been shown in this population. The tablet for oral suspension is not recommended for use in adults.

Kinetics of special patient groups

No special kinetic studies have been conducted in patients with hepatic and renal insufficiency.

Liver dysfunction

Metabolism is the main mechanism of elimination of both artemether and lumefantrine and may be impaired in patients with impaired hepatic function. 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 impairment of liver function (see "Warnings and precautions").

Nierenfunktionsstörungen

Basierend auf den pharmakokinetischen Daten bei gesunden Probanden, die auf keine oder nur eine unbedeutende renale Ausscheidung von Lumefantrin, Artemether und DHA hinweisen, wird bei der Anwendung von Riamet Dispersible oder Riamet Baby bei Patienten mit Nierenfunktionsstörungen keine Dosisanpassung empfohlen.

Kinder (Körpergewicht ≥5 bis <35 kg)

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

Infants and newborns weighing between 2 kg and less than 5 kg

Study B2306, a multicenter, open-label, single-arm study, was conducted with 20 infants/young children in Africa. This study showed that artemether and DHA exposure was on average 2 to 3 times higher in infants/young children weighing <5 kg and over 28 days of age with uncomplicated *P. falciparum* malaria who received 1 dispersible tablet (20 mg Arthemether/120 mg lumefantrine) twice daily for 3 days compared to paediatric patients weighing ≥5 kg; who have been treated with the same dose of Riamet (i.e. 1 dispersible tablet of 20 mg/120 mg per dose). These exposures are higher than the 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 of pediatric patients with a body weight ≥5 kg.

The results of Study B2307 showed that treatment of infants and neonates (weighing between 2 kg and less than 5 kg) with acute uncomplicated *P. falciparum* malaria with a dose of 5 mg/60 mg artemether/ lumefantrine (i.e., 2 tablets of Riamet Baby) twice daily for 3 days results in systemic exposure within the concentration ranges considered safe and effective. These concentration ranges have already been observed in paediatric patients (body weight ≥5 kg and <15 kg) treated with a dose of 20 mg/120 mg (Table 5) (see "Properties/Effects").

Table 5: Geometric mean (90% CI) for infants and neonates < 5 kg body weight who received 5 mg/60 mg Artemether/lumefantrine twice daily for 3 days as part of 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)	
Lumefantrin			
n	22	6	Upper limit of the 90% CI should not be less than 212 ng/mL
Concentration on day 8 (168h) (ng/mL)	353 (250, 498)	480 (265, 870)	
C_{max} (ng/mL)	3180 (2530, 4000)	3510 (1880, 6540)	90%-KIs sollten 3900 ng/mL enthalten
*Die Zielkonzentrationen stammen aus der Riamet-Studie B2303, die mit pädiatrischen Patienten mit einem Körpergewicht von ≥5 und <15 kg durchgeführt wurde, die Riamet dispergierbare Tabletten (20 mg/120 mg) gemäss den Angaben in der Gebrauchs- und Fachinforamtion erhielten.			

Ethnische Zugehörigkeit

Die Pharmakokinetik von Artemether, DHA und Lumefantrin in der japanischen Bevölkerung erwies sich als mit der in anderen Populationen korrelierend.

Präklinische Daten

Neurotoxizität

Studies in dogs and rats have shown that intramuscular injections of Artemether resulted in brain lesions. Lesions observed mainly in the brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis, and dark neurons. Lesions have been observed in rats receiving 25 mg/kg Artemether for 7 or 14 days, as well as in dogs receiving 20 mg/kg for 8 days or longer. However, no lesions were observed after shorter administration of the drug and after oral administration. The estimated 24-hour AUC of Artemether after seven days of dosing at the no-observed-effect level (10 mg/kg/day administered intramuscularly) is approximately seven times the estimated 24-hour AUC of Artemether in humans on day 1 of the standard three-day oral regimen; oral exposure decreases in humans over the following days, increasing the margin of exposure. Dogs receiving 143 mg/kg p.o. Artemether showed a statistically measurable effect on the hearing threshold at 20 dB.

The exposures (AUC0-24h) of artemether and dihydroartemether, an active metabolite of the same structure, were 1294 and 2253 ng/mL at day 1, respectively, which is twice the exposure in adults (AUC0-24h = 1070 and 422 ng.h/mL, respectively). Exposures to the respective substances decreased in dogs to 52 and 363 ng/mL on day 3; while exposures in humans also decreased, they were higher on day 3 than in dogs (640 and 1208 ng.h/mL for artemether and dihydroartemether, respectively). Exposures in animals were comparable to clinical exposures (day 1) or lower (day 3).

Mutagenicity

No mutagenicity was observed in an artemether/lumefantrine (1:6) combination in vitro and in vivo assays. In the micronucleus test, myelotoxicity was observed at all doses of 500, 1000 and 2000 mg/kg, but near-complete recovery was observed 48 hours after dosing.

Carcinogenicity

Because of the short treatment time, no carcinogenicity studies have been performed with the Artemether/Lumefantrine combination.

Reproductive toxicity

Reproductive toxicity studies with oral administration of the Artemether/Lumefantrine combination in rats showed a maternotoxic effect and increasing post-implantation loss at doses ≥50 mg/kg (equivalent to approximately 7 mg/kg Artemether). The Artemether/Lumefantrine combination was not embryotoxic in rats at the dosage of 25 mg/kg (equivalent to approx. 3.6 mg/kg Artemether). Following oral administration of the Artemether/Lumefantrine combination to rabbits, maternotoxicity and increased post-implantation loss were observed at a dose of 175 mg/kg (equivalent to 25 mg/kg Artemether), while the next lower dose of 105 mg/kg (equivalent to 15 mg/kg Artemether) was free of treatment-related effects.

It is known that artemisinins are embryotoxic in animals. Reproductive toxicity studies with artemisinin derivatives showed increased post-implantation loss and teratogenicity (a low incidence of cardiovascular and skeletal malformations) in rats at doses of 6 mg/kg artesunate and 19.4 mg/kg artemedher. In rats, 3 mg/kg artemether was determined as a non-toxic dose.

In rabbits, artemether caused maternotoxicity and increased post-implantation losses at a dose of 30 mg/kg, but no materno/embryo/foeto toxicity at doses up to 25 mg/kg. The artemisinin derivative artesunate caused a low incidence of cardiovascular and skeletal malformations in rabbits at 5 mg/kg, the lowest dose applied.

Die embryotoxische Artemetherdosis, 20 mg/kg/Tag bei der Ratte, bewirkt eine ähnliche Artemether- und Dihydroartemisinin-Exposition wie bei Menschen.

Fertilität

Bei Dosen von 1000 mg/kg/Tag der Artemether/Lumenfantrin-Kombination trat eine reduzierte Fertilität auf, wobei ausserdem eine veränderte Spermienmotilität, eine verminderte epididymale Spermienzahl, erhöhtes Hodengewicht sowie Embryotoxizität und andere reproduktive Effekte (verminderte Anzahl von Implantationen und entwicklungsfähigen Embryonen, gesteigerte Präimplantationsverluste) beobachtet wurden. Allgemeine Toxizität wurde bei männlichen und weiblichen Tieren bei Dosen ≥300 mg/kg/Tag beobachtet. Der No-Adverse-Effect-Level bezüglich Fertilität betrug 300 mg/kg/Tag. Die Bedeutung dieser Beobachtung für den Menschen ist nicht bekannt.

Toxizitätsstudien bei juvenilen Tieren

Eine spezifische Studie zur Untersuchung der Neurotoxizität von Artemether bei juvenilen Ratten beinhaltete die orale Verabreichung von Artemether während vier verschiedener Dosierungsintervalle in Dosen von 30 oder 80 mg/kg/Tag an den Tagen 7 bis 13 post partum sowie in Dosen von 30 oder 120 mg/kg/Tag an den Tagen 14 bis 21, 22 bis 28 oder 29 bis 36 post partum. Mortalität, klinische Zeichen und Verminderungen der Parameter des Körpergewichts waren während der ersten beiden Dosierungsintervalle am prägnantesten. Trotz der beobachteten systemischen Toxizität wurden keine Wirkungen von Artemether auf die durchgeführten Funktionstests beobachtet und es gab keine Hinweise auf eine direkte neurotoxische Wirkung von oral verabreichtem Artemether auf das Gehirn juveniler Ratten.

Studien bei juvenilen Ratten deuten darauf hin, dass sehr junge Tiere (im Alter von 7-21 Tagen) empfindlicher gegenüber Artemether sind als erwachsene Tiere. Bei geringfügig älteren Tieren (Alter 3-5 Wochen) besteht kein Unterschied der Empfindlichkeit nach 13-wöchiger Verabreichung von Artemether/Lumefantrin.

Kardiovaskuläre Pharmakologie

In Toxizitätsstudien an Hunden wurden erst ab Dosen, bei denen die Expositionen nicht viel höher liegen als bei der therapeutischen Anwendung beim Menschen (≥600 mg/kg/d Artemether), einige Hinweise auf QTc-Verlängerung beobachtet (Sicherheitsabstand von 1.3-2.2 mal für Artemether wenn C_{max} unabhängig berechnet wurde).

In an *in vitro* study of HERG channels sustainably expressed from a HEK293 cell line, lumefantrine and its major metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the ion channels responsible for cardiac repolarization. However, this was lower than that of the other malaria drugs examined. The estimated IC_{50} values result in the following order with regard to the potency for blocking HERG channels: halofantrine (IC50=0.04 micromolar) > chloroquine (2.5 micromolar) > mefloquine (2.6 micromolar) > desbutyl-lumefantrine (5.5 micromolar) > lumefantrine (8.1 micromolar). Additional studies were conducted to assess the effects of Artemether and its active metabolite dihydroartemisinin on the HERG stream. At concentrations that caused significant inhibition, the safety margins of artemether and dihydroartemisinin are greater than 100 when estimated by the total therapeutic concentration at C_{max} and estimated by the calculated free C_{max} over 1000. On the basis of the available non-clinical data, the potential for QTc prolongation in humans should not be ignored.

Other notes

Durability

Riamet Dispersible and Riamet Baby

The medicine may only be used up to the date marked "EXP" on the package.

Special storage instructions

Riamet Dispersible and Riamet Baby

Keep out of reach of children.

Do not store above 30 °C.

Store in its original packaging, protected from heat and moisture.

Handling of children and toddlers

Riamet Dispersible

For the treatment of children and infants weighing 5kg or more, the pack of 12 dispersible tablets can be prescribed. The doctor or pharmacist should inform the parents or caregiver about the application to the child to be treated and inform them that a different number of tablets (due to body weight) is needed for a complete treatment. Depending on the required amount of tablets, the whole package is not needed. After successful treatment, the surplus tablets should be disposed of properly or returned to a pharmacy.

Riamet Baby

The pack of 12 dispersible tablets is prescribed for the treatment of infants and newborns with a body weight between 2 kg and less than 5 kg. The doctor or pharmacist should explain to the parents or caregivers how to use the medicine in the child being treated and inform them that all tablets must be taken for the entire treatment.

Licence number

58528, 67664(Swissmedic).

Packs

Riamet Dispersible

Packs of 12 dispersible tablets [A]

Riamet Baby

Packs of 12 dispersible tablets [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch; Domicile: 6343 Rotkreuz.

State of information

February 2025