HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 July 2008

RIAMET 20 mg/120 mg, tablet in blister packs
Pack of 24 (CIP: 563 043-8)

Applicant: NOVARTIS PHARMA S.A.S.

Artemether/lumefantrine

ATC Code: P01BE52

List I
Medicine for hospital prescription only

Date of Marketing Authorisation (MA) and its variations: 23 April 2001, 28 August 2002, 23 April 2007, 14 December 2007, 19 June 2008

Reason for request: Inclusion on the list of medicines approved for use by hospitals and various public services in the extension of indication: Treatment of acute uncomplicated *Plasmodium falciparum* malaria infection in **children and infants over 5 kg**.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Artemether /lumefantrine

1.2. Background

RIAMET is a fixed-dose combination of two active ingredients: artemether, a rapid-acting antimalarial and lumefantrine (not used as monotherapy) with a more lasting action.

1.3. Indication

Treatment of acute uncomplicated *Plasmodium falciparum* malaria infection in adults, **children and infants over 5kg**

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

1.4. Dosage

To increase absorption, RIAMET should be taken with food or a milky drink. RIAMET may be administered if patients are unable to tolerate food, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For administration to small children and infants, the tablets may be crushed.

Adults and children from 12 years weighing 35kg and above:
The total dose comprises six doses of four tablets i.e. a total of 24 tablets, given over a period of 60 hours according to the following regimen:
First dose given at the time of diagnosis: 4 tablets,
Then five further doses of 4 tablets given at 8, 24, 36, 48 and 60 hours after the first dose.

Children and infants weighing 5kg to less than 35kg:
The total recommended dose is 6 doses of from 1 to 3 tablets according to body weight:

- Body weight from 5 kg to less than 15 kg:
First dose given at the time of diagnosis: 1 tablet,
Then 5 further doses of 1 tablet given at 8, 24, 36, 48 and 60 hours after the first dose.

- Body weight from 15 kg to less than 25 kg:
First dose given at the time of diagnosis: 2 tablets,
Then five further doses of 2 tablets given at 8, 24, 36, 48 and 60 hours after the first dose.

- Body weight from 25 kg to less than 35 kg:
First dose given at the time of diagnosis: 3 tablets,
Then five further doses of 3 tablets given at 8, 24, 36, 48 and 60 hours after the first dose.

Elderly:
Although no studies have been carried out in the elderly, no special precautions or dosage adjustments are considered necessary in this population.

Renal or hepatic impairment:
Caution is advised when administering Riamet® to patients with severe renal or hepatic problems. In these patients, ECG and blood potassium monitoring is advised.

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

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (WHO, 2007)

P : antiparasitic agents, insecticides
P01 : antiprotozoal agents
P01B : antimalarial drugs
P01BE : artemisinin and derivatives
P01BE52 : artemether as adjunctive therapy

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

The proprietary medicine RIAMET is the only combination containing an artemisinin derivative with an European MA.

Table 1: comparator medicines in the treatment of acute uncomplicated malaria infection and their registration status (pharmacy sale or hospital use).

Product	INN	Indication
Included in the list of medicines reimbursed by National Insurance and approved for use by hospitals		
Nivaquine® 100 mg tablet (Pack of 20 - Pack of 100)	chloroquine	Curative treatment of malaria. **Adult and child over 10 kg**
Nivaquine® 25 mg/5 ml syrup (150 ml)	chloroquine	Curative treatment of malaria. **Adult and child over 10 kg**
Quinimax® 125 mg tablet (Pack of 18)	quinine alkaloids	Treatment of acute uncomplicated malaria, in particular in the case of resistance to 4-amino-quinoline drugs. **Adult and child over 9 kg**
Quinimax® 500 mg tablet (Pack of 9)	quinine alkaloids	Treatment of acute uncomplicated malaria, in particular in case of resistance to 4-amino-quinoline drugs. **Adult and child over 9 kg**
Included in the list of medicines reimbursed by National Insurance alone		
Quinine hydrochloride. Lafran® 250 mg tablet (Pack of 20)	quinine	Treatment of acute uncomplicated malaria, in particular in case of resistance to 4-amino-quinoline drugs. **Adult and child over 30 kg**
Quinine hydrochloride Lafran® 500 mg tablet (Pack of 20)	quinine	Treatment of acute uncomplicated malaria, in particular in case of resistance to 4-amino-quinoline drugs. **Adults**
Quinine sulphate Lafran® 250 mg tablet (Pack of 20)	quinine	Treatment of acute uncomplicated malaria, in particular in case of resistance to 4-amino-quinoline drugs.
Quinine sulphate Lafran® 500 mg tablet (Pack of 20)	quinine	Treatment of acute uncomplicated malaria, in particular in case of resistance to 4-amino-quinoline drugs.
Included in the list of medicines approved for use by hospitals alone		
Fansidar® 500 mg/25 mg tablet (Pack of 3)	Sulfadoxine and pyrimethamine	Treatment of acute uncomplicated *Plasmodium falciparum* malaria in case of resistance to 4-amino-quinoline drugs or contraindication to other antimalarial agents. **May be used in children under 12 kg (or less than 30 months)**
Halfan® 250 mg tablet (Pack of 6)	halofantrine	Treatment of acute uncomplicated *Plasmodium falciparum* malaria. **Adult and child over 10 kg**
Halfan® 100 mg/5 ml oral solution (45 ml)	halofantrine	Treatment of acute uncomplicated *Plasmodium falciparum* malaria. **Adult and child over 10 kg**
Lafran® 250 mg tablet (Pack of 8)	mefloquine	Treatment of acute uncomplicated malaria contracted in particular in areas of resistance to 4-amino-quinoline drugs (chloroquine). **Adult and child over 5 kg**
Malarone® 250 mg/100 mg* tablet (Pack of 12) **- Malarone® 62.5 mg/25 mg CHILD*, tablet (Pack of 12)**	atovaquone proguanil	Treatment of acute uncomplicated *Plasmodium falciparum* malaria **Adult and child aged over 12 years** **- Extension of indication <u>in the child from 5 kg</u> (MA variation of 14 May 2008, not yet examined by the TC)**

