HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 February 2012

EURARTESIM 160 mg/20 mg, film-coated tablets
B/3 (CIP code: 217 520-6)

EURARTESIM 320 mg/40 mg, film-coated tablets
B/12 (CIP code: 217 519-8)

Applicant: SIGMA-TAU FRANCE

artenimol/piperaquine
ATC code: P01BF05 (artemisinin and derivatives, combinations)

List I

Date of Marketing Authorisation (centralised procedure): 27 October 2011

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

Artenimol[1]/Piperaquine

1.2. Indication

"EURARTESIM is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more.
Consideration should be given to official guidance on the choice and appropriate local use of antimalarial agents. "

1.3. Dosage

"Administration
EURARTESIM should be administered over 3 consecutive days for a total of 3 doses. Each dose should be taken at the same time each day.
Dosage
Dosing should be based on body weight, as shown in the table below:

Body weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	PQP	DHA	
5 to < 7	80	10	½ × 160 mg/20 mg tablet
7 to < 13	160	20	1 160 mg/20 mg tablet
13 to < 24	320	40	1 320 mg/40 mg tablet
24 to < 36	640	80	2 320 mg/40 mg tablets
36 to < 75	960	120	3 320 mg/40 mg tablets
75 to 100	1280	160	4 320 mg/40 mg tablets
➢ 100	There are no data on which to base a dose recommendation in patients weighing > 100 kg		

If a patient vomits within 30 minutes of taking EURARTESIM, the whole dose should be re-administered; if a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing should not be attempted more than twice. If the second dose is vomited, alternative antimalarial therapy should be instituted.
If a dose is missed, it should be taken as soon as possible and then the recommended regimen continued until the full course of treatment has been completed.
There are no data on a second course of treatment.
Patients should not receive more than 2 courses of EURARTESIM over a 12-month period. Due to the long elimination half-life of piperaquine, the second course of EURARTESIM should not be administered within 2 months of finishing the first course.

Hepatic and renal impairment
EURARTESIM has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering EURARTESIM to these patients.

Elderly
Clinical studies of EURARTESIM tablets did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for underlying heart disorders, caution should be exercised when administering the product to the elderly.

[1] Artenimol is also called dihydroartemisinin

Paediatric population
The tolerance and efficacy of EURARTESIM in children aged less than 6 months and in children weighing less than 5 kg has not been established. No data are available for these paediatric subgroups.

Method of administration
EURARTESIM should be taken orally with water and without food.
Each dose should be taken at least 3 hours after the last meal. Patients should not consume any food within 3 hours after each dose. For patients unable to swallow the tablets, such as infants and young children, EURARTESIM may be crushed and mixed with water. The mixture should be used immediately after preparation."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

P	Antiparasitic products, insecticides
P01	Antiprotozoals
P01B	Antimalarials
P01BF	Artemisinin and derivatives, combinations
P01BF05	Artenimol and piperaquine

2.2. Medicines in the same therapeutic category

In France, only one artemisinin-based combination indicated in the treatment of uncomplicated *Plasmodium falciparum* malaria is currently available:
RIAMET® 20 mg/120 mg, tablet (B/24): combination of artemether and lumefantrine, indicated in the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants weighing over 5 kg (inclusion in the list of medicines approved for hospital use and the list of medicines for delivery to out-patients).

Antimalarial agents that can be administered by mouth and indicated for the treatment of malaria are presented in the table below.

Proprietary medicinal product	INN	Indication
Inclusion in the list of medicines reimbursed by National Insurance and approved for hospital use		
Nivaquine® 100 mg tablet (B/20 - B/100)	chloroquine	Curative treatment of malaria. **Adults and children over 10 kg**
Nivaquine® 25 mg/5 ml syrup (150 ml)	chloroquine	Curative treatment of malaria. **Adults and children**
Quinimax® 125 mg tablet (B/18)	quinine alkaloids	Treatment of simple malaria, especially in cases of resistance to amino-4-quinoleins. **Adults and children weighing over 9 kg**
Quinimax® 500 mg tablet (B/9)	quinine alkaloids	Treatment of simple malaria, especially in cases of resistance to amino-4-quinoleins. **Adults and children over 9 kg**
Inclusion in the list of medicines reimbursed by National Insurance only		
Quinine c. Lafran® 224.75 mg tablet (B/20)	quinine	Treatment of simple malaria, especially in cases of resistance to amino-4-quinoleins. **Adults and children over 30 kg**
Quinine c. Lafran® 449.5 mg tablet (B/20)	quinine	Treatment of simple malaria, especially in cases of resistance to amino-4-quinoleins. **Adults, not suitable for children**
Quinine s. Lafran® 217.2 mg tablet (B/20)	quinine	Treatment of simple malaria, especially in cases of resistance to amino-4-quinoleins. **Adults and children over 30 kg**
Quinine s. Lafran® 434.4 mg tablet (B/20)	quinine	Treatment of simple malaria, especially in cases of resistance to amino-4-quinoleins. **Adults, not suitable for children**

