RIAMET®

Composition

Active substances: Artemether, lumefantrine

Excipients: Tableting excipients.

Pharmaceutical form and quantity of active substance per unit

Tablets containing 20 mg artemether and 120 mg lumefantrine.

Indications/Potential uses

Riamet is indicated for the treatment of adults, infants and children (body weight ≥5 kg) with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Riamet 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 is effective against both drug-sensitive and drug-resistant *P. falciparum*, it is 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

Although patients with acute malaria are often averse to food, they should take each Riamet dose with food or drinks containing fat such as milk. 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 significantly improves absorption of artemether and lumefantrine.

In the event of vomiting within one hour of administration a repeat dose should be taken.
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 tablet at the time of diagnosis or as soon as symptoms appear, 1 tablet again after 8 h and then 1 tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 tablets).

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

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

The tablet(s) may be crushed for administration to infants and children. Dispersible tablets are also available for administration to paediatric patients.

**Dosage in adults and children weighing ≥35 kg or from 12 years of age:**

- 4 tablets as a single dose at the time of diagnosis or as soon as symptoms appear, 4 tablets again after 8 h and then 4 tablets twice daily (morning and evening) on each of the following two days (total course comprises 24 tablets).

**Dosage in special populations**

**Infants weighing less than 5 kg**

The safety and efficacy of Riamet have not been established in infants weighing less than 5 kg. No dosing recommendation can be made (see “Clinical efficacy” under “Properties/Actions” and “Pharmacokinetics”).

**Elderly patients**
Although no studies have been carried out in patients over 65 years of age, no special precautions or dose adjustments are considered necessary in such patients.

*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 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.

*New and recrudescent infections*

Data for a limited number of patients show that new and recrudescent infections can be treated with a second course of Riamet.

*Contraindications*

- 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.
- First trimester of pregnancy in situations where other suitable and effective antimalarials are available (see “Pregnancy/Breastfeeding”).
- 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 has not been evaluated for prophylaxis and is therefore not indicated for this use.

Riamet has 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 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 has not been evaluated in, and is 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 is active against blood stages of *P. vivax*, but not against its hypnozoites (= dormant form/dormant stage in hepatocytes).
Like other antimalarials (e.g. halofantrine, quinine, quinidine), Riamet may cause QTc interval prolongation (see “Properties/Actions” and QT/QTc prolongation).

There are no study data on the efficacy and safety of Riamet 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, 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 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 in patients previously treated with Riamet. The ECG should be closely monitored both when treatment is given in this order and when Riamet 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 is administered following treatment with mefloquine, it is particularly important to ensure that Riamet is taken together with food as lumefantrine levels may otherwise be insufficient.

In patients previously treated with halofantrine Riamet should not be administered earlier than 1 month after the last halofantrine dose (see “Interactions with antimalarials” under “Interactions”).
**With other medicinal products:** Riamet should not be used concomitantly with medicinal products metabolised by CYP2D6 (see “Contraindications”) and caution is required when combining Riamet 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 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 “Properties/Actions”).

**Interactions**

Not all mechanisms of pharmacological and pharmacokinetic interactions are known.

Concomitant use of Riamet 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 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 may previously have been treated with other antimalarials. Therefore, interactions with mefloquine and quinine were investigated in a study in healthy volunteers.

If Riamet is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine. In patients previously treated with halofantrine Riamet 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 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 ($C_{\text{max}}$ 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 and mefloquine should therefore be avoided.
Patients should be instructed to eat something with each dose of Riamet as this decisively improves absorption of artemether and lumefantrine, thus compensating for the decrease in bioavailability.

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\text{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 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 should be used with caution when co-administered with medicinal products that inhibit CYP3A4. Administration of artemether with double-concentrated grapefruit juice in 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 (see “Warnings and precautions”).

*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 alone. Concomitant use of strong CYP3A4 inducers, such as rifampicin, carbamazepine, phenytoin or St. John’s wort, and Riamet 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 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 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 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”).

