APPLICATION FOR INCLUSION OF ARTEMETHER/LUMEFANTRINE POWDER FOR ORAL SUSPENSION FOR PAEDIATRIC USE IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

Generic name: artemether/lumefantrine paediatric powder for suspension

Trade name: Co-Artesiane® suspension

Contact Information:

Dafra Pharma nv
Slachthuisstraat 30/7
B-2300 Turnhout
Belgium

Tel: +32(0)14 61 78 20
Fax: +32(0)14 61 78 59
info@dafra.be
www.dafra.be

Table of Contents

APPLICATION FOR INCLUSION OF ARTEMETHER/LUMEFANTRINE POWDER FOR ORAL SUSPENSION FOR PAEDIATRIC USE IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

1. Summary statement of the proposal for inclusion

The essential drug artemether/lumefantrine fixed dose combination (fdc) tablets, also known as Coartem®, urgently required a similar fdc preparation suitable for children. A syrup would be ideal but this cannot be made for reasons of stability at longer term and under tropical conditions. Therefore a powder for oral suspension, containing artemether/lumefantrine in the same 1/6 ratio, called Co-Artesiane®, has been made available. After adding water a stable oral suspension is obtained suitable for children. The product proposed fulfils all criteria.

2. Name of the focal point in WHO submitting or supporting the application

3. Name of the organisation(s) consulted and/or supporting the application

4. International Nonproprietary Name (INN, generic name) of the medicine

Artemeter/lumefantrine powder for oral suspension is a fixed dose combination of two antimalarial drugs with the INN names artemether and lumefantrine (benflumetol). In the public market the product is known under the brand name Co-Artesiane® oral suspension.

5. Formulation proposed for inclusion: powder for oral suspension for paediatric use

5.1. Chemical characteristics

Artemether (β-artemether) is the most active derivative of the artemisinines, a new class of antimalarial drugs derived from artemisinin. The latter compound is extracted from the plant *Artemisia annua* and artemether is prepared semi-synthetically.

Lumefantrine is a synthetic aryl amino alcohol similar to mefloquine and halofantrine.

5.2. <u>The formulation for paediatric use only</u>

Artemether/lumefantrine powder for oral suspension is available as a dry yellow powder containing 7.9 mg β-artemether/ 47.4 mg lumefantrine per g powder. After addition of water a stable oral suspension is made.

Two qualitative and quantitative compositions are available:

- Artemether/lumefantrine powder for oral suspension *60 ml* (fixed dose combination of 180 mg β-artemether and 1080 mg lumefantrine)

Ingredients	**mg**	**Quality reference**
<u>Active substances</u>		
β-artemether	180,0	Int. Ph.
Lumefantrine	1080,0	Internal monograph (based on Eur.Ph.)
<u>Excipientia</u>		
Saccharose		Eur. Ph.
Microcrystalline Celluse		Eur. Ph.
Citric acid		Eur. Ph.
Xanthan gum		Eur. Ph.
Methyl-p-hydroxybenzoate		Eur. Ph.
Propyl-p-hydroxybenzoate		Eur.Ph.
Coconut flavour		Eur. food grade
Silicium colloidal anhydrous		Eur.Ph

- Artemether/lumefantrine powder for oral suspension *120 ml* (fixed dose combination of 360 mg β-artemether and 2160 mg lumefantrine).

Ingredients	mg	Quality reference
Active substances		
β-artemether	360,0	Int. Ph.
Lumefantrine	2160,0	Internal monograph (based on Eur.Ph.)
Excipientia		
Saccharose		Eur. Ph.
Microcrystalline Cellulose		Eur. Ph.
Citric acid		Eur. Ph.
Xanthan gum		Eur. Ph.
Methyl-p-hydroxybenzoate		Eur. Ph.
Propyl-p-hydroxybenzoate		Eur.Ph.
Coconut flavour		Eur. food grade
Silicium colloidal anhydrous		Eur.Ph

Function of the excipients:

Excipientia	Function
Saccharose	Filler
Microcrystalline cellulose	Disperser, mucilage provider
Citric acid	Buffer
Xanthan gum	Mucilage provider
Methyl-p-hydroxybenzoate	Preservatives
Propyl-p-hydroxybenzoate	Preservatives
Coconut flavour	Flavour
Silicium colloidal anhydrous	Glidant

5.3. Stability of the formulation/suspension

FORMULATION:

Stability tests show that the formulation in a closed vial is stable for 3 years at room temperatures, protected from light. The manufacturer recommends that it should not be stored above 30^{o} C.

SUSPENSION:

Stability stress tests were carried out. After reconstitution and/or first opening of the product Co-Artesiane® powder for oral suspension, the powder is suspended with water and kept at 30°C in a humidity room of 65% during 30 days. Samples are taken at time zero and then at time points 14 days and 30 days. Artemether and lumefantrine were assayed by HPLC .

As can be seen the assay gives adequate results (concentrations of the active pharmaceutical ingredient should be above the 90 % level) so the product is perfectly stable for the time period considered.. Even during storage at 30°C the made up suspension is keeping its full quality over a period of 30 days.

Batch Co-Artesiane	% Artemether	% Lumefantrine
T0	100	100
T14	96	96
T30	92	97

Results at time T=0, T= 14 days and T= 30 days. Results are expressed in percentage compared to the value at time zero.

6. International availability – sources, if possible manufacturers

6.1. Sources and manufacturers

Dafra Pharma has the capacity to produce the formulation according to Good Manufacturing Practice (GMP) and in sufficient large quantities. The formulation artemether/lumefantrine powder for oral suspension is manufactured under licence by MPF bv, Appelhof 13, NL-8465 RX Oudehaske, Netherlands and distributed by Dafra Pharma nv, Slachthuisstraat 30/7, B-2300 Turnhout, Belgium. Cambrex Profarmaco Ltd, Industriepark Roosveld 2/6, B-3400 Landen, Belgium) and Saokim Pharma Ltd, Vinh phuc pro, nDong da district-Hanoi, Vietnam

are responsible for the production of the raw material β-artemether. Lumefantrine is manufactured by Chongquing Porton Industry Co Ltd, Majiagou, Qingping Town, Hechuan, Chongqing, China.

6.2. History of the product

Rational for the new oral suspension powder:

The development of artemether/lumefantrine powder for oral suspension started in 2001, based on two important facts:

> Artemether and lumefantrine do not interact in a negative manner in tablets. This could be demonstrated in stability studies of the artemether/lumefantrine tablets. The product Coartem® from Novartis has an expiry date of 2 years and Dafra's explorations in this field gave similar results.
>
> Artemether in a powder for oral suspension is stable for at least 2 years. Dafra Pharma developed in 1999 Artesiane® powder for oral suspension containing Artemether. Addition of water to this artemether powder generates a "stable" oral suspension. The floating API particles (and all not water soluble particles) were kept in suspension in such a manner that precipitation of these floating particles does not take place.

