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TRANSPARENCY COMMITTEE

Opinion

19 February 2014

EURARTESIM 320 mg/40 mg, film-coated tablet

B/12 tablets (CIP: 34009 217 519 8 7)

Applicant: SIGMA-TAU FRANCE

INN	artenimol/piperaquine
ATC Code (2013):	P01BF05 (antimalarials: artemisinin and derivatives, combinations)
Reason for the review	**Inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17)
Indication concerned	**"Treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more."**

AB	**The actual benefit of EURARTESIM in the treatment of uncomplicated *Plasmodium falciparum* malaria is substantial.**
IAB	**Given its efficacy in the treatment of uncomplicated malaria, particularly in the case of multidrug-resistant strains and a lower risk of developing resistance with combinations containing artemisinin derivatives compared with traditional monotherapies, particularly in children and in malaria-endemic areas (particularly in French Guiana and Mayotte), the proprietary medicinal product EURARTESIM, like the proprietary medicinal product RIAMET, provides a minor improvement in actual benefit (IAB IV) in the treatment of uncomplicated *Plasmodium falciparum* malaria.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	27 October 2011 (centralised procedure)
Prescribing and dispensing conditions/special status	List I

ATC Classification	2013	
	P	Antiparasitic products, insecticides and repellants
	P01	Antiprotozoals
	P01B	Antimalarials
	P01BF	Artemisinin and derivatives, combinations
	P01BF05	Artenimol and piperaquine

02 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product EURARTESIM 320 mg/40 mg film-coated tablet on the list of medicines refundable by National Health Insurance.

This proprietary medicinal product has been included on the list of medicines approved for hospital use since April 2012 (Official Gazette of 4 April 2012). The Transparency Committee's opinion recommending this inclusion, delivered on 29 February 2012, concludes that:

- "The actual benefit of the proprietary medicinal product EURARTESIM is substantial."
- " Given an efficacy comparable with that of RIAMET and the limited safety data – especially cardiac safety – despite its simplified administration regimen (once daily on an empty stomach, for 3 days), EURARTESIM does not provide any improvement in actual benefit (IAB V) compared with RIAMET in the treatment of uncomplicated *P. falciparum* malaria."

03 THERAPEUTIC 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 guidelines on the choice of antimalarial treatment appropriate for local treatment of malaria."

04 DOSAGE

"*Administration*
EURARTESIM should be administered over three consecutive days for a total of three doses 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	1x160 mg/20 mg tablet
13 to < 24	320	40	1x320 mg/40 mg tablet
24 to < 36	640	80	2x320 mg/40 mg tablets
36 to < 75	960	120	3x320 mg/40 mg tablets
75 to 100	1280	160	4x320 mg/40 mg tablets
> 100	There are no data on which to base a dose recommendation in patients weighing > 100 kg		

**PQP = piperaquine; **DHA = dihydroartemisinin (or artenimol).*

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.
No more than two courses of EURARTESIM may be given within a 12 month period. A second course of EURARTESIM should not be given within 2 months after the first course, due to the long elimination half-life of piperaquine

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.

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

Method of administration
EURARTESIM should be taken orally with water and without food.
Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose. For patients unable to swallow the tablets, such as infants and young children, the tablets may be crushed and mixed with water. The mixture should be used immediately after preparation."

05 THERAPEUTIC NEED

Delayed or inappropriate treatment of uncomplicated *P. falciparum* malaria may evolve into a serious form which may be life-threatening for the patient.
The curative treatment of malaria depends on the clinical form of malaria, the area, whether or not it is possible to administer an oral treatment, the Plasmodiophora species involved and the foreseeable existence of drug resistance.

According to the WHO[1], the provision of treatment combinations containing a derivative of artemisinin is essential and is a recognised response to the need to counter the risk that *P. falciparum* will become resistant to monotherapies and the spread of multidrug resistance to traditional antimalarials. In France, the only combinations containing a derivative of artemisinin and with a Marketing Authorisation are the artemether + lumefantrine (RIAMET) and dihydroartemisinin + piperaquine (EURARTESIM) combinations.

In French Guiana and Mayotte, the only overseas departments and regions where malaria is endemic, the treatment is increasingly based on combinations of antimalarials with different mechanisms of action, taking into account the spread of multidrug resistance to traditional antimalarials and the risk of resistance to substances used in monotherapy. In this geographical area, the routine use of proprietary medicinal products RIAMET and EURARTESIM is a satisfactory alternative to the atovaquone-proguanil (MALARONE) combination.
In metropolitan France (non-endemic area) where the multidrug resistant strains are rarer among the cases of imported malaria and where the risk of selection does not arise in the absence of transmission, these dual therapies are a useful alternative to the atovaquone-proguanil (MALARONE) combination and mefloquine (LARIAM), especially given the poor tolerance sometimes observed with these treatments.