Inclusion on the list of medicines approved for hospital use only		
Fansidar® 500 mg/25 mg tablet (B/3)	sulfadoxine pyrimethamine	Treatment of uncomplicated *Plasmodium falciparum* malaria in cases of resistance to amino-4-quinoleines or of contraindication to other antimalarials. **May be used in children weighing less than 12 kg (i.e. aged under 30 months)**
Halfan® 250 mg tablet (B/6)	halofantrine	Treatment of simple malaria caused by *Plasmodium falciparum*. **Adults and children weighing over 10 kg**
Halfan® 100 mg/5 ml oral solution (45 ml)	halofantrine	Treatment of simple malaria caused by *Plasmodium falciparum*. **Adults and children weighing over 10 kg**
Lariam® 250 mg* tablet (B/8)	mefloquine	Treatment of simple malaria, in particular contracted in areas of resistance to amino-4-quinoleines (chloroquine). **Adults and children weighing over 5 kg**
Malarone® 250 mg/100 mg* tablet (B/12)	atovaquone-proguanil	Treatment of simple (uncomplicated) malaria caused by *Plasmodium falciparum* **Adults and children weighing over 11 kg**
Malarone® 62.5 mg/25 mg CHILDREN, tablet (B/12)	atovaquone-proguanil	Treatment of simple (uncomplicated) malaria caused by *Plasmodium falciparum* **Children weighing from 5 kg up to 11 kg**
RIAMET® 20 mg/120 mg, tablet (B/24)	artemether/ lumefantrine	Treatment of uncomplicated malaria caused by *Plasmodium falciparum* **Adults, children and infants weighing over 5 kg**

*Proprietary medicinal product also refundable (65%) on presentation of a medical prescription: This payment arrangement applies only to those covered by the French Guiana National Health Insurance. The only therapeutic indication for which National Health Insurance cover is provided is: Text of the Official Journal of 14 February 2007 "prophylactic treatment of malaria in subjects covered by the French Guiana National Health Insurance not living in malaria-infected regions and making a single stay or occasional stays of 3 months or less in a malaria-endemic region of French Guiana".

2.3. Medicines with a similar therapeutic aim

This refers to the other medicinal products that may be used in the treatment of uncomplicated *Plasmodium falciparum* malaria, including injectable forms for use when oral administration is impossible.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical data assessing the efficacy of the artenimol/piperaquine combination rely on two phase III studies conducted in a highly malaria-endemic region[2]:

- a controlled study versus the artemether/lumefantrine combination, conducted in an African paediatric population (Burkina Faso, Kenya, Mozambique, Uganda, Zambia) between August 2005 and July 2006.
- a controlled study versus the artesunate/mefloquine combination, conducted in an Asian population (India, Laos, Thailand), between July 2005 and April 2007.

Artemisinin combination therapies (ACTs) used as comparators have proved their worth in this indication and are recommended by the WHO for use in the front line in endemic regions.[3]

[2] Group 3, according to the WHO definition (areas of high prevalence of chloroquine resistance and multidrug-resistance)
[3] WHO. Guidelines for the Treatment of Malaria. 2011, Second Edition. http://www.who.int/topics/malaria/fr/

However, only the artemether/lumefantrine combination (RIAMET) has European Marketing Authorisation for the treatment of malaria.

There is no clinical study available in a European population of imported malaria cases. While the data presented may be transferable to French Guiana and Mayotte (endemic regions), they are on that account less readily transferable to metropolitan France (imported malaria).

3.1.1. Study DM040011

Study objective

This is an open, controlled, non-inferiority study (delta threshold = 5%), the objective of which was to compare the efficacy of the "artenimol/piperaquine" fixed-dose combination with the "artemether/lumefantrine" fixed-dose combination in the treatment of uncomplicated *Plasmodium falciparum* malaria in an African paediatric population.

Eligibility criteria

- Main inclusion criteria:
  - aged from 6 to 59 months, inclusive,
  - weight over 5 kg,
  - monoparasitic *P. falciparum* infection, confirmed microscopically (parasitaemia between 2,000 and 200,000/µl), a history of fever or presence of fever (≥ 37.5°C),
- Main non-inclusion criteria:
  - severe malaria according to WHO criteria,[3]
  - presence of critical signs: being unable to drink, vomiting (> 2 in 24 hours), recent convulsions (> 1 in 24 hours), unconscious state, inability to sit down or stand,
  - prophylaxis with a treatment having an antimalarial action.

Treatments

Eligible children were randomly assigned (in a ratio of 2:1) to either the "artenimol/piperaquine" group or the "artemether/lumefantrine" group. The children were treated for 3 consecutive days, with the dosages adjusted for the weight of the children in accordance with the Summary of Product Characteristics (Tables 1 and 2).