Based on these two facts it would be obvious to evaluate whether the simple addition of lumefantrine to the already existing artemether (Artesiane®) powder for oral suspension would be feasible. A stability study of the powder and of the a reconstituted oral suspension gave the answer. Both are stable. Results from the oral suspension showed that no breakdown of any of the API's takes place within 4 weeks when kept at 30°C. Results from official stability studies (40°C, 75% humidity for 6 months and 2 years at 30°C and 65% humidity) showed that the product is stable. One critical point in the development was the changing of the bitter taste of the artemether/lumefantrine oral suspension. Orange flavour, used in the first made artemether only powder for oral suspension was not strong enough to compensate the bitterness. A new taste, coconut flavour, was introduced.

In retrospect there was rather little exploratory work involved. The fact that Artemether and lumefantrine do not interact in an appreciable manner made the development rather straightforward.

Marketing History:

The licences for production and export were obtained from the Belgian authorities on the 24th of April in 2004. During the period 24 April 2004 and 31 August 2006 over 150.000 treatment suspensions of the combination were sold worldwide, meanly on the private market in Africa. It is expected that in the next years this number will grow exponentially because of:

- There are still registration procedures running in a number of Asian and a few African countries.
- The WHO strongly recommends the use of Artemisinin-based Combination Therapies and more in particular the artemether/lumefantrine combination therapy, instead of monotherapies for treatment of uncomplicated *P.falciparum* malaria. Since that time many countries switched to the recommended first line treatment artemether/lumefantrine. This caused an increase in the export of the artemether/lumefantrine fdc tablet formulation. However, the tablet formulation is not recommended in small children below 10 kg, so there is a group were no recommended treatment is available. The artemether/lumefantrine fdc oral suspension formulation can be used for treatment of small children below 10 kg and is easy to administer. For this reason, the need for paediatric formulation will follow the trend of the tablet formulation.
- Dafra Pharma had already built op a market for the artemether only powder for oral suspension. During the period 1 January 2004 and 31 Augustus 2006 a total of 1.605.147 oral suspension bottles were sold. Because the WHO recommends since January 2006 the use of combination therapies for treatment of uncomplicated *P. falciparum* malaria, the active promotion of this formulation was stopped and the product is being withdrawn progressively. It can be expected that all countries accepting the artemether only oral suspension will switch gradually to the new combination artemether/lumefantrine powder for oral suspension in the course of 2006 - 2007.

6.3. International availability and production capacity

The current maximal production capacity is 260.000 oral suspensions per month (3 million bottles per year). Dependent on the quantities needed the product can be scaled up to 10 million bottles per year ore more when needed. There is no restriction on the availability of the raw materials artemether and lumefantrine.

7. Whether listing is requested as an individual medicine or as an example of a group

Artemether/lumefantrine powder for oral suspension must be listed as an example of the pharmacotherapeuric group antimalarial medicines for curative treatment, subdivision artemether/lumefantrine combination therapy. In this group a tablet containing 20mg artemether and 120mg lumefantrine is available. However, this tablet is not suitable in children below 10kg. So there is a group were no recommended treatment is available. For this reason a paediatric oral suspension for the treatment of small children is ideal for inclusion on the WHO Model List for Essential Medicines for children.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Malaria threatens almost half the world population and is one of the most important infectious diseases worldwide. The annual number of malaria cases worldwide is estimated to be around 500 million and over 90 % of malaria cases and the great majority of malaria deaths occur in sub-Saharan Africa. The mortality, recently estimated at 1.5 million people every year, has risen in recent years, probably due to increasing resistance to the common classical antimalarial drugs. In *P. falciparum* infection, resistance has been observed to almost all currently used antimalarials, like amodiaquine, chloroquine, mefloquine, quinine and sulfadoxine/pyrimethamine (SP).

Fortunately, Chinese scientist isolated a new very potent and effective anti-malarial drug out of the plant *Artemisia Annua*, known as artemisinin. Artemisinin and its derivatives are very potent and effective anti-malarial drugs (Heemskerk W et al, 2006; Krishna S, 2004 and

WHO, 2006) and for patients with *P. falciparum* malaria resistant to the common antimalarial drugs, the use of artemisinin and its derivatives is essential (WHO, 2000b; 2001a, b).
The importance of artemisinin and its derivatives was recognised by the WHO Expert Committee on Essential Drugs (WHO 2000a). Artemisinins were first available as monotherapy. However, monotherapy must be adhered to for at least five days, but often seven days. In practice, adherence to these relatively long treatment regimens is low. This behaviour may result in late recrudescence and in developing resistance.
Therefore, the WHO recommended the use of Artemisinin-based Combination Therapies (ACT's). These ACT's have several distinct advantages in that: (1) they produce rapid clinical and parasitological cure; (2) there is as yet no documented parasite resistance to them and resistance to the combinations is most unlikely to occur; (3) they reduce gametocyte carrier rates and (4) they are generally well tolerated (Heemskerk W et al, 2006; Krishna S, 2004 and WHO 2001a and 2006). At present, only the ad hoc combination of artesunate with mefloquine, amodiaquine, chloroquine or SP were widely used operationally in areas of multidrug resistant *P. falciparum* malaria. However, fixed combinations of artemisinin derivatives should have operational advantages since they should be easier to use and provide greater compliance in the target populations than ad hoc combinations (WHO, 2001a and b).

Artemether/lumefantrine (Coartem®) is manufactured by Novartis and is the first fixed-dose antimalarial combination (fdc) of an artemisinin derivative which has been widely studied and registered for the treatment of acute multi-drug resistant *P. falciparum* malaria. The importance of the combination of artemether/lumefantrine in a fdc tablet formulation was in 2001 emphasised by the informal consultation on Antimalarial Drug Combination Therapy and the WHO recommended guidelines for its use (WHO, 2001a) In May 2001, Novartis made a unique public-private collaboration agreement with the World Health Organization (WHO) in the fight against malaria. The essence of the agreement is that Novartis commits to make Coartem® available on a "not-for-profit" basis for distribution to public sector agencies of malaria-endemic developing countries. In April 2002 the artemether/lumefantrine tablet (Coartem®) was added to the Model List of Essential Drugs in April 2002. The drug has passed extensive efficacy and safety trails, and has been approved by more than 75 regulatory agencies. There are two different treatment regimes available: the four-dose and the six-dose regimen. Since 2001 it is known that the six-dose regimen has the highest efficacy and reliability and is therefore recommended by the WHO as the standard treatment.

Dafra Pharma in corporation with Biostatistical Centre, University of Leuven, Belgium and Fondation ACT-ion Afrique, Bruxelles, Belgium performed in 2006 a multi-treatment meta-analysis to assess the relative effect of each combination therapy to any other combination therapy (Lesaffre E et al, 2006). An analysis based on papers published until December 2005 was done and is reported. The results of the combination therapies were presented to artesunate + SP as standard, but other standards could have been taken. From the data it is clear that the most attractive result for the variable ACPR (and thus lack of recrudescence) is given by the combination artemether/lumefantrine (figure 1).