Given these points:
- In French Guiana and Mayotte (malaria-endemic areas), the artemether + lumefantrine (RIAMET) and dihydroartemisinin + piperaquine (EURARTESIM) combinations are the main curative treatments for uncomplicated *P. falciparum* malaria.
- In metropolitan France, the atovaquone + proguanil (MALARONE), artemether + lumefantrine (RIAMET) and dihydroartemisinin + piperaquine (EURARTESIM) combinations, as well as mefloquine (LARIAM) are the main curative treatments for uncomplicated *P. falciparum* malaria.

Currently, none of these reference medicines are refundable as pharmacy only medicines for the curative treatment of uncomplicated *P. falciparum* malaria. Only the proprietary medicinal products MALARONE and LARIAM are refundable as pharmacy only medicines for malaria prophylaxis by National Health Insurance in French Guiana. In addition, their inclusion on the list of medicines refundable by the whole French National Health Insurance system could facilitate access to treatment for the patients able to be cared for in outpatients and thus avoid hospitalisations.

[1] WHO (World Health Organization). Guidelines for the treatment of malaria - 2nd ed. March 2010.

06 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of EURARTESIM are the curative treatments for **first-line** uncomplicated *P. falciparum* malaria according to recommendations from the WHO[1,2] and the SPILF [French Speaking Infectious Disease Society][3], **and are available in France:**

NAME (INN) *Company*	Date of TC opinion (reason for the review)	AB	IAB	Reimbursement
MALARONE and generic drugs (atovaquone + proguanil) *GlaxoSmithKline*	19/03/2008 (re-assessment*)	Substantial	-	Hospital use
	18/02/2009 (indication extension for paediatrics)		IABV in therapeutic use	
LARIAM (mefloquine) *Roche*	19/03/2008 (re-assessment*)	Substantial	-	Hospital use
RIAMET (artemether + lumefantrine) *Novartis Pharma S.A.S.*	14/03/2007 (re-assessment**)	Substantial	-	Hospital use
	16/07/2008 (indication extension for paediatrics)		IAB IV in therapeutic use	

* Re-assessment at the request of the Directorate-General for Health in the prophylactic treatment of malaria for French Guiana and Mayotte National Health Insurance.

** Re-assessment at the request of the Directorate-General for Health in view of an inclusion on the list of medicines approved for hospital use.

[2] WHO (World Health Organization). International travel and health. January 2012.

[3] SPILF (Société de Pathologie Infectieuse de Langue Française). Prise en charge et prévention du paludisme d'importation à *Plasmodium falciparum* : recommandations pour la pratique clinique 2007 (révision de la Conférence de Consensus 1999) - Texte long. November 2007.

07 SUMMARY OF PREVIOUS ASSESSMENTS

In its previous opinions, the conclusions of the Committee were as follows:

Date of opinion	**29 February 2012 (Inclusion for hospital use in adults, children and infants 6 months and over and weighing 5 kg or more)**
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 traditional treatments are becoming increasingly common. This parasitic disease is now covered by a WHO monitoring programme[1]. Dual therapy with artenimol and piperaquine (EURARTESIM) is intended as curative treatment. The efficacy/adverse effects ratio is high so long as the contraindications (including congenital QTc-interval prolongation and a history of certain heart diseases), warnings and precautions for use are observed. This is a first-line therapy. There are treatment alternatives. Public health benefit The public health burden of malaria is inconsiderable in France, given the limited number of cases (around 4600 cases in metropolitan France and 4000 cases in French Guiana and Mayotte)[4,5]. 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 French Guiana and Mayotte, where malaria is endemic, having access to artemisinin-based treatment combinations does constitutes 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 multidrug resistance to traditional antimalarials.[6] Based on the results of the two non-inferiority studies, the proprietary medicinal product EURARTESIM is unlikely to have any additional impact in terms of morbidity or mortality compared with the already existing alternatives. Consequently, this proprietary medicinal product is not expected to benefit public health. The actual benefit of the proprietary medicinal product EURARTESIM is substantial.
IAB	"Given an efficacy comparable to that of RIAMET and the limited safety data – especially cardiac safety – despite its simplified administration regimen (once daily on an empty stomach, for 3 days), EURARTESIM does not provide any improvement in actual benefit (IAB V) compared with RIAMET in the treatment of uncomplicated *P. falciparum* malaria. "