*Pregnancy/Breast-feeding*

*Pregnancy*

There have been no controlled clinical studies of the safe use of Riamet during pregnancy.

Data from animal studies suggest that Riamet may cause severe birth defects when administered during the first trimester of pregnancy (see “Contraindications” 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”).

Safety data from an observational study during pregnancy in approximately 500 women who received Riamet (including over 150 women who received Riamet in the first trimester) and published data of another over 500 pregnant women who received artemether/lumefantrine (including over 50 patients who received artemether/lumefantrine in the first trimester) did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates. In addition, there was no apparent increase in adverse pregnancy outcomes based on data from two published studies (an open-label, randomised study with over
800 patients treated with Riamet in the second or third trimester and an observational study with 183 patients treated with artemisinin derivatives in the first trimester, of whom 10 received Riamet).

Nonetheless, Riamet should not be administered during the first trimester of pregnancy if other effective antimalarials are available. However, Riamet should not be withheld in life-threatening situations where no other effective antimalarials are available (see “Contraindications”).

During the second and third trimesters the medicinal product should only be used if absolutely necessary.

**Women of childbearing potential**

As Riamet is contraindicated during the first trimester of pregnancy, women should not become pregnant during antimalarial treatment with Riamet. This includes women prescribed Riamet 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 hormonal contraception and an additional, non-hormonal method of contraception in the event of stand-by emergency treatment during travel, while using Riamet and until the start of the next menstruation after treatment with Riamet (see “Warnings and precautions”).

**Breast-feeding**

Animal data suggest that Riamet passes into breast milk; however, human data are not available. Breast-feeding women should not take Riamet. 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 treatment.

**Effects on ability to drive and to use machines**

Patients receiving Riamet 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 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).

Column 1 presents a pooled safety analysis of adverse effects from clinical studies in adults and adolescents of >12 years of age or with a body weight of ≥35 kg administered 6 doses. Column 2 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.

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td>Rare: Hypersensitivity reactions</td>
<td>Very common: Decreased appetite</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Very common: Decreased appetite</td>
</tr>
<tr>
<td>Very common: Sleep disorders (30.08%)</td>
<td>Uncommon: Sleep disorders</td>
</tr>
</tbody>
</table>
Uncommon:
Sleeplessness

Nervous system disorders

Very common: Common: Headache, dizziness
Headache (79.38%), dizziness (55.97%) Uncommon:
Somnolence, hyponaesthesia, ataxia, clonus

Cardiac disorders

Very common: Common: Prolonged electrocardiogram
Palpitations (22.48%) QT (including QTc prolongations >60 ms and/or absolute QTc values >500 ms) Uncommon:
Palpitations

Respiratory disorders

Common: Cough Very common: Cough (23.5%)

Gastrointestinal disorders
Very common: Vomiting (30.08%), abdominal pain (27.13%), nausea (45.27%)
Common: Diarrhoea

Hepatobiliary disorders

Uncommon: Increased liver function values (ALT)
Common: Increased liver function values

Skin and subcutaneous tissue disorders

Common: Rash, pruritus
Uncommon: Urticaria
Common: Rash
Uncommon: Pruritus, urticaria

Musculoskeletal disorders

Very common: Arthralgia (49.92%), myalgia (51.32%)
Common: Arthralgia, myalgia

General disorders

Very common: Asthenia, fatigue
Uncommon: Gait disturbance

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).

Listing of adverse effects from spontaneous post-marketing reports

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.

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

Riamet contains a fixed combination of artemether and lumefantrine in the ratio of 1:6, 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.