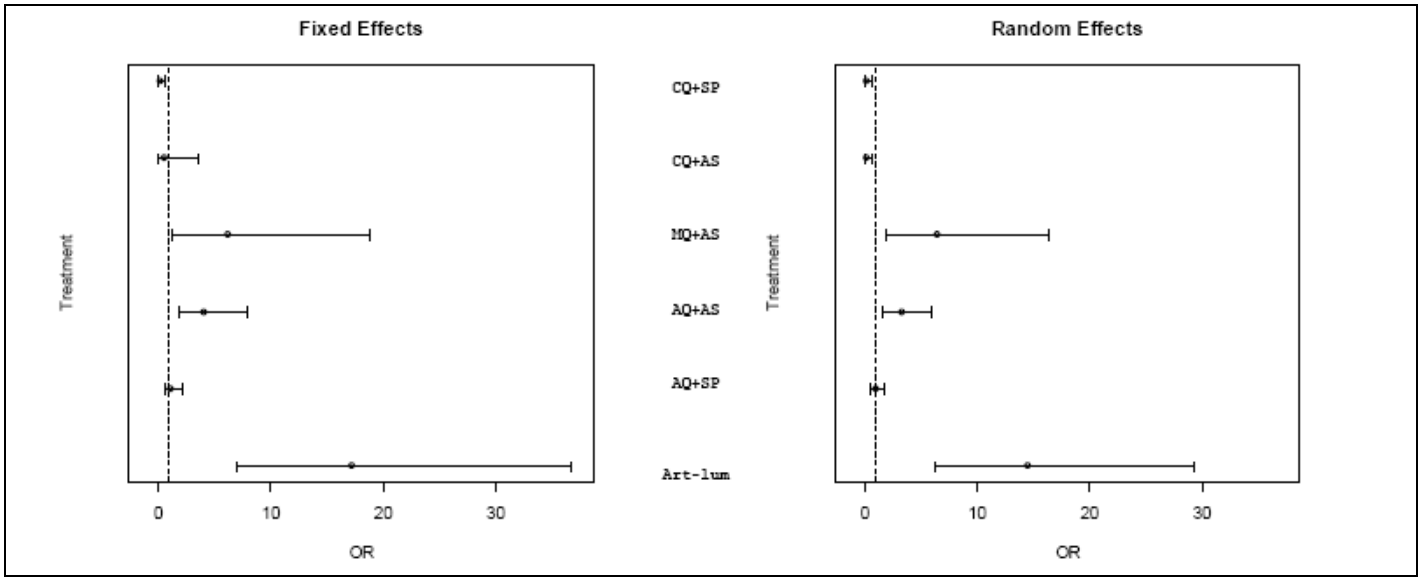


Figure 1: Posterior information for odds ratios of each combination treatment with respect to the combination of SP + AS (=dotted line) for ACPR at day 28 PCR corrected. Irrespective of taken into account fixed or random effects, the combination AL gives the best results for the variables concerned. LEGEND: CQ = chloroquine, SP = sulfadoxine/pyrimethamine, AS = artesunate, MQ = mefloquine, AQ = amodiaquine, Art = artemether and Lum = lumefantrine.

WHO has recently issued the Guidelines for the Treatment of Malaria after reviewing the available safety and efficacy data (WHO, 2006). Coartem® is recommended by the WHO as first line treatment of uncomplicated *P. falciparum* malaria in patient's ≥ 10 kg. For patient's ≤ 10 kg there is no recommended formulation available. So far, Coartem® is administered to infants and small children in a grossly crushed form of the tablet mixed with water which is hampered by its bitter taste. This situation is not ideal because oral drugs for small children should be well tolerated and have a good palatability. For this reason, there is a need for a paediatric formulation of artemether/lumefantrine to treat children in general and in particular small children ≤ 10 kg.

9. Treatment details

9.1. Method of administration

After opening the bottle, drinking water is added and carefully brought to the mark point indicating 60 or 120 ml level. After adding the water, the mixture is vigorously shaken until all powder has disappeared from the bottom and a yellow oral suspension is being formed. The composition of the powder is such that this process takes only a few seconds. It will be necessary to readjust the volume to the 60 ml or 120 ml mark. This oral suspension is stable for at least 14 days. Although the oral suspension powder does not precipitate to the bottom, it is advisable to shake the bottle before so there is an homogeneous distribution of the active ingredients. A subunit of 5 ml of the 60 or 120 ml made oral suspension contains 15 mg artemether and 90 mg lumefantrine.

9.2. Dosage

The dose depends on the severity of the case and the clinical situation of the patient. In general: 4 mg artemether/kg body weight in combination with a 6 fold of that that dose for lumefantrine per day, administered as a single dose.

For each patient it will be calculated how many millilitres should be administered. It is recommended to round off the dosage to the nearest subdivision. However, it should be remarked that this is an average dosing scheme. Depending on the severity of the case and the clinical situation of the patient the dose may be increased.

Body weight	**Number of millilitres**		
	1° day	**2° day**	**3° day**
5 kg	7 ml	7 ml	7 ml
7,5 kg	10 ml	10 ml	10 ml
10 kg	14 ml	14 ml	14 ml
15 kg	20 ml	20 ml	20 ml

9.3. Duration

There is no need to divide doses. High peak levels are obtained when artemether is administered once a day. This daily dose must be repeated during the following two days.

9.4. WHO treatment guidelines

WHO treatment guidelines on the use of artemether/lumefantrine were republished in 2006 (WHO, 2006). These WHO recommendations state that: The six-dose regimen of artemether lumefantrine (Coartem® tablet containing 20 mg of artemether and 120 mg of lumefantrine) twice a day for 3 days is the recommended treatment for patients ≥ 10 kg. Treatment of children ≤ 10 kg and treatment of pregnant women with Coartem® is not recommended.

The WHO recommended regimen for all patients and in all situations is therefore as follows:

Body Weight in kg (age in years)	**No. of tablets at approximate timing and dosing***					
	0h	8h	24h	36h	48h	60h
5-14 (<3)	1	1	1	1	1	1
15-24 (≥3-8)	2	2	2	2	2	2
25-34 (≥9-14)	3	3	3	3	3	3
>34 (>14)	4	4	4	4	4	4

* The regimen can be expressed more simply for ease of use at the programme level as follows: the second dose on the first day should be given any time between 8h and 12h after the first dose. Dosage on the second and third days is twice a day (morning and evening).