Table 1: Daily dosage of artenimol/piperaquine (Study DM040011)

Body weight (kg)	Artenimol/piperaquine dosage	Number of tablets/day
4* - 6	80 mg PQP/10 mg DHA	½**
7 - 12	160 mg PQP/20 mg DHA	1**
13 - 23	320 mg PQP/40 mg DHA	1
24 - 35	320 mg PQP/40 mg DHA	2

*5 kg was the minimum weight for inclusion; **: paediatric dosage
DHA = artenimol; PQP = piperaquine

Table 2: Daily dosage of artemether/lumefantrine (Study DM040011)

Body weight (kg)	Dose of the AL combination mg	Number of tablets/dose	Number of tablets/day
5 - < 15	20 mg A/120 mg L	1	2
15 - < 25	40 mg A/240 mg L	2	4
25 - < 35	60 mg A/360 mg L	3	6

A = artemether; L = lumefantrine

Primary efficacy endpoint

The primary efficacy endpoint was the 28-day PCR-corrected clinical and parasitological cure rate, defined as a negative parasitaemia on D28, without having first reached any of the early treatment failure, late treatment failure or late parasitological failure criteria.

The non-inferiority of artenimol/piperaquine compared to artemether/lumefantrine was established if the lower limit of the 97.5% confidence interval (unilateral test) of the difference between the 28-day PCR-corrected cure rates on D28 was greater than -5%.

Note: The PCR-corrected cure rate looks at the proportion of patients who have not presented any parasite recrudescence. Patients who have been re-infected over the period under consideration were thus not assessed as actual failures. PCR is the test that makes it possible to distinguish recrudescent from newly-acquired Plasmodium infections.

Early treatment failure:

- *appearance of severe signs or severe malaria on D0, D1, D2 or D3 with the presence of parasitaemia*
- *parasite density on D2 > D0 regardless of the axillary temperature*
- *parasitaemia on D3 with fever (axillary temperature ≥ 37.5°C)*
- *parasitaemia on D3 ≥ 25% of that on D0*

Late treatment failure:

- *appearance of severe signs or severe malaria after D3 with the presence of parasitaemia*
- *parasitaemia and fever between D4 and D28 without any sign of previous failure*

Late parasitological failure:

- *reappearance of parasitaemia between D4 and D28 without any fever (axillary temperature < 37.5°C without having previously responded to any early failure criterion or late treatment failure criterion)*

Secondary endpoints, in particular:

- PCR-corrected cure rate on D14 and D42
- Uncorrected cure rate on D14, D28 and D42
- Percentage of patients in treatment failure (early or late failure and actual treatment failure)
- Number of patients with gametocytes
- Treatment compliance

Study population

Of the 1553 patients included, 1039 children were randomly assigned to the artenimol/piperaquine group and 514 to the artemether/lumefantrine group.
Overall, the two populations were comparable. The mean age was 2.42 years (0.51-6.99 years; mean weight 11.19 kg) in the artenimol/piperaquine group and 2.44 years (0.49-4.98 years; mean weight 11.29 kg) in the artemether/lumefantrine group. On inclusion, the median parasite density was similar in the two groups: 27,245 parasites/µl versus 27,760 parasites/µl. The number of children with a starting haemoglobin rate < 70 g/l was 140 (13.6%) versus 63 (12.7%).

Results

In the *per protocol* (PP) population, the 28-day PCR-corrected cure rates were 95.7% (910/951) in the artenimol/piperaquine group versus 95.7% (442/462) in the artemether/lumefantrine group (p = 0.998). The lower limit of the unilateral confidence interval of the difference between the two groups was -2.24%, which established the non-inferiority of the artenimol/piperaquine combination with respect to the artemether/lumefantrine combination (non-inferiority margin defined as -5%). Analysis of the Intention to Treat Population (mITT) gave similar results: 92.7% (952/1027) versus 94.8% (471/497), lower limit of the unilateral confidence interval of the difference = -4.59%.

The results for the secondary endpoints are presented in Table 3. The actual failure rate (early failures and late failures being regarded by PCR as recrudescences) was similar in both treatment groups (2.7% versus 2.6%).

Table 3: Efficacy with respect to secondary endpoints (Study DM040011)