*Medicine reimbursed in retail pharmacy (65%): this only applies to socially insured persons in French Guyana. The only therapeutic indication entitling to management and reimbursement by National Insurance is: Text in the *Journal Officiel* of 14 February 2007 "prophylactic treatment of malaria for socially insured persons in Guiana not residing in malaria-endemic areas and staying once or occasionally for less than 3 months in malarious areas of French Guiana".

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Two clinical studies are presented:

- One study conducted in the child from 5 to 25 kg, which allowed the extension of indication of RIAMET to **infants and children over 5 kg** (study 2403),
- One non-comparative phase IV study, conducted in non-immune adults (study 2401). This study was performed in link withcommitments made at the initial MA. Its objective was to evaluate the efficacy and safety (including in particular ECG monitoring and a pharmacokinetic analysis) of RIAMET in non-immune patients. It led to a MA variation dated on 14 December 2007 (update of sections 5.1 and 5.2 in the Summary of Product Characteristics).

3.1.1. **Study in infants and children over 5 kg (study 2403)**[1]

This non-comparative study, conducted in a malaria-endemic area[2], evaluated the safety (primary objective) and efficacy of the artemether-lumefantrine combination (20 mg/120 mg) in children (n=310) from 5 to 25 kg with microscopy-confirmed uncomplicated *Plasmodium falciparum* malaria (1,000 – 100,000/mm^3 parasitemia).

A 6-dose regimen was used over a total duration of 60 hours: first dose at the time of diagnosis (To), then 8, 24, 36, 48 and 60 hours after the first dose. The dose was adjusted according to body weight (5 - <10 kg: one tablet; 10 - <15 kg: one tablet; 15 - $\leq$ 25 kg: two tablets). Treatment was administered during meals or with a milky drink in order to improve the absorption of the active ingredients. Patients were hospitalised during treatment until clearance of parasites and fever and they were then followed up on an outpatient basis until day 28 after the start of the treatment.

The median parasite clearance time was from 24 to 36 hours and median fever clearance time was approximately 8 hours in the different groups.

Table 2: Parasite clearance rates at 7, 14 and 28 days according to body weight

	Body weight			**Total**
	5 - < 10 kg	**10 - < 15 kg**	**15 - ≤ 25 kg**	
ITT Population	(n=154)	(n=110)	(n=46)	(n=310)
D 7	98.7 %	98.2 %	100 %	98.7 %
D 14	98.1 %	97.3 %	97.8 %	97.7 %
D 28	86.4 %	85.5 %	89.1 %	86.5 %
ITT Population, corrected by PCR*	(n=154)	(n=110)	(n=46)	(n=310)
D 7	98.7 %	98.2 %	100 %	98.7 %
D 14	98.1 %	97.3 %	97.8 %	97.7 %
D 28	94.2 %	93.6 %	93.5 %	93.9 %
Evaluable population (PP) **	(n=152)	(n=108)	(n=45)	(n=305)
D 7	100 %	100 %	100 %	100 %
D 14	100 %	100 %	100 %	100 %
D 28	89.3 %	87.9 %	90.9 %	89.0 %
PP Population, corrected by PCR*	(n=152)	(n=108)	(n=45)	(n=305)
D 7	100 %	100 %	100 %	100 %
D 14	100 %	100 %	100 %	100 %
D 28	97.3 %	96.3 %	95.5 %	96.7 %

*PCR is used to distinguish between a true relapse (reactivated sequestered parasites) and a second infection.

** Evaluable population: presence of *P. falciparum* at D_0, blood parasite levels measured up to the date of analysis (D7, D14 or D28), premature study discontinuations due to a reappearance of *P. falciparum*, no concomitant antimalarial drug taken apart from authorised emergency medication.

[1] Falade C, Makanga M, Premji Z, et al. Efficacy and safety of artemether-lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria. Royal Society of tropical medicine and hygiene. 2005;99:459-467

[2] The study took place in Africa in three centres (Nigeria, Kenya and Tanzania) between July 2002 and February 2003.

3.1.2. **Study in non-immune adults (study 2401)**

This non-comparative study evaluated the efficacy and safety (in particular ECG monitoring and a pharmacokinetic analysis) of the artemether-lumefantrine combination in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in patients (N=165) not immunised against malaria[3].

The dosing regimen of the artemether-lumefantrine combination comprised 6 doses of 4 tablets each, over a total duration of 60 hours: first dose at the time of diagnosis (To), then 8, 24, 36, 48 and 60 hours after the first dose. Patients were followed up for 28 days after the start of treatment.

The 28-day cure rate (patients with blood clearance of asexual parasites within 7 days after the start of treatment with no relapse during the 28 days following the start of treatment) was 74.1% (120/162) in the ITT population and 96% (119/124) in the population defined as evaluable. Thirty patients prematurely discontinued treatment (including 17 lost to follow-up, 6 protocol violations, 3 lack of efficacy or poor safety, 2 withdrawals of consent and 2 other reasons) and were considered as treatment failures.

The results of this study agreed with the efficacy and safety profile reported during studies performed in semi-immune patients.

3.2. Safety

The evaluation of the safety profile of RIAMET in infants and children over 5 kg is based on the clinical data of study 2403 where 310 children from 5 to 25 kg were treated with a 6-dose regimen (dose adjusted according to body weight) distributed over a total period of 60 hours. The incidence of adverse events was 72.6% and the incidence of adverse reactions was 25%. The most frequent adverse reactions were: vomiting (4.5%), diarrhoea (3.5%), anaemia (4.8%), hypereosinophilia (3.9%), clonus (4.2%). A single patient discontinued treatment because of the onset of an adverse reaction. One patient presented a serious adverse reaction requiring hospitalisation (urticaria).
An asymptomatic prolongation of the QTc interval > 30 msec was observed in 35% of children with a body weight between 5 and 10 kg, 34.1% of children with a body weight between 10 and 15 kg and 23% of the children with a body weight between 15 and 25 kg. The proportion of patients with aprolongation of the QTc > 60 msec was 5.5 %.

The safety profile of RIAMET observed in children complied with the expected effects observed during prior studies in adults.

3.3. Conclusion

The efficacy of the fixed-dose artemether-lumefantrine (20 mg/120 mg) combination in infants and children over 5 kg was evaluated in a non-comparative clinical study (study 2403) performed in a malaria-endemic area in 310 children from 5 to 25 kg with an acute uncomplicated *Plasmodium falciparum* malaria infection (1,000 – 100,000/mm^3 parasitemia). The dosing regimen was 6 doses of 1 to 2 tablets (according to body weight) over a total duration of 60 hours.

The 28-day cure rate[4] was 86.5 % in the ITT population (93.9% in the PCR-corrected ITT population[5]) and 96.7% in the population defined as evaluable.

Overall, the response observed in this paediatric population was of similar magnitude to that described in adults at the MA dosages (6 doses of 4 tab., over 3 days).
The safety profile complied with the expected effects (including prolonged QTc interval, with no clinical repercussions) that were observed during previous studies in adults.

[3] This study was performed in Germany, France, Italy, Holland, Switzerland and Colombia.
[4]Primary efficacy endpoint according to WHO recommendations: Patients with blood clearance of asexual parasites within 7 days of the start of treatment with no relapse during the 28 days after the start of treatment.
[5]PCR is used to distinguish between a recurrence (reactivation of sequestered parasites) and a second infection.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Malaria is a serious disease which is potentially fatal when caused by *Plasmodium falciparum*. *Plasmodium falciparum* strains resistant to conventional therapies are becoming more and more frequent.
This parasite disease is the subject of a WHO control program[6].

Combination therapy with artemether-lumefantrine (RIAMET) is used for curative treatment.

The efficacy/safety ratio is high, provided that the contraindications (including congenital prolongation of QTc interval and a medical history of certain heart diseases) and the warnings and precautions for use are respected.

The RIAMET is the only combination containing an artemisinin derivative with an European MA.
There are alternative treatments.