10.Summary of comparative effectiveness in a variety of clinical settings

During the recent years different research groups, in different countries, studied the efficacy and tolerance of the combination artemether/lumefantrine. The general conclusion is that this combination is very effective for the treatment of malaria in terms of controlling symptoms and killing parasites. This finding was first proven by von Seidlein et al (von Seidlein et al, 1997) and latter confirmed by other study groups. (Hatz C et al, 1998; van Vugt M et al, 1998; von Seidlein L, 1998; Looareesuwan S et al, 1999; Kshirsagar NA et al, 2000; Krudsood S, 2003; Mayxay M, 2004; Omari et al, 2004; Stohrer JM et al, 2004; Tall A et al, 2004; Barnes KI et al, 2005; Davis et al, 2005; Elamin et al, 2005; Hutagalung R et al, 2005; Jima et al, 2005; Koram KA et al, 2005; Martensson A et al, 2005; Mutabingwa TK et al, 2005; van den Broek IV et al, 2005; Zurovac et al, 2005; Bukirwa H et al, 2006; Fanello et al, 2006; Guthmann JP et al, 2006; Mohamed AO et al, 2006 and Mulenga M et al, 2006)

There are two treatment or dosage regimens available as a fdc tablet: the six-dose combination versus the four-dose combination. The efficacy of six doses versus four doses of

artemether/lumefantrine in multidrug-resistant *P. falciparum* malaria was often the object of research. To see clear in this vast amount of data produced on artemether/lumefantrine four-dose and six-dose treatment regimens two reviews were made by the Cochrane database.

- A clear view on the six-dose regimen of artemether/lumefantrine is given by the review of Omari et al in 2005 (Omari et al, 2005). They aimed to summarize the existing evidence of the six-dose regimen of artemether/lumefantrine and how it compares with the other antimalarial drugs for treating uncomplicated P.falciparum malaria, including mefloquine, SP and chloroquine. Nine trials (4547 participants) tested the six-dose regimen. Total failure at day 28 for artemether/lumefantrine was lower when compared with amodiaquine, amodiaquine plus SP, but not with chloroquine plus SP. In comparisons with artemisinin derivative combinations, artemether/lumefantrine performed better than amodiaquine plus artesunate, worse than mefloquine plus artesunate, and no differently to dihydroartemisinin-napthoquine-trimethoprim. The conclusion made by the author's is that the six-dose regimen of artemether/lumefantrine appears more effective than antimalarial regimens not containing artemisinin derivatives.

- In 2006 Omari et al published a new review on the four-dose regimen (Omari et al, 2006). They aimed to evaluate the four-dose regimen of artemether/lumefantrine and how it compares with the other antimalarial drugs for treating uncomplicated *P.falciparum* malaria, including mefloquine, SP and chloroquine. Seven trials (2057 participants) tested a four-dose regimen. More people tended to fail treatment with artemether/lumefantrine than with other drugs, including SP, halofantrine, and mefloquine. When compared with chloroquine, artemether/lumefantrine was better in two trials, but over 50% of the participants treated with chloroquine had total failure by day 28. Fewer people failed treatment with the six-dose regimen compared to the four-dose regimen. The conclusion made in this review is that the four-dose regimen of artemether/lumefantrine seems to be less effective than regimens against which it has been tested and that the six-dose regimen is superior to the four-dose regimen. The trial carried out by van Vught et al (Van Vugt et al. 1999) first showed that the six-dose regime is better. This finding was confirmed by all the other research groups investigating the combination artemether/lumefantrine for the treatment of multidrug-resistant *P. falciparum* malaria (van Vugt et al, 2000; Lefevre et al, 2001; Omari et al, 2003; Fogg et al, 2004; Falade et al, 2005; Alecrim et al, 2006 and Makanga M et al, 2006)

Since none of the studies in the past compare all combinations, it is not easy to see clear in this vast amount of data produced on ACT's. Therefore, Dafra Pharma in corporation with Biostatistical Centre, University of Leuven, Belgium and Fondation ACT-ion Afrique, Bruxelles, Belgium performed in 2006 a multi-treatment meta-analysis to assess the relative effect of each combination therapy to any other combination therapy (Lesaffre E et al, 2006). An analysis based on papers published until December 2005 was done and is reported. We presented the results of the combination therapies to artesunate + SP as standard, but other standards could have been taken. From the data it is clear that there is no difference between the results obtained with artesunate + SP and those obtained with artesunate + amodiaquine and amodiaquine + SP (the last is limited to one study only). Favourable results were obtained with the combination artesunate + mefloquine, but these data come only from studies in SE Asia. By far the most attractive result for the variable ACPR on day 28 (and thus lack of recrudescence) is given by the combination artemether/lumefantrine (figure 1, p.7).

CONCLUSION: Based on the available efficacy data the fdc-tablet artemether/lumefantrine in the six-dose treatment regimen is the best to use for the treatment of uncomplicated P. falciparum malaria.

Dafra Pharma developed a paediatric formulation of the combination artemether/lumefantrine powder for oral suspension. The dosages are calculated to be the same as those given with the six-dose fdc combination artemether/lumefantrine. The fdc combination artemether/ lumefantrine was shown to be safe and effective as demonstrated in a large number of studies involving thousands of patients. It was considered necessary to study the new galenic formulation in children. The accent of the 3 clinical trials prior to registration was focused on acceptability, efficacy and safety of the new antimalarial drug based on well known active substances. The total number of patients enrolled in the pre-registration clinical trials was 259.

- The first study conducted in Abidjan, Ivory Cost in 2002-2003 enrolled 120 children with a mean age of 46 ± 35.2 months. It evaluated the efficacy and tolerance of a paediatric formulation (powder for oral suspension) in two different forms: artemether only (Artesiane®) 5-day treatment (dose 4 mg/kg day 1 and 2mg/kg day 2-5) or 3-day treatment (dose 4 mg/kg day for 3 days), compared with a combination therapy of artemether/lumefantrine in a fixed dose oral suspension (Co-Artesiane®). Therapeutic efficacy ranged from 95% to 100% for all three protocols. In the group treated with a 5-day artemether only oral suspension a therapeutic success of 95% was noticed. One case

of early treatment failure was noticed and also one case of late recrudescence. 100% cure was observed in the 3-day artemether only oral suspension group. In the group treated with a 3-day artemether/lumefantrine oral suspension therapeutic success of 98% was obtained, with one case of late parasitological failure. Fever clearance was rapid for all three products within 24 hours. Mean parasite clearance seems quicker for the 3-day artemeter only oral suspension group and for the group treated with the 3-day artemether/lumefantrine oral suspension, with a reduction of 100% on day four. The patient's state of recovery was judged to be very satisfactory on the 5th day for the 117 cured patients, with parasitaemia remaining negative on day 14 for all three protocols. The authors concluded that therapy with artemether only oral suspension in a three day dosage of 4 mg/kg can be recommended as treatment for simple malaria. The same conclusions could be made for the artemether/lumefantrine combination oral suspension (Kouame KJ et al, 2003, Report available at Dafra Pharma nv).

- A second study conducted in Kassala, Sudan in September 2005 - November 2005 evaluated the efficacy of artemether/lumefantrine oral suspension (Co-Artesiane®) in the treatment of uncomplicated malaria among 48 children with age ranging between 6-59 months. The study showed a full efficacy (therapeutic success of 100%) of the artemether/lumefantrine oral suspension in the treatment of uncomplicated *P. falciparum* malaria in this area. No cases of treatment failure were detected during the 28-days of follow-up. The results have been published in June 2006 in Tropical Journal of Pharmaceutical Research (Salah MT et al, 2006).