Per protocol population (PP)			
n (%)	A/P* (n = 951)	A/L* (n = 462)	Lower limit (p)
PCR-corrected cure rate (D14)	924 (97.2%)	453 (98.0%)	-2.53% (0.319)
PCR-corrected cure rate (D42)	879 (92.4%)	436 (94.4%)	-4.63% (0.177)
PCR-uncorrected cure rate (D14)	924 (97.2%)	448 (97.0%)	-1.69% (0.841)
Uncorrected cure rate (D28)	884 (92.9%)	376 (81.4%)	+7.67% (<0.001)
Uncorrected cure rate (D42)	746 (78.4%)	319 (69.0%)	+4.4% (<0.001)
Rate of new *Plasmodium sp.* infection (D42)	122 (12.8%)	109 (23.6%)	--
Treatment failure rate (D28) Actual failure rate	52 (5.5%) 26 (2.7%)	74 (16.0%) 12 (2.6%)	--
Treatment failure rate (D42) Actual failure rate	178 (18.7%) 53 (5.6%)	122 (26.4%) 17 (3.7%)	--
Number of patients with gametocytes	D0: 108 (11.4%) D7: 86 (9.0%) D14: 43 (4.6%) D28: 4 (0.4%) D42: 10 (1.1%)	D0: 60 (13.0%) D7: 19 (4.1%) D14: 1 (0.2%) D28: 2 (0.4%) D42: 7 (1.5%)	--
Modified Intention to Treat Population (mITT)			
n (%)	A/P* (n = 1027)	A/L* (n = 497)	Lower limit (p)
PCR-corrected cure rate (D14)	972 (94.6%)	483 (97.2%)	-4.64% (0.025)
PCR-corrected cure rate (D42)	921 (89.7%)	464 (93.4%)	-6.55% (0.019)
Uncorrected cure rate (D14)	969 (94.4%)	474 (95.4%)	-3.34% (0.405)
Uncorrected cure rate (D28)	910 (88.6%)	391 (78.7%)	+5.84% (<0.001)
Uncorrected cure rate (D42)	769 (74.9%)	330 (66.4%)	+3.55% (0.001)
Rate of new *Plasmodium sp.* infection (D42)	126 (12.0%)	112 (22.5%)	--
Treatment failure rate (D28) Actual failure rate	74 (7.2%) 38 (3.7%)	87 (17.5%) 14 (2.8%)	
Treatment failure rate (D42) Actual failure rate	203 (19.8%) 65 (6.3%)	138 (27.8%) 20 (4.0%)	--
Number of patients with gametocytes	D0: 121 (11.8%) D7: 91 (8.9%) D14: 47 (4.6%) D28: 6 (0.6%) D42: 11 (1.1%)	D0: 66 (13.3%) D7: 21 (4.2%) D14: 1 (0.2%) D28: 3 (0.6%) D42: 7 (1.4%)	--

* A/P = artenimol/piperaquine; A/L = artemether/lumefantrine

In the PP analysis, treatment compliance was 100% in both groups. In the mITT analysis it was 97.3% versus 99.0%.

3.1.2. Study DM040010

Study objective

This was an open, controlled, non-inferiority study (delta threshold = 5%), the objective of which was to compare the efficacy of the "artenimol/piperaquine" combination with that of the "artesunate + mefloquine" dual therapy in the treatment of uncomplicated *Plasmodium falciparum* malaria in an Asian population.

Main eligibility criteria

- Inclusion criteria:
  - aged from 3 months to 65 years
  - monoparasitic *P. falciparum* infection, confirmed microscopically (parasitaemia between 80 and 200,000/µl)

- Non-inclusion criteria:
  - pregnant or breastfeeding women
  - mefloquine treatment during the preceding 60 days
  - artesunate + mefloquine treatment during the previous 3 months
  - parasitaemia with *P. falciparum* trophozoites > 40/1000 red corpuscles

Treatments

Patients were randomly assigned (ratio of 2:1) to either the "artenimol/piperaquine" group or to the "artesunate + mefloquine" group.

Artenimol/piperaquine was administered on 3 consecutive days and at the same time of day and the dosages were adjusted according to weight (Table 4).

Artesunate was administered over 3 days and mefloquine was administered at the same time as the artesunate on only the last 2 days (Table 5).

Table 4: Daily dosage of artenimol/piperaquine (Study DM040010)

Body weight (kg)	Artenimol/piperaquine dosage	Number of tablets/day
5* - 6	80 mg PQP/10 mg DHA	½**
7 – 12	160 mg PQP/20 mg DHA	1**
13 - 23	320 mg PQP/40 mg DHA	1
24 - 35	320 mg PQP/40 mg DHA	2
36 – 75	320 mg PQP/40 mg DHA	3

*: 5 kg was the minimum weight to be included; **: paediatric dose
DHA = artenimol; PQP = piperaquine

Table 5: Daily dosage of the Artesunate + Mefloquine combination (Study DM040010)

Active ingredient	Daily dose	Number of individual doses dependent on weight
Artesunate	4 mg/kg/day	50 kg: 4 tablets of 50 mg/day 10 kg: 4 ml/day of suspension at 10 mg/ml
Mefloquine	25 mg/kg in 2 doses	50 kg: 5 tablets of 250 mg/day 10 kg: 5 ml/day of suspension at 50 mg/ml

Primary efficacy endpoint

The primary efficacy endpoint was the PCR-corrected clinical and parasitological cure rate on D63, defined as a negative parasitaemia on D63, regardless of the axillary temperature, without having first reached any of the early treatment failure, late treatment failure or late parasitological failure criteria.

The non-inferiority of artenimol/piperaquine with respect to the artesunate/mefloquine combination was established if the lower limit of the 97.5% confidence interval (unilateral test) of the difference between the PCR-corrected cure rates on D63 was greater than -5%.

Secondary endpoints, in particular:

- PCR-corrected cure rate on D28 and D42
- Uncorrected cure rate on D28, D42 and D63
- Percentage of patients experiencing treatment failure

Study population

Of the 1150 patients included, 769 patients were randomly assigned to the artenimol/piperaquine group and 381 to the artesunate/mefloquine group. The majority of patients were adults (over 75%). The mean age was 25.4 years (0.68-61.58) in the artenimol/piperaquine group versus 25.9 (1.03-62.43) in the artesunate + mefloquine group.

On inclusion, the median parasite density was similar in the two groups: 10,267 parasites/µl versus 9,797 parasites/µl. The number of patients with a starting haemoglobin rate < 70 g/l was 25 (3.4%) versus 7 (1.9%).