[4] CNR Paludisme. Rapport d'activités. Année 2010. Bilan 2006-2010.
[5] Tarantola A, et al. Le paludisme en France : métropole et outre-mer. Med Mal Infect, 2011(41) : pp 301-306.
[6] Organisation mondiale de la Santé Directives pour le traitement du paludisme – 2011- 2ème édition - Available at http://whqlibdoc.who.int/publications/2011/9789242547924_fre.pdf

08 ANALYSIS NEW AVAILABLE DATA

08.1 Efficacy

8.1.1 Summary of data taken into consideration in the Transparency Committee's previous opinion (opinion of 29 February 2012)

The clinical data evaluating the efficacy of the dihydroartemisinin + piperaquine combination in the treatment of uncomplicated *P. falciparum* malaria were reviewed by the Committee in its previous opinion, dated 29 February 2012. They are based on two phase III, open-label studies performed in a strong malaria-endemic area:

- a controlled study performed in a population of African children, which showed the non-inferiority (delta threshold = 5 %) of the dihydroartemisinin + piperaquine combination versus the artemether + lumefantrine (RIAMET) combination on the PCR-corrected cure rates measured on D28 (95.7 % *versus* 95.7 %).
- a controlled study performed in an Asian, mainly adult, population, which showed the non-inferiority (delta threshold = 5 %) of the dihydroartemisinin + piperaquine combination versus the artesunate + mefloquine combination (not available in France) on the PCR-corrected cure rates measured on D63 (98.7 % *versus* 97.0 %).

8.1.2 New data

The company has not provided any new clinical efficacy data.

08.2 Adverse effects

SPC data:
The most common adverse effects are: cough, pyrexia, headaches, anaemia, asthenia, vomiting, abdominal pain and QTc-interval prolongation. These effects are generally not very severe. Effects such as cough, pyrexia, headaches, anaemia, asthenia and digestive disorders are consistent with those which may be expected in patients presenting with acute malaria.
No change has been made to the SPC since the Committee's previous opinion (29 February 2012).

Data from pharmacovigilance:
The company has provided the last periodic safety update report (PSUR) about EURARTESIM, covering the period of 1 November 2012 to 30 April 2013. The analysis of these data has not shown any new signal.

Some serious risks have undergone special monitoring, particularly within the context of a risk management plan (RMP):

- Identified risk:
  - QTc-interval prolongation: two non-serious cases and of a moderate intensity have been reported within the context of a phase I study.
- Potential risks:
  - Neurotoxicity: no case has been reported;
  - Phototoxicity: no case reported;

- Toxicity for reproduction: no significant difference was shown during the studies conducted in Africa and Indonesia to compare EURARTESIM with other antimalarial treatments (other combinations containing artemisin derivatives or a pyrimethamine-based combination). The main adverse events observed among the 449 patients treated with EURARTESIM during the second or third trimester of pregnancy were one case of congenital umbilical hernia (0.2 %), one case of perinatal mortality (0.2 %) and seven cases of stillbirth (1.6 %).
  For the record, the SPC 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 effective and appropriate antimalarials are available (see sections 4.4 and 4.6 of the SPC).

08.3 Usage data

According to the GERS [Group for the Production and Elaboration of Statistics] data (pharmacies and hospitals), around 1430 boxes of EURARTESIM were sold in France between June 2012 and September 2013.

08.4 Summary & discussion

These new data are not likely to change the Transparency Committee's previous conclusions (opinion of 29 February 2012) on the efficacy and safety of EURARTESIM in the treatment of uncomplicated *P. falciparum* malaria and allow the use of this medicinal product in outpatients to be considered.

09 THERAPEUTIC USE

The scientific data acquired on malaria and its treatment methods have also been taken into account.[1,2,3,7] Therapeutic use of EURARTESIM has not been changed since the Committee's previous opinion (29 February 2012).

The WHO recommends the following as first-line therapy for uncomplicated *P. falciparum* malaria (in 2011):

- In malaria-endemic areas, a combination containing a derivative of artemisinin:
  - artemether + lumefantrine (RIAMET)
  - dihydroartemisinin + piperaquine (EURARTESIM)
  - artesunate + amodiaquine (not available in France)
  - artesunate + mefloquine (not available in France)
  - artesunate + sulphadoxine-pyrimethamine (not available in France)
- In non-endemic areas in cases of imported malaria, a combination of:
  - atovaquone + proguanil (MALARONE)
  - artemether + lumefantrine (RIAMET)
  - dihydroartemisinin + piperaquine (EURARTESIM)
  - oral quinine + doxycycline or clindamycin

The SPILF recommends the following as first-line therapy in France for uncomplicated *P. falciparum* malaria (in 2007):

- In adults:
  - 1st-line: atovaquone + proguanil (MALARONE) or artemether + lumefantrine (RIAMET)
  - 2nd-line: oral quinine or mefloquine (LARIAM)
  - 3rd-line: halofantrine (HALFAN)
- In children and infants:
  - 1st-line: mefloquine (LARIAM), atovaquone + proguanil (MALARONE) or artemether + lumefantrine (RIAMET)
  - 2nd-line: halofantrine (HALFAN) or oral quinine
- In newborns:
  - 1st-line: quinine IV, followed by switching to a single halofantrine treatment (HALFAN)
- Special cases: travellers returning from areas where there are high levels of resistance to mefloquine and halofantrine (the Amazon, including French Guiana, frontier regions between Thailand, Myanmar, Laos and Cambodia):
  - 1st-line: atovaquone + proguanil (MALARONE), artemether + lumefantrine (RIAMET) or oral quinine + doxycycline or clindamycin

It should be noted that proprietary medicinal product EURARTESIM was not available in France when the SPLIF recommendation was drafted in 2007. In its opinion of 15 February 2012 relating to the application for inclusion for hospital use of this proprietary medicinal product, the Transparency Committee had concluded that "EURARTESIM is a first line therapy for uncomplicated *P. falciparum* malaria as an alternative to RIAMET or MALARONE in adults and children, and LARIAM in children, mainly because of its clinical efficacy and a simple dosing regimen. However, data on safety, especially cardiac safety, are as yet limited (see SPC “Contraindications”, “Special warnings and precautions for use”)."

◗ Conclusion:

EURARTESIM retains its role in the treatment of uncomplicated *P. falciparum* malaria. Its availability to pharmacies aims to facilitate access to this medicine for certain patients who are able to be treated in outpatients and avoid hospitalisations. The Committee issues a reminder that the

[7] InVS (Institute de Veille Sanitaire) [Health Monitoring Institute]. Recommandations sanitaires pour les voyageurs, 2013. Avis du Haut Conseil de la Santé Publique (HCSP [High Council for Public Health]) du 25 avril 2013. Bulletin Épidémiologique Hebdomadaire (BEH [Weekly Epidemiological Report]). 4 juin 2013/n° 22-23.

outpatient treatment of adults is restricted to patients with no hospitalisation criteria[8] and that hospitalising young children is recommended in all cases. Any delay in the treatment of malaria can be fatal if *P. falciparum* is involved. Uncomplicated forms, with no digestive intolerance, are treated orally. Severe malaria is treated by intravenous quinine in intensive care.

[8] Hospitalisation criteria: sign of severity, at-risk area, digestive intolerance preventing oral treatment, sociocultural or economic factors compromising the purchase of and/or good compliance with treatment, people living alone, distance from a hospital, no medicines readily available in pharmacies, impossibility of follow-up, particularly on the 3rd and 7th days of treatment, platelets < 50,000/mm3, haemoglobin < 10 g/dl, creatinine > 150 µmol/l, parasitaemia > 2%.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ *P. falciparum* malaria is a serious disease on account of its potential deadliness. Strains that are resistant to traditional treatments are becoming increasingly common. This parasitic disease is now covered by a WHO monitoring programme.[1]

◗ The dihydroartemisinin + piperaquine (EURARTESIM) combination is intended as curative treatment for uncomplicated *P. falciparum* malaria.

◗ The efficacy/adverse effects ratio of this proprietary medicinal product is high so long as the contraindications (including congenital QTc interval prolongation and a history of certain heart diseases), warnings and precautions for use are observed.

◗ This is a first-line therapy.

◗ Alternative medicinal products to this proprietary medicinal product exist.

◗ Public health benefit:
The public health burden due to malaria is inconsiderable in France, given the limited number of cases (around 3500 cases each year in France).[9,10,11,12,13,14,15]
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 French Guiana and Mayotte, where malaria is endemic, having access to artemisinin-based treatment combinations does constitutes 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 multidrug resistance to traditional antimalarials[1].
Given the available data, a theoretical impact is expected on the reduction of morbidity and mortality linked to uncomplicated *Plasmodium falciparum* malaria. Given the small number of subjects potentially affected by treatment with artemisinin-based combinations in France, no impact on a population level is expected.
Consequently, given the response which EURARTESIM could provide to the specific need for the affected populations in French Guiana and Mayotte, a minor public health benefit is expected for this proprietary medicinal product.