- A third study evaluated the therapeutic efficacy or Adequate Clinical and Parasitological Response (ACPR) of SP, the fdc tablet combination of artemether/lumefantrine (Coartem®) and artemether/lumefantrine powder for oral suspension (Co-Artesiane®) in children with a follow-up time of 28 days. It was conducted by the Malaria Board of Zambia and in collaboration with WHO. The study, focussed on small children, took place in Zambia at five sentinel sites: Chongwe, Mpongwe, Chipata, Isoka, Mansana and Sesheke. 286 children under 10 kg were enrolled at the five sentinel sites to study the efficacy of SP. 242 were evaluated and the mean ACPR was 75.16% (95%CI 68.87-81.44). SP can no longer be relied upon as treatment for uncomplicated *P. falciparum* malaria since it is no longer effective. 282 children aged 12-60 months and weighting more than 10 kg (inclusion criteria) were enrolled on the fdc tablet combination of

artemether/lumefantrine study arm at the five study sites. Mean 28-day ACPR was found to be 98% and 100% (95% CI 97.7-100) after PCR correction (to correct for reinfection). The conclusion was made that the fdc tablet combination of artemether/lumefantrine is still effective in treating uncomplicated malaria in Zambia. However, there is need to find a better option for children weighting ≤ 10 kg who can not take this formulation. To test the efficacy of artemether/lumefantrine powder for oral suspension 111 children weighting less than 10 kg were enrolled at only two study sites (Chongwe and Chipata). 91 of them were evaluated and the ACPR was found to be 100% (95% CI 96.0-100). Artemether/lumefantrine powder for oral suspension was effective in treating uncomplicated malaria in Zambian children weighting less than 10 kg, an age group normally excluded from taking the fdc tablet formulation of artemether/lumefantrine. (Chanda P and Hawela M, 2006, draft report) Only the results obtained from artemether/lumefantrine powder for oral suspension at two study sites were published (Chanda et al, 2006).

11.Summary of comparative evidence on safety

11.1. Safety and tolerability

The combination artemether/lumefantrine was placed on the Model List of Essential Drugs in April 2002. The WHO and RBM recommended in 2006 the use of artemether/lumefantrine as first line treatment. It has been estimated that over 100 million people have been treated with the drug including over 5000 more patients in clinical trials. During the recent years (1997 – 2006) different research groups, in different countries, studied the safety and tolerance of the combination artemether/lumefantrine. These studies were detailed and carried out with particular attention given to potential cardiotoxicity and neurotoxicity since animal studies had found that artemisinin derivatives are potential neurotoxic and lumefantrine belongs to a chemical class of compounds, like halofantrine, displaying cardiotoxic potential.

- The first human study with the combination artemether/lumefantrine was carried out by von Seidlein in 1997. His study group found no signs of neurological complications. They observed in 50% of the treated cases a transient QTc increase similar to the QTc changes after treatment with SP and chloroquine. The apparent cardiac effects have been attributed

to changes during the early phase of malaria and are independent of the type of antimalarial therapy given (von Seidlein et al, 1997).

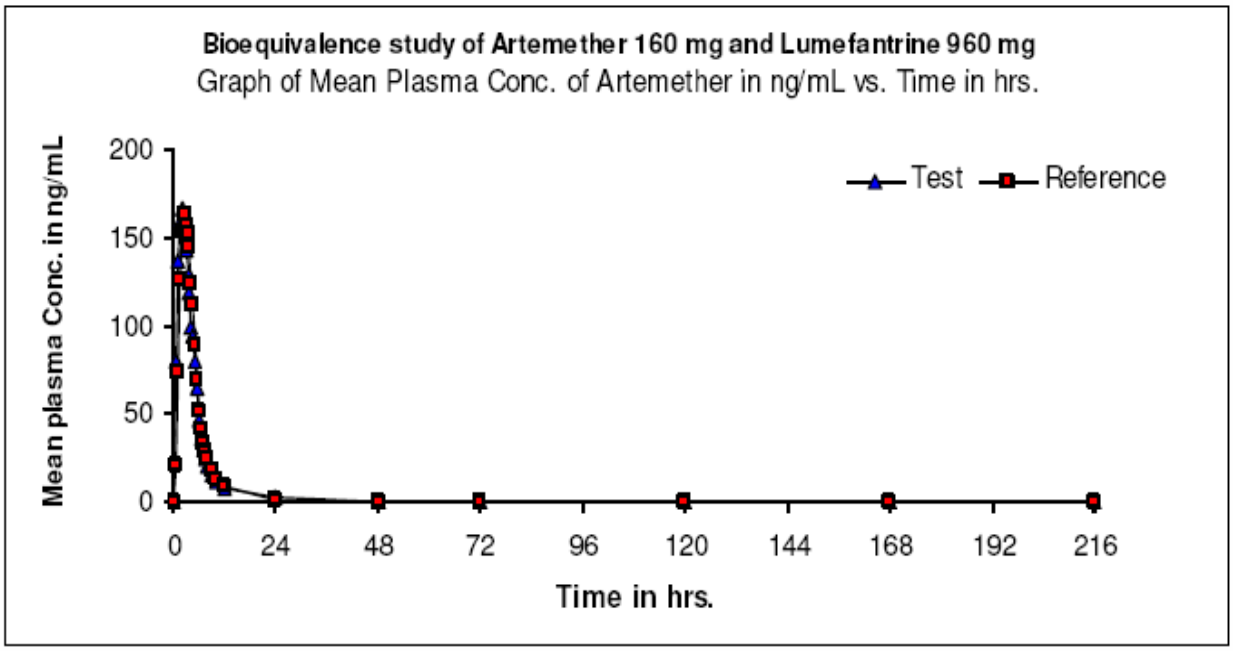
- A comprehensive evaluation of the safety and tolerance of artemether/lumefantrine was carried out by Bakshi et al in 2000. His study group analysed the safety data on the combination artemether/lumefantrine between 1997 and 2000 Bakshi et al. 15 trials were included. The most commonly reported and possibly drug-related adverse effects to the combination therapy were on gastrointestinal (abdominal pain, anorexia, nausea, vomiting and diarrhoea) and central nervous (headache, dizziness) systems. Pruritus and rash were reported by less than 2% of patients. More than 90% of these reported adverse events, many of which overlapped with the clinical symptomatology of acute malaria, were rated mild to moderate in severity. The combination was better tolerated than the comparator drugs used in the trials. Higher incidences of vomiting and pruritis were observed with chloroquine. Dizziness, nausea and vomiting were more common with mefloquine. Somnolence with SP and dizziness, abdominal pain, nausea and vomiting were more frequent with quinine (Bakshi R et al, 2000).