> Public Health Benefit
> The treatment of acute uncomplicated *Plasmodium falciparum* malaria infection in children and infants of 5kg and above is a low public health burden in France.
> Malaria control requiring an integrated approach with both prevention and treatment by effective antimalarials, that does not come within the scope of a National public health priority. However, in French Guiana and Mayotte where malaria is endemic, the availability of drug combinations with artemisinin is recognised as a answer by WHO for countering the risk of *P. falciparum* resistance to monotherapies and emergence of multidrug-resistance to conventional antimalarials.
> According to available data, a theoretical impact is expected on the reduction of morbidity and mortality related to acute uncomplicated *Plasmodium falciparum* malaria infection. Taking into account the small number of children potentially concerned by the artemether-lumefantrine combination treatment (Riamet) in France, no impact is expected at population level.
> Consequently, taking into account the response that RIAMET may provide to the specific need of populations concerned in French Guiana and Mayotte, this medicine is expected to have a low public health benefit.

The actual medical benefit of RIAMET is substantial.

4.2. Improvement in actual benefit

Taking into account the efficacy of RIAMET in the treatment of acute uncomplicated malaria infection, in particular in case of multidrug-resistant strains, and the current knowledge on its safety, this medicine provides a low improvement in the actual medical benefit (level IV) in the management of acute uncomplicated *Plasmodium falciparum* malaria infection in infants and children over 5 kg.

4.3. Therapeutic use

The recommendations revised in October 2007 by SPILF[7] recommend for the treatment of uncomplicated *P. falciparum* malaria infection in France:

In adults:

- First-line therapy: atovaquone-proguanil (MALARONE) or artemether-lumefantrine (RIAMET)
- 2nd-line therapy: quinine (QUINIMAX, QUININE LAFRAN) or mefloquine (LARIAM)
- 3rd-line therapy: halofantrine (in specific settings, in hospital with ECG monitoring)

[6] World Health Organisation. Guidelines for the treatment of malaria.
[7] Clinical practice guidelines "Management and prevention of imported Plasmodium falciparum malaria. 2007 revision of the 1999 consensus conference. By the French Language Society of Infectious Diseases".

In children:

Drugs for first line therapy are:

- mefloquine, often given after a domperidone anti-emetic product.
- or atovaquone-proguanil
- or artemether-lumefantrine

Because of its cardiotoxicity and the risk of relapse after a single course, halofantrine is used for second-line treatment, although it is supplied as a suspension which is convenient in children. It is only indicated when there is no other alternative and requires monitoring by an experienced team.
Oral quinine, which requires perfect compliance to a seven day treatment regimen, is used for second-line therapy. In symptomatic newborn infants, treatment is started by IV quinine followed by a single course of halofantrine.

Specific cases

Travellers returning from Amazonia (including French Guyana), or border areas between Thailand, Myanmar, Laos and Cambodia: in these zones where there is a high level of resistance to mefloquine and halofantrine, alternative treatments are atovaquone-proguanil or artemether-lumefantrine combinations or quinine combined with doxycycline, 200 mg once daily for 7 days, or clindamycin, 10 mg/kg every 8 hours for 7 days.

4.4. Target Population

The epidemiology of malaria infection in France need to distinguish two situations:

- Imported cases of malaria infection: approximately 4,400 cases in 2007 in the Metropolitan France (a reduction of 16.5 % compared to 2006), with 82% of *P. falciparum* malaria cases including more than 110 serious cases with an average of twenty deaths per year since 2000[8].
- Cases outside the metropolitan France: Approximately 3000 annually malaria cases in French Guyana in 2002 and 2003[9], with approximately 75% caused by *P. falciparum*[10]. The overseas departmental community of Mayotte is also a malaria endemic area with 600 to 800 cases per year (2003-2005) caused by *P. falciparum* in 90% of cases.

National data from CNRMI[11] describe a stable proportion of imported paediatric cases of malaria infection in France, around 22% between 1997 and 2000.

The indication of RIAMET is restricted to acute uncomplicated *P. falciparum* malaria infection in patients without gastrointestinal disorders and with no contraindications (including congenital prolongation of the QTc interval and a history of certain cardiac disorders).

4.5. Transparency Committee recommendations

The Transparency Committee recommends the inclusion of RIAMET on the list of medicines approved for use by hospitals and various public services in the extension of indication and at the MA dosages.

[8] Traveller's health and health recommendations 2008. BEH 2008; n°23–24/2006 28 June 2008
[9] INVS. Epidemiological monitoring of malaria in French Guiana. February 2006
[10] Third Consensus Conference on Malaria at Cayenne, French Guiana - 4 and 5 October 2002
[11] O. Eloy, F.Bruneel, C.Diebold et al. Imported Malaria in the child. Experience at Versailles hospital centre (1997-2001). *Annales de Biologie Clinique. Volume 61, Numéro 4, 449-53, Juillet 2003, Pratique quotidienne*.