[9] InVS (Health Monitoring Institute). CNR Paludisme - Rapport d'activités - Année 2011. April 2011.
[10] InVS (Health Monitoring Institute). Paludisme d'importation à la Réunion - Bilan de l'année 2012. Point épidémiologique. N°18 au 25 avril 2013.
[11] InVS (Health Monitoring Institute). Surveillance du paludisme à Mayotte : bilan 2012. Point épidémiologique. N° 17 au 25 avril 2013.
[12] InVS (Health Monitoring Institute). Surveillance du paludisme en Guyane - Bulletin périodique : juin - août 2012. Le point épidémiologique. N° 02 / 2012.
[13] InVS (Health Monitoring Institute). Surveillance du paludisme en Guyane - Bulletin périodique : septembre 2012 - janvier 2013. Le point épidémiologique. N° 01 / 2013.
[14] InVS (Health Monitoring Institute). Surveillance du paludisme en Guyane - Bulletin périodique : janvier - mars 2013. Le point épidémiologique. N° 02 / 2013.
[15] InVS (Health Monitoring Institute). Surveillance du paludisme en Guyane - Bulletin périodique : avril - juin 2013. Le point épidémiologique. N° 03 / 2013.

Taking account of these points, the Committee considers that the actual benefit of EURARTESIM is substantial in the indication and at the dosages in the Marketing Authorisation.

The Committee recommends inclusion of EURARTESIM 320 mg/40 mg film-coated tablet on the list of medicines reimbursed by National Health Insurance in the indication and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

Given its efficacy in the treatment of uncomplicated malaria, particularly in the case of multidrug-resistant strains and a lower risk of developing resistance with combinations containing artemisinin derivatives compared with traditional monotherapies, particularly in children and in malaria-endemic areas (particularly in French Guiana and Mayotte), the proprietary medicinal product EURARTESIM, like the proprietary medicinal product RIAMET, provides a minor improvement in actual benefit (IAB IV) in the treatment of uncomplicated *Plasmodium falciparum* malaria.

010.3 Target population

The target population of EURARTESIM is made up of patients with uncomplicated *P. falciparum* malaria in adults, children and infants weighing 5 kg or more.
The epidemiology of malaria in France distinguishes between two situations: the imported cases and native cases.

Imported cases (metropolitan France and overseas departments and regions where malaria is not endemic):
In metropolitan France, 1891 cases of imported malaria were reported in 2011 (including four deaths), 84% of which were due to *P. falciparum.*[9] Taking account of any under-reporting, the number of cases of imported malaria can be estimated at 3559 for 2011.[9]
On Reunion Island, 47 cases of imported malaria were reported in 2012 (including 1 death), 94% of which were due to *P. falciparum.*[10]
In Mayotte, 47 cases of imported malaria were reported in 2012 (no deaths), 91% of which were due to *P. falciparum.*[11]

Native cases (overseas departments and regions where malaria is endemic):
In French Guiana, 1048 cases of native malaria were reported between June 2012 and June 2013 (no deaths), 29% of which were due to *P. falciparum.*[12,13,14,15]
In Mayotte, 25 cases of native malaria were reported in 2012 (no deaths), 91% of which were due to *P. falciparum.*[11]

Conclusion:
The number of cases of *P. falciparum* malaria (metropolitan France and overseas departments and regions) would be around 3500 a year.
This estimation does not take into account the potential underestimation in the overseas departments and regions.
In practice, the target population of EURARTESIM is smaller because of the absence of indication in the treatment of severe malaria, the absence of indication in children under 5 kg, and the potential contraindications, including congenital QTc-interval prolongation and a history of certain heart diseases. This target population however is difficult to quantity.

In conclusion, on the basis of the most recent epidemiological data, **the target population of EURARTESIM can be estimated to be up to 3500 patients a year.**

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

The boxed packaging of 12 tablets is suitable for the prescribing conditions in patients weighing 75kg or more.
It is not suitable for the prescribing conditions as regards dosage and treatment duration in patients weighing 75kg and under.

◗ Other requests

The Committee regrets that there is no provision for pharmacies in metropolitan France of MALARONE and LARIAM alternatives for the curative treatment for uncomplicated *Plasmodium falciparum* malaria.