- These findings that the combination of artemether/lumefantrine is safe and only causes mild side effects (trouble of sleeping, nausea, vomiting, abdominal pain, dizziness and pruritus) were conformed by all later conducted clinical trails between 2000 and 2006: (Lefevre et al. 2001; Krudsood S et al, 2003; Omari et al. 2003; Mayxay M, 2004; Omari et al, 2004; Stohrer JM et al, 2004; Tall A et al, 2004; Barnes KI et al, 2005; Davis et al. 2005; Elamin et al. 2005; Falade et al, 2005; Hutagalung R et al, 2005; Jima et al. 2005; Koram KA et al. 2005; Martensson A et al. 2005; Mutabingwa TK et al, 2005; Omari et al, 2005; van den Broek IV et al. 2005; Zurovac et al. 2005; Alecrim et al. 2006, Bukirwa H et al, 2006; Fanello et al, 2006; Guthmann JP et al, 2006; Makanga M et al, 2006; Mohamed AO et al, 2006 and Mulenga M et al, 2006).

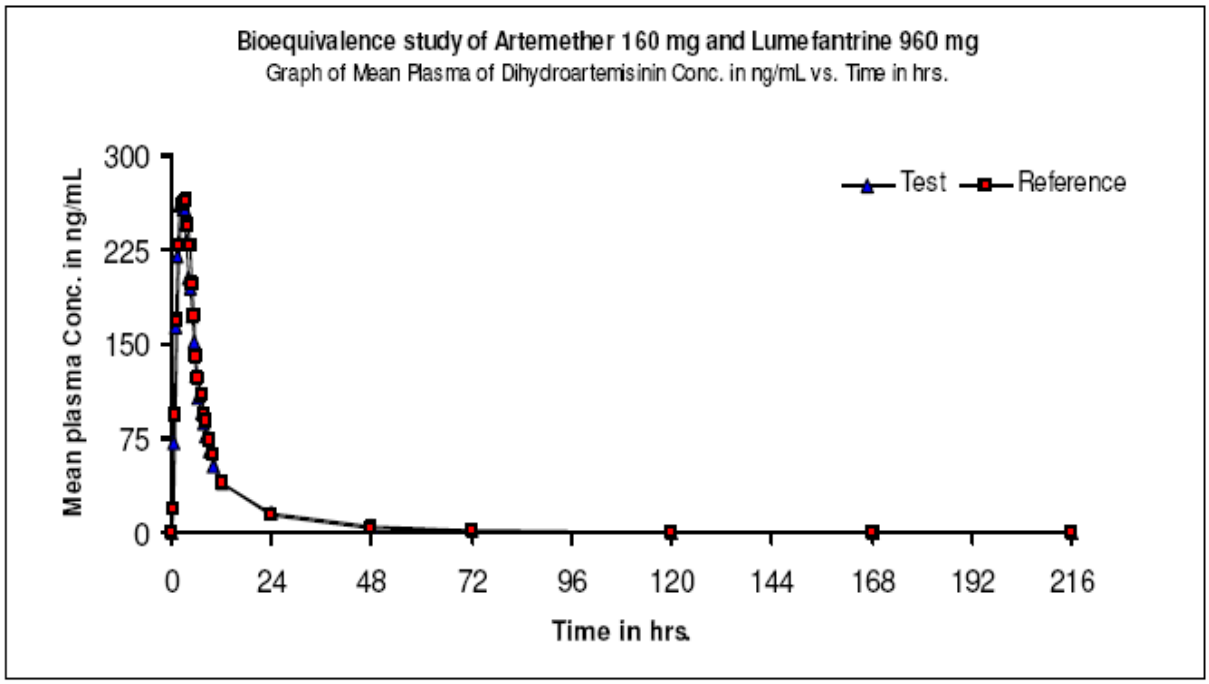
- Dafra Pharma developed a paediatric formulation of the combination artemether/lumefantrine, called Co-Artesiane® powder for oral suspension. In the 3 clinical trails (above) initiated by Dafra Pharma, the conclusion that the combination is safe and only has mild side-effect could also be stated: only 3 of the 259 patients reported mild and spontaneously resolving side-effects like nausea and diarrhoea and no severe drug effects were reported.

- Dafra Pharma, in cooperation with Bombay Bio-Research Centre, held between February and March 2007 a relative bioavailability study. This study was designed to evaluate the comparative bioavailability of Artemether, its metabolite Dihydroartemisinin, and Lumefantrine of the test product Co-Artesiane® dry powder for oral suspension ((containing β-Artemether 360 mg and Lumefantrine 2160 mg in 45.6 g dry powder for oral suspension of 120 ml) of Dafra Pharma NV, Belgium with that of the reference product Coartem® tablets (containing Artemether 20 mg and Lumefantrine 120 mg) of Novartis Pharmaceuticals Limited, EU in 42 (+ 6) standbys normal, healthy, adult, human subjects using a crossover, randomized design under fed conditions with a washout period of at least 21 days. Two times a dose of 160 mg Artemether and 960 mg Lumefantrine was administered (8 tablets Coartem® or 53 ml Co-Artesiane® powder for oral suspension. Primary Pharmacokinetic parameters: C_{max}, AUC_{0-216} and AUC_{0-inf} were studied for both the investigational products to confirm Bioequivalence. 48 healthy adult human subjects who met all inclusion and none of the exclusion criteria were recruited in the trial. 46 subjects completed the study. Blood samples taken for all the 46 subjects at various time points between 0h and 216h, were analysed for determining the plasma levels and calculate the pharmacokinetic parameters C_{max}, AUC_{0-216} and AUC_{0-inf} . Pre and post study pathological evaluation was performed to evaluate safety of subjects before and after completion of study. Pre and during vital parameters were evaluated as per protocol requirements to assess safety of dose. Data of 42 subjects is reported. No adverse events and major abnormalities or variations in vital parameters due to test or reference medication were observed and reported during the trial. After calculating the pharmacokinetic parameters C_{max}, AUC_{0-216} and AUC_{0-inf} , these parameters were evaluated for % Ratio and 90% confidence interval (constructed with statistical software) from Log-transformed data. The %ratios for LnC_{max}, $LnAUC_{0-216}$ and $LnAUC_{0-inf}$ calculated for Artemether, Dihydroartemisinin and Lumefantrine were found to be in the range with their respective calculated 90% CI's. All primary pharmacokinetic parameters were within acceptance criteria of 80 to 125%. Based on the clinical, analytical and statistical data values for 90% Confidence Interval the overall conclusion can be made that Co-artesiane® dry powder for oral suspension was found to be bioequivalent when compared with Coartem® tablets of Novartis Pharmaceuticals Limited, EU and that both medications were safe for administration. The results are presented in the figures below:

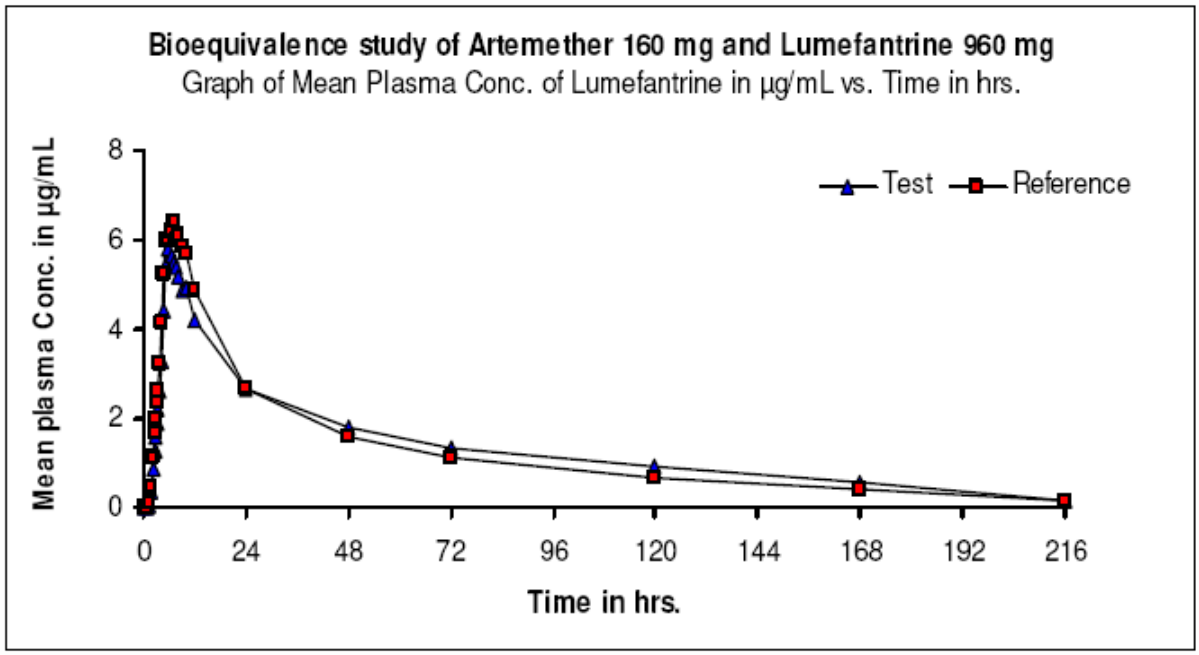
Graph of Mean Plasma Conc. of Artemether in ng/mL vs. Time in hrs.



Graph of Mean Plasma Conc. of Dihydroartemisinine in ng/mL vs. Time in hrs.



Graph of Mean Plasma Conc. of Lumefantrine in ng/mL vs. Time in hrs.



Potential Neurotoxicity:

Animal studies have demonstrated limited symptomatic and pathological evidence of neurotoxicity following the intramuscular administration of artemether and arteether (Brewer et al, 1994; Petras et al, 1993, Genovese et al, 1995). However, the relevance of these studies to humans is unclear. To date, no significant neurotoxicity has been reported from the use of artemisinin derivatives in more than 2 million people using these drugs (WHO, 1998, 1999, 2001b). These effects were not observed in animal models following oral administration of artemisinin derivatives.

There were no serious or persistent neurological adverse reactions to oral administration of artemether/lumefantrine either in the clinical studies described above or in preclinical studies in rats or dogs.

There have been no reports to the WHO or other agencies of QTc prolongation since the marketing of the combination and its use in over 1.2 million patients.

Potential cardiotoxicity:

Lumefantrine belongs to a chemical class of compounds that includes mefloquine and halofantrine. Halofantrine has been shown to prolong QTc intervals at standard recommended doses and there have been rare reports of serious ventricular dysrhythmias, sometimes fatal.

In the review carried out by Bakshi et al in 2000 serial electrocardiograms were available for 713 patients given artemether/lumefantrine. The frequency of QTc interval prolongation was similar to or lower than that observed with chloroquine, mefloquine or artesunate plus mefloquine and significantly lower than with halofantrine; these changes were considerably less frequent than with quinine or halofantrine. All patients with QTc interval prolongation remained asymptomatic and no adverse clinical cardiac events were reported (Bakshi et al., 2000, Kshirsagar et al., 2000; Lefèvre et al., 2001; Price, 2000, van Vugt et al., 1999).

A Study had been carried out in 42 healthy male volunteers by Bindschetler et al to determine whether prior treatment with mefloquine would affect lumefantrine cardiotoxity. They showed that there were no clinically significant differences in the QTc-interval after sequential treatment of mefloquine and artemether/lumefantrine relative to either treatment given alone (Bindschedler et al, 2000).

Effects of artemether/lumefantrine and halofantrine on the QTc-interval have been compared in a randomised double-blind cross-over study in 13 healthy male adults. Electrocardiograms were recorded from 48hrs before drug administration and 48 hrs thereafter. The maximum QTc-interval (QTc = QT/√RR) was compared before and after treatments and within treatments, fitting a general linear model. Drug plasma concentrations were determined concomitantly. All subjects showed an increase in QTc-interval after halofantrine treatment, the mean maximum increase being 28msec. The QTc-interval remained unchanged after administration of artemether/lumefantrine. The difference between treatments was statistically significant (Bindschedler et al, 2002).

CONCLUSION: halofantrine caused significant, exposure-dependent increase in the QTc interval. No such effect was seen with the combination artemether/lumefantrine.

A drug interaction study with quinine was carried out to determine whether the concomitant administration of quinine and artemether/lumefantrine exacerbated the potential cardiotoxicity of either drug (Lefèvre et al., 2002a). Artemether/lumefantrine alone had no effect on QTc

interval. The infusion of quinine alone caused transient prolongation of QTc-interval with this effect being slightly but significantly greater than when quinine was infused after artemether/lumefantrine. However, these prolongations were small in magnitude and were not followed by abnormal clinical signs or symptoms. The changes were not considered to be clinically important. The pharmacokinetics of lumefantrine and quinine were not influenced by the presence of other drugs while exposure to artemether and dihydroartemisninin appeared to be lower under the combined treatment of artemether/lumefantrine and quinine. The latter was considered to be clinically irrelevant.

Ketoconazole is amongst the potent inhibitors of the cytochrome enzyme, CYP3A4. As artemether and lumefantrine are metabolised by the same enzyme, a study was carried out to determine whether the metabolism of artemether/lumefantrine was inhibited by ketaconazole. The results showed that the study medications were all safe and well tolerated after both treatments. No changes in ECG and no effects on QTc interval were observed with any of the treatments, given alone or in combination. The pharmacokinetics of artemether, its metabolite dihydroartemisinin and lumefantrine were influenced by ketaconazole (exposure increased by a factor 1.3-2.5). This effect was not considered to be clinically relevant (Lefèvre et al., 2002b).

CONCLUSION: there is no clinically significant change on the QTc interval with the combination artemether/lumefantrine and quinine or with artemether/lumefantrine and ketonazole.

The effect of lumefantrine, desbutyl-lumefantrine, halofantrine, chloroquine and mefloquine on HERG currents recorded from stably transfected HEK293 cells has also been studied. Compounds which inhibit HERG current have been shown to prolong the cardiac potential and therefore QTc-interval in man. All of the compounds examined in this study inhibited HERG currents stably expressed in HEK293 cells. From the estimated IC50 values the order of potency of HERG current block was halofantrine > chloroquine ≥ mefloquine > desbutyl-lumefantrine > lumefantrine (Traebert M et al, 2004).