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 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

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Population</th>
<th>Year/study location</th>
</tr>
</thead>
<tbody>
<tr>
<td>A025</td>
<td>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</td>
<td>6 doses over 60 hours: 118</td>
<td>Adults/children (≤12 years, n=43)</td>
<td>1996-97 Thailand</td>
</tr>
<tr>
<td>A026</td>
<td>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)</td>
<td>150 Mefloquine-artesunate: 50</td>
<td>Adults/children (2-12 years, n=34)</td>
<td>1997-98 Thailand</td>
</tr>
<tr>
<td>A028</td>
<td>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)</td>
<td>164 Mefloquine-artesunate: 55</td>
<td>Adults</td>
<td>1998-99 Thailand</td>
</tr>
</tbody>
</table>
### Table 2: Summary of clinical efficacy results:

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Age</th>
<th>Polymerase chain reaction (PCR)-corrected 28-day cure rate</th>
<th>Median FCT&lt;sup&gt;2&lt;/sup&gt; [25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt; percentile]</th>
<th>Median PCT&lt;sup&gt;2&lt;/sup&gt; [25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt; percentile]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A025&lt;sup&gt;4&lt;/sup&gt;</td>
<td>3-62 years</td>
<td>93/96 (96.9)</td>
<td>n&lt;sup&gt;3&lt;/sup&gt;=59 35 hours [20, 46]</td>
<td>n=118 44 hours [22, 47]</td>
</tr>
<tr>
<td>A026</td>
<td>2-63 years</td>
<td>130/133 (97.7)</td>
<td>n&lt;sup&gt;3&lt;/sup&gt;=87 22 hours [19, 44]</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Study Table:

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Population</th>
<th>Year/Study location</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2401</td>
<td>6-dose regimen in comparison with mefloquine-artesunate (MAS) Open-label, randomised (3:1), non-comparative study on the efficacy and safety of the 6-dose regimen in non-immune patients</td>
<td>165</td>
<td>Adults</td>
<td>2001-05 Europe, Colombia</td>
</tr>
<tr>
<td>A2403</td>
<td>Open-label, non-comparative study on the efficacy and safety of the 6-dose regimen</td>
<td>310</td>
<td>Infants/children</td>
<td>2002-03 3 countries (5-25 kg) in Africa</td>
</tr>
<tr>
<td>B2303</td>
<td>Investigator-blind, randomised (1:1), parallel-group study on the efficacy and safety of the 6-dose regimen</td>
<td>Riamet crushed tablet: 452</td>
<td>Infants/children</td>
<td>2006-07 5 countries (5-35 kg) in Africa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riamet Dispersible tablet: 447</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3: Studies of clinical efficacy by body weight in paediatric patients

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Weight category</th>
<th>Median PCT (^2) [25(^{th}), 75(^{th}) percentile]</th>
<th>PCR-corrected 28-day cure rate (^2) n/N (%) in evaluable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2403</td>
<td>5-&lt;10 kg</td>
<td>24 [24, 36]</td>
<td>145/149 (97.3)</td>
</tr>
<tr>
<td></td>
<td>10-&lt;15 kg</td>
<td>35 [24, 36]</td>
<td>103/107 (96.3)</td>
</tr>
<tr>
<td></td>
<td>15-25 kg</td>
<td>24 [24, 36]</td>
<td>41/43 (95.3)</td>
</tr>
</tbody>
</table>

1. Efficacy (cure rate) based on blood smear microscopy
2. mITT population
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.

CT: Riamet tablets administered as crushed tablets

DT: Riamet Dispersible tablets
<table>
<thead>
<tr>
<th>Study no.</th>
<th>Weight category</th>
<th>Median PCT[^1] (\text{[25}^{\text{th}}, 75^{\text{th}}) percentile]</th>
<th>PCR-corrected 28-day cure rate[^2] n/N (%) in evaluable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study B2303[^CT]</td>
<td>5-&lt;10 kg</td>
<td>36 [24, 36]</td>
<td>65/69 (94.2)</td>
</tr>
<tr>
<td></td>
<td>10-&lt;15 kg</td>
<td>35 [24, 36]</td>
<td>174/179 (97.2)</td>
</tr>
<tr>
<td></td>
<td>15-&lt;25 kg</td>
<td>35 [24, 36]</td>
<td>134/140 (95.7)</td>
</tr>
<tr>
<td></td>
<td>25-35 kg</td>
<td>26 [24, 36]</td>
<td>30/31 (96.8)</td>
</tr>
<tr>
<td>Study B2303[^DT]</td>
<td>5-&lt;10 kg</td>
<td>36 [24, 43]</td>
<td>74/78 (94.9)</td>
</tr>
<tr>
<td></td>
<td>10-&lt;15 kg</td>
<td>35 [24, 36]</td>
<td>156/168 (92.9)</td>
</tr>
<tr>
<td></td>
<td>15-&lt;25 kg</td>
<td>25 [24, 36]</td>
<td>137/142 (96.5)</td>
</tr>
<tr>
<td></td>
<td>25-35 kg</td>
<td>26 [24, 36]</td>
<td>27/28 (96.4)</td>
</tr>
</tbody>
</table>

\[^1\] mITT population  
\[^2\] 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.

Riamet is 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 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, $C_{\text{max}}$).

**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 crushed tablets led to lower systemic exposure to artemether and its metabolite dihydroartemisinin (DHA) than the intact tablets, while exposure to lumefantrine was slightly higher with the crushed tablets than with the intact tablets (see Table 4).

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

<table>
<thead>
<tr>
<th></th>
<th>Intact tablets (n=48)</th>
<th>Crushed tablets (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artemether</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>83.8 ± 59.7</td>
<td>48.0 ± 22.2</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>2.00 [0.75-6.00]</td>
<td>2.00 [0.50-6.00]</td>
</tr>
<tr>
<td>AUC$_{\text{last}}$ (ng·h/ml)</td>
<td>259 ± 150</td>
<td>195 ± 93.0</td>
</tr>
<tr>
<td></td>
<td>DHA</td>
<td>Lumefantrine</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>90.4 ± 48.9</td>
<td>9.8 ± 4.2</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>2.00 [0.75-6.00]</td>
<td>8.00 [5.00-12.00]</td>
</tr>
<tr>
<td>AUC_{last} (ng·h/ml)</td>
<td>285 ± 98.0</td>
<td>243 ± 117</td>
</tr>
</tbody>
</table>

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 or in elderly patients.

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 in patients with renal impairment or in elderly patients (>65 years of age).

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”).

Children

The few available pharmacokinetic data are from two studies in paediatric malaria patients (≥5 to <35 kg body weight) given a dosage based on mg/kg body weight as described in the “Dosage/Administration” section.
Systemic exposure to artemether, DHA and lumefantrine in infants and children was comparable to that measured for the recommended dosage regimen for adult malaria patients.

**Infants weighing <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 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.

**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 (AUC\textsubscript{0-24h}) to artemether and dihydroartemether, an active metabolite of similar structure, were 1294 and 2253 ng/ml, respectively, on day 1, corresponding in total to twice the adult exposures (AUC\textsubscript{0-24h} 1070 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 1208 ng.h/ml for artemether and dihydroartemether, respectively). Exposures in animals were similar to (day 1) or lower than (day 3) clinical exposures.

\textit{Mutagenicity}

There have been no reports of mutagenicity in \textit{in vitro} and \textit{in vivo} tests using a (1:6) combination of artemether and lumefantrine. In the micronucleus test myelotoxicity was seen at all dosages (500, 1000 and 2000 mg/kg), but recovery was reported to be almost complete 48 hours after dosing.

\textit{Carcinogenicity}

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

\textit{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 in 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 1000 mg/kg/day; altered sperm motility, reduced epididymal sperm count, increased testes weight and embryotoxicity and other reproductive effects (decreased number of implants 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 \( C_{\text{max}} \) 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 \( C_{\text{max}} \) or greater than 1000 if they are estimated using the calculated free \( C_{\text{max}} \). Based on the available non-clinical data the potential for QTc prolongation in humans cannot be discounted.

Other information

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Do not store above 30°C.

Protect from moisture and store in the original pack.

Keep out of the reach of children.

Use and handling in children and infants
The pack containing 24 tablets may be prescribed for the treatment of children and infants. 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.

**Swissmedic number**

54594

**Pack sizes**

Packs containing 24 tablets [A]

**Marketing authorisation holder**

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

**Information last revised**

July 2018