Results

In the PP population, the PCR-corrected cure rates were 98.7% (659/668) in the artenimol/piperaquine group versus 97.0% (326/336) in the artesunate + mefloquine group (p = 0.074). The lower limit of the unilateral confidence interval of the difference between the two groups was -0.39%, which established the non-inferiority of the artenimol/piperaquine combination with respect to the artesunate + mefloquine combination (non-inferiority margin predefined as -5%). Analysis of the intention to treat population (mITT) gave similar results: 97.0% (704/726) versus 95.3% (344/361), lower limit of the unilateral confidence interval of the difference = -0.84%.

The results for the secondary endpoints are presented in Table 7. The actual failure rate on D63 (early failures and late failures being regarded by PCR as recrudescences) was similar in both groups (1.65 versus 2.98). On D28, D42 and D63, the PCR-corrected cure rates and uncorrected cure rates favoured artenimol/piperaquine, in light of the less frequent recrudescences and new Plasmodium infections, in the artenimol/piperaquine group than in the artesunate + mefloquine group.

Table 6: Efficacy with respect to secondary endpoints (Study DM040010)

Per protocol population (PP)			
n (%)	A/P combination* (n = 668)	Ar/M combination* (n = 336)	p
PCR-corrected cure rate (D28)	667 (99.9%)	329 (97.9%)	0.001
PCR-corrected cure rate (D42)	663 (99.3%)	328 (97.6%)	0.031
Uncorrected cure rate (D28)	656 (98.2%)	315 (93.8%)	<0.001
Uncorrected cure rate (D42)	609 (91.2%)	287 (85.4%)	0.006
Uncorrected cure rate (D63)	504 (75.5%)	223 (66.4%)	0.002
Treatment failure rate (D63) Actual failure rate	86 (12.9%) 11 (1.7%)	53 (15.8%) 10 (3.0%)	-- --
Number of patients with gametocytes	D7: 48 (7.2%) D14: 25 (3.7%) D21: 10 (1.5%) D28: 7 (1.1%)	D7: 14 (3.9%) D14: 3 (0.8%) D21: 0 D28: 0	--
Modified Intention to Treat Population (mITT)			
n (%)	A/P combination* (n = 726)	Ar/M combination* (n = 361)	p
PCR-corrected cure rate (D28)	715 (98.5%)	348 (96.4%)	0.028
PCR-corrected cure rate (D42)	709 (97.7%)	346 (95.8%)	0.096
Uncorrected cure rate (D28)	693 (95.5%)	328 (90.9%)	0.003
Uncorrected cure rate (D42)	630 (86.8%)	291 (80.6%)	0.008
Uncorrected cure rate (D63)	516 (71.1%)	227 (62.9%)	0.006
Treatment failure rate (D63) Actual failure rate	105 (14.5%) 16 (2.2%)	58 (16.1%) 10 (2.8%)	-- --
Number of patients with gametocytes	D7: 52 (7.2%) D14: 28 (3.9%) D21: 12 (1.7%) D28: 9 (1.2%)	D7: 14 (3.9%) D14: 3 (0.9%) D21: 0 D28: 0	--

*A/P = Artenimol/Piperaquine; Ar/M = Artesunate + Mefloquine

3.2. Adverse effects

The tolerance data come mainly from phase III studies that had assessed the efficacy of artenimol/piperaquine.

Study DM040011

Tolerance was assessed in 1038 patients who had received at least one dose of artenimol/piperaquine and 510 patients who had received at least one dose of artemether + lumefantrine.

The incidence of adverse events was 79.3% in the artenimol/piperaquine group and 80.6% in the artemether + lumefantrine group.

In the majority of cases, these events were considered to be of low severity (50.3% versus 49.2%) or moderate severity (25.6% versus 28.4%). Serious adverse events were more common in the artenimol/piperaquine group than in the artemether + lumefantrine group (1.73% versus 1%). There was one death in each group.
Adverse events regarded as being treatment-related were reported in 71% of patients treated with artenimol/piperaquine and in 72% of patients treated with artemether + lumefantrine; the most common adverse effects in the artenimol/piperaquine group were: cough (32%), pyrexia (22.4%), flu syndrome (16.0%), *P. falciparum* infection (14.1%), diarrhoea (9.4%), vomiting (5.5%) and anorexia (5.2%). The adverse effects for which at least a 2% greater difference in incidence was observed between the two groups are presented in Table 7.

Table 7: Adverse effects for which at least a 2% greater difference in incidence was observed in the tolerance population

Organs	**A/P***	**A/L***
Adverse effects	**%**	**%**
Blood disorders	7.13	9.22
General disorders	23.60	25.69
Infections and infestations	36.51	41.57
Flu syndrome	15.99	13.92
P. falciparum malaria	14.07	19.41
Metabolic and nutritional disorders	5.49	7.25
Anorexia	5.20	7.25

*A/P = artenimol/piperaquine; A/L = artemether + lumefantrine

Study DM040010
Tolerance was assessed in 767 patients who had received at least one dose of artenimol/piperaquine and 381 patients who had received at least one dose of the artesunate + mefloquine combination.
The incidence of adverse events was 69% in the artenimol/piperaquine group and 72% in the artesunate + mefloquine group. In the majority of cases, these events were considered to be of low severity (55.2% versus 57.7%) or moderate severity (12.4% versus 12.6%).
Serious adverse events were more common in the artenimol/piperaquine group than in the artesunate + mefloquine group (1.6% versus 0.8%). However, the proportion of serious adverse events considered to be attributable to the treatments was similar in both groups (0.8% versus 0.8%). No deaths occurred in this study.
The incidence of adverse events considered to be treatment-related was 25% in both groups, the most common having been in the artenimol/piperaquine group: headache (3.9%), QTc-interval prolongation (3.4%), *P. falciparum* infection (3.0%), anaemia (2.8%), eosinophilia (1.7%), fall in haemoglobin (1.7%), sinus tachycardia (1.7%), asthenia (1.6%), decreased haematocrit (1.6%), pyrexia (1.5%), decreased erythrocyte count (1.4%). The adverse effects for which at least a 2% greater difference in incidence was observed between the two groups are presented in Table 8.

Table 8: Adverse effects for which at least a 2% greater difference in incidence was observed in the tolerance population

Organs	**A/P***		**Ar/M***	
Adverse effects	**n**	**%**	**n**	**%**
Gastrointestinal disorders	**12**	**1.6**	**21**	**5.5**
Nausea	2	0.3	12	3.1
General disorders	**21**	**2.7**	**16**	**4.2**
Asthenia	12	1.6	14	3.7
Nervous system disorders	**36**	**4.7**	**26**	**6.8**
Dizziness	4	0.5	13	3.4

*A/P = artenimol/piperaquine; Ar/M = Artesunate + Mefloquine

Cardiotoxicity
Cardiotoxicity, including QT-interval prolongation, was analysed in both phase III studies, but also specifically in a phase I study conducted in healthy volunteers (Study DM-09-006). In this phase I study, the maximum mean QTc-interval increases with respect to artemether + lumefantrine (RIAMET) were 36 msec when the treatment was taken with a fat-rich meal, 26 msec with a low-calorie diet and 13 msec after fasting.

In the two phase III studies, artenimol/piperaquine was more often associated with QT-interval prolongation than the comparator treatments. However, QT prolongation was significantly greater with artenimol/piperaquine than with the comparator treatments on D2, but not on D7 (Table 9).

Table 9: Mean measurements of QT prolongation in studies DM040010 and DM040011

	DM040010		DM040011	
(msec)	A/P	Ar/M	A/P	A/L
ΔQT D0-D2	54.18*	41.39	38.25*	30.54
ΔQTcB D0-D2	5.17*	-0.83	12.20*	6.95
ΔQTcF D0-D2	22.93*	14.65	23.64*	17.30
ΔQT D0-D7	27.62	33.03	23.61	24.95
ΔQTcB D0-D7	0.26	1.60	-1.12	-0.58
ΔQTcF D0-D7	10.47	13.39	9.58	10.47

*statistically significant difference with respect to the comparator treatment
A/P = Artenimol/Piperaquine, Ar/M = Artesunate + Mefloquine , A/L = Artemether + Lumefantrine

In the two studies, 7 patients (5 from Study DM040010 and 2 from Study DM04011) treated with artenimol/piperaquine had a QTc > 500 msec versus 2 patients in the artemether + lumefantrine group (Study DM04011) and none in the artesunate + mefloquine group (Study DM04010).
The incidence of clinical events associated with a QT prolongation was similar in various treatment groups (Table 10).

Table 10: Incidence of clinical events associated with a QT prolongation

Adverse events	**Study DM04010**		**Study DM04011**		**Aggregated data from the 2 studies**	
	A/P (n = 767)	**Ar/M (n = 381)**	**A/P (n = 1038)**	**A/L (n = 540)**	**A/P (n = 1805)**	**Comparators (n = 891)**
Sudden death	0 (0%)	0 (0%)	1 (0.1%)	1 (0.2%)	1 (0.1%)	1 (0.1%)
Syncope	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Epileptic seizure	0 (0%)	1 (0.3%)	4 (0.4%)	1 (0.2%)	4 (0.2%)	2 (0.2%)
Fever fit	0 (0%)	0 (0%)	2 (0.2%)	0 (0%)	2 (0.1%)	0 (0%)
Grand Mal epileptic seizure	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Dizziness	11 (1.4%)	24 (6.3%)	0 (0%)	0 (0%)	11 (0.6%)	24 (2.7%)
QT or QTc-prolongation	43 (5.6%)	16 (4.2%)	26 (2.5%)	13 (2.5%)	69 (3.8%)	29 (3.3%)
Conduction disorders	17 (2.2%)	5 (1.3%)	1 (0.1%)	1 (0.2%)	18 (1.0%)	6 (0.7%)
Cardiac events (total)	137 (17.9%)	45 (11.8%)	66 (6.4%)	37 (7.3%)	203 (11.3%)	82 (9.2%)
Serious cardiac events	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)

A/P = Artenimol/Piperaquine, Ar/M = Artesunate + Mefloquine , A/L = Artemether + Lumefantrine

Teratogenic effects

There are no relevant data available on the use of artenimol and piperaquine in pregnant women. The SPC for EURARTESIM mentions that, in light of animal data, EURARTESIM is liable to cause serious malformations when it is administered in the first trimester of pregnancy. Consequently, EURARTESIM should not be used during pregnancy if other appropriate and effective antimalarials are available (see sections 4.4 and 4.6 of the SPC).

Risk management plan (RMP)

Placing EURARTESIM on the market is conditional upon a risk management plan being put in place to monitor aspects relating to tolerance of use. These additional pharmacovigilance measures include observational studies, and in particular:

- a European cardiotoxicity study: combination of artenimol with piperaquine and QT prolongation, as well as factors predicting QT prolongation and its clinical impact,
- a tolerance study in patients (n = 10,000) showing signs and symptoms of uncomplicated malaria confirmed by a rapid diagnostic test (RDT), or with the aid of WHO diagnostic criteria (INESS study) if the RDT is unavailable,
- setting up of a European register to obtain further information on tolerance in pregnant women: in order to assess the prevalence of live births, congenital malformations and the fetal and maternal impact among pregnant women exposed to the artenimol/piperaquine combination at all times during pregnancy.

3.3. Conclusion

The artemisinine-based artenimol/piperaquine fixed-dose combination was assessed in the treatment of uncomplicated *Plasmodium falciparum* malaria during the course of two controlled but open studies carried out in an endemic malaria region. The primary efficacy endpoint was the 28-day PCR-corrected cure rate *(proportion of patients without parasite recrudescence).*

In the study carried out in a population of African children, the artenimol/piperaquine combination was not inferior (delta threshold = 5%) to the artemether/lumefantrine combination (RIAMET) in its impact on the 28-day PCR-corrected cure rate (95.7% versus 95.7%).

In the study conducted in a predominantly adult (> 75%) Asian population, the artenimol/piperaquine combination was not inferior (delta threshold = 5%) to the artesunate/mefloquine combination (not available in France) on the 63-day PCR-corrected cure rate (98.7% versus 97.0%).

In both studies the PCR-uncorrected cure rates were higher than in the artenimol/piperaquine comparator groups thanks to a smaller reinfection rate with the artenimol/piperaquine combination (post-treatment prophylaxis). On the other hand, the number of patients carrying circulating gametocytes (indicator of the effect on malaria transmission) appeared to be higher in the artenimol/piperaquine group than in the comparator groups.

Overall, the tolerance profile observed in these studies was comparable to that of the comparator drugs. QT prolongation, however, was greater in the first 48 hours with artenimol/piperaquine than with the comparator drugs, including two cases with a prolongation > 500 msec, though without any clinical relevance in these two studies. The main risk identified with this medicinal product is its cardiotoxicity. QT prolongation increases with the intake of fatty foods, which justifies recommending that it be taken on an empty stomach (see SPC).

These data, including those relating to tolerance, collected in an endemic region cannot readily be extrapolated to imported malaria, aspects of which and the conditions for collection are rather specific compared to the malaria in endemic regions.

There is no comparison available with atovaquone-proguanil (MALARONE) which is a front-line treatment, as an alternative to RIAMET, for imported uncomplicated *P. falciparum* malaria.

The Committee takes note of the risk management plan that has been set up with a view to better documentation and monitoring of aspects relating to tolerance of use, including cardiotoxicity and teratogenicity.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Malaria is a serious disease on account of its potential deadliness when *Plasmodium falciparum* is involved. Strains of *Plasmodium falciparum* that are resistant to classic treatments are becoming increasingly common.
This parasitic disease is now covered by a WHO monitoring programme.[4]
Dual therapy with artenimol and piperaquine (artenimol/piperaquine) falls within the framework of a curative treatment.

The efficacy/tolerance ratio is high so long as the contraindications (including congenital QTc-interval prolongation and certain heart disease antecedents), warnings and precautions for use are observed.

This medicinal product is a first-line therapy.

There are treatment alternatives.

Public health benefit:
The public health burden due to malaria is inconsiderable in France, given the limited number of cases (around 4600 cases in metropolitan France and 4000 cases in Guiana and Mayotte).[5,6]
Improving the fight against malaria constitutes a major worldwide public health priority, with malaria already being targeted by a control programme run by the World Health Organisation. The fight against the disease vector remains the principal means of reducing malaria transmission at community level and the management of malaria cases (diagnosis and treatment) remains an essential component of any anti-malaria campaign.
In France, the fight against malaria, which requires an integrated approach that comprises prevention and treatment with effective antimalarials, is not considered to be a public health priority established at national level.
However, in Guiana and Mayotte, where malaria is endemic, having access to artemisinine-based treatment combinations does constitute a response recognised by the WHO to the need to counter the risk that *P. falciparum* will become resistant to monotherapies and the spread of multiresistance to classic antimalarials.[7]
Based on the results of the 2 non-inferiority studies, the proprietary medicinal product EURARTESIM is unlikely to have any additional impact in terms of morbidity or mortality compared to the already existing alternatives.
Consequently, this proprietary medicinal product is not expected to benefit public health.

The actual benefit of this proprietary medicinal product EURARTESIM is substantial.

4.2. Improvement in actual benefit (IAB)

Given an efficacy comparable to that of RIAMET and the limited tolerance data – especially cardiac tolerance – despite its simplified administration regimen (once daily on an empty stomach, for 3 days), EURARTESIM does not offer any actual medical benefit (ASMR V) compared to RIAMET in the management of uncomplicated *P. falciparum* malaria.

[4] World Health Organization. Guidelines for the treatment of malaria.
[5] CNR Paludisme [French national reference centre on malaria]. Activity Report for 2010. Balance sheet for 2006-2010
[6] Tarantola A, et al. Le paludisme en France: métropole et outre-mer. Med Mal Infect, 2011(41): pp 301-306
[7] World Health Organisation guidelines for the treatment of malaria – 2011 – Second Edition – available at http://whqlibdoc.who.int/publications/2011/9789242547924_fre.pdf

4.3. Therapeutic use

In 2011, the WHO[8] recommended the following as first-line treatment for uncomplicated *Plasmodium falciparum* malaria:

- in endemic regions, an artemisinine-based combination.
  - artemether plus lumefantrine (RIAMET)
  - artesunate plus amodiaquine
  - artesunate plus mefloquine
  - artesunate plus sulfadoxine-pyrimethamine
  - dihydroartemisinin plus piperaquine (EURARTESIM)
- in non-endemic regions (in cases of imported malaria)
  - atovaquone + proguanil (MALARONE),
  - artemether + lumefantrine (RIAMET),
  - dihydroartemisinin + piperaquine (EURARTESIM),
  - quinine + doxycycline or clindamycin.

In October 2007, the SPILF[9] recommended the following as first-line treatment for uncomplicated *P. falciparum* malaria:

- In adults:
  - as first-line treatment: atavaquone/proguanil (MALARONE) or artemether/lumefantrine (RIAMET)
  - as second-line treatment: quinine (QUINIMAX, QUININE LAFRAN) or mefloquine (LARIAM)
  - as third-line treatment: halofantrine (HALFAN) in a hospital setting with ECG monitoring
- In children and infants:
  - as first-line treatment: mefloquine (LARIAM), atovaquone/proguanil (MALARONE), artemether/lumefantrine (RIAMET),
  - as second line treatment:
    - halofantrine (HALFAN) which, despite being presented as a suspension, is convenient for children, and is a second-line treatment on account of its cardiotoxicity and the risk of a relapse after a single treatment. It is only indicated in cases of necessity and under the supervision of an experienced team.
    - oral quinine (QUINIMAX), which requires perfect compliance with a seven-day treatment.
- In newborns: quinine IV, followed by switching to a single halofantrine treatment.

- Special cases:
  Travellers returning from areas where there were high levels of resistance to mefloquine and halofantrine (the Amazon, including Guiana, frontier regions between Thailand, Myanmar, Laos and Cambodia), first-line therapy: atovaquone/proguanil (MALARONE), artemether/lumefantrine (RIAMET), quinine in combination with doxycycline or clindamycin.

[8] WHO. Guidelines for the Treatment of Malaria. 2011, Second Edition. Available at http://www.who.int/topics/malaria/fr/

[9] Recommendations for clinical practice "management and prevention of imported *Plasmodium falciparum* malaria. 2007 review of the 1999 consensus conference. By the French-Language Society of Infectious Pathology".

Therapeutic use of EURARTESIM

In France, EURARTESIM is a first-line treatment for uncomplicated malaria caused by *P. falciparum* as an alternative to RIAMET or MALARONE in adults and children, and to LARIAM in children, mainly on account of its clinical efficacy and simple dosage regimen. However, data on tolerance, especially cardiac tolerance, are as yet limited (see SPC "Contraindications", "Special warnings and precautions for use").

4.4. Target population

The epidemiology of malaria in France presents two distinct situations:

- cases of imported malaria: about 4600 cases in 2010 in metropolitan France (an increase of 7.5% over the 2009 figure), of which 86% are caused by *P. falciparum* and 7.4% (181) of these are serious. In 2010, there were 8 reported deaths.[10]
- cases outside metropolitan France: about 3345 malaria cases were reported in French Guiana in 2009, over 50% of which were caused by *P. falciparum*. Mayotte is also an endemic region for malaria, with 400 to 800 cases annually (2003-2009), 90% of them caused by *P. falciparum.*[11]

The indication for the proprietary medicinal product EURARTESIM is restricted to uncomplicated *P. falciparum* malaria, without gastrointestinal disorders and in the absence of contraindications (including congenital QTc-interval prolongation and certain heart disease antecedents).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosages in the Marketing Authorisation.

[10] Passenger health and health recommendations 2011. BEH [weekly health bulletin] 2011; no. 18-19 of 17 May 2011
[11] Tarantola A, et al. Le paludisme en France: métropole et outre-mer. Med Mal Infect, 2011(41): pp 301-306