CONCLUSION: lumefantrine and its debutyl metabolite have less potential for QTc interval prolongation than mefloquine, chloroquine and halofantrine.

11.2. Use in pregnancy and lactation

Not applicable because artemether/lumefantrine powder for oral suspension is for paediatric use only.

11.3. Drug interactions

Lumefantrine:

The following recommendations are given when lumefantrine is administered: avoid grapefruit juice; antiarrhythmics (such as amiodarone, disopyramide, flecainide, procainamide and quinidine), antibacterials (such as macrolides and quinolines), all antidepressants, antifungals (such as imidazoles and triazoles), terfenadine, other antimalarials, all antipsychotic drugs and beta-blockers (such as metoprolol and sotalol). However, there is no clear evidence that co-administration with these drugs would be harmful (WHO, 2006)

Artemether:

The pharmacokinetics of a single oral dose of artemether (300 mg) and pyrimethamine (100 mg) given as each individual drug alone or as a drug combination (artemether 300 mg plus pyrimethamine 100 mg), were investigated in 8 healthy male Thai volunteers (Tan-ariya et al. 1998a) and in vitro (Tan-ariya et al. 1998b). Both artemether and pyrimethamine were rapidly absorbed after oral administration. Elimination of pyrimethamine was however, a relatively slow process compared with artemether, and thus resulted in a long terminal phase elimination half-life (50-106 hours). Pharmacokinetics of artemether and dihydroartemisinin following a single oral dose of artemether alone or in combination with pyrimethamine were unaffected. In contrast, coadministration of artemether resulted in significantly increased Cmax (medians of 818 vs 1,180 ng/ml) and contracted the apparent volume of distribution (medians of 3 vs 2.56 l/kg) of pyrimethamine.

Using a multiresistant strain (T-996) from Thailand and a chloroquine-resistant strain (LS-21) from India, anti Plasmodium falciparum synergism has been shown with artemether and benflumetol (lumefantrine) (Hassan Alin et al. 1999). This phenomenon resembles the synergistic interaction of artemisinin derivatives and mefloquine.

van Agtmael et al. (1998) could not find any changes in the pharmacokinetic properties of artemether and its active metabolite dihydroartemisinin when given orally alone or in combination with either CYP2D6-inhibitor quinidine or CYP2C19-inhibitor omeprazole.

Artemether combined with quinidine revealed no significant changes in the plasma concentrations of either artemether or dihydroartemisinin.

According to (Baune et al. 1999) artemether has no significant influence on halofantrine metabolism by human liver microsomes.

Grapefruit juice significantly increases the oral bioavailability of artemether without an effect on the elimination half-life. These findings suggest an important role for intestinal CYP3A4 in the presystemic metabolism of artemether (van Agtmael et al. 1999).

Dietary fat increases the oral bioavailability of artemether (White et al. 1999).

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

Cost per treatment dose:

Co-Artesiane® powder for oral suspension 60 ml (fixed dose combination of 180 mg β-artemether and 1080 mg lumefantrine)

- For sale in the private market in developing counties = 3.3 € per paediatric treatment dose
- For sale in the public sector in developing counties = 1.49 € per paediatric treatment dose

Co-Artesiane powder for oral suspension 120 ml (fixed dose combination of 360 mg β-artemether and 2160 mg lumefantrine).

- For sale in the private market in developing counties = 4 € per paediatric treatment dose
- For sale in the public sector in developing counties = 1.98 € per paediatric treatment dose

Cost comparison with Coartem®:

- For sale in the public sector in developing counties = 90 dollar cent per treatment dose for children between 10-14 kg

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

The drug has been submitted to Unicef / WHO prequalification and to the European authorities in 2006. Product Licence for this drug has been obtained in 2004, 24 April.

An overview of the regulatory situation in other countries is presented below:

Registration is achieved in the following 23 countries: Angola; Benin; Burkina Faso; Cameroun; Cote d'Ivoire; Gabon; Guinee; Kenya; Liberia; Malawi; Mali; Mauritanië; Niger; Nigeria; Rép Congo; Rép. Dém. Congo; Rwanda; Senegal; Tanzania; Tchad; Togo; Uganda and Zambia.

14. Availability of pharmaceutical standards

Pharmacopeal standards for artemether have been established by WHO (International Pharmacopoeia, 4th edition, 2006).
Lumefantrine standard: In House Standard Dafra Pharma, according to the European Pharmacopoeia.
Fixed combination: No standard.

15. Proposed text for the WHO Model Formulary

SUMMARY OF PRODUCT CHARACTERISTICS

Name of the medicinal product

Artemether/lumefantrine powder for oral paediatric suspension.

International Nonproprietary Name

There are no INNs for drug combinations. The INNs for the components are artemether and lumefantrine.

Pharmaceutical dosage form

Artemether/lumefantrine oral suspension is available as a dry yellow powder for oral suspension containing 7.9 mg β-artemether/ 47.4 mg lumefantrine per g powder. After addition of water a stable oral suspension for paediatric use is made.

Presentation

Plastic (polyethylene) vial containing artemether and lumefantrine in a dry powder mixture for making up an oral suspension with water. After adding water the solution becomes yellow and the product has the pleasant taste of coconut.

Each package carries a package leaflet and a graded beaker with marks at 5 ml intervals

Two qualitative and quantitative compositions are available

- Artemether/lumefantrine powder for oral suspension 60 ml is a fixed dose combination of 180 mg β-artemether and 1080 mg lumefantrine.
- Artemether/lumefantrine powder for oral suspension 120 ml is a fixed dose combination of 360 mg β-artemether and 2160 mg lumefantrine.

CLINICAL PARTICULARS

Therapeutic indications

Artemether/lumefantrine is indicated for the treatment of malaria in children, caused by all forms of Plasmodium including severe malaria caused by multiple drug resistant strains of *P. falciparum*.

Dose and method of administration

For ORAL use only

Artemether/lumefantrine oral suspension has especially been designed for use in children. The dose depends on the severity of the case and the clinical situation of the patient.

In general: 4 ml artemether/kg body weight in combination with lumefantrine per day.

This dose should be repeated during three consecutive days.

The daily dose should be administered in one single administration.

NOTE: A full course therapy of three days is essential in order to avoid recrudescence.
Vomiting within one hour requires repeating the dose.

Making up the Artemether/lumefantrine oral suspension:

After opening the vial (breaking the seal), drinking water is added and carefully brought to the mark point indicating 60 ml or 120 ml level. When adding water the mixture turns yellow. After adding the water the mixture is vigorously shaken until all powder has disappeared from the bottom and an oral suspension is being formed. The composition of the powders is such that this process takes only a few seconds. It may be necessary to readjust the volume to the 60 ml or 120 ml mark. This oral suspension is stable for several days. It is advisable to shake the vial before use.

A subunit of 5 ml contains 15 mg artemether and 90 mg lumefantrine. For each patient it will be calculated how many millilitres should be administered. It is recommended to round off the dosage to the nearest subdivision.

Practical scheme for administering the correct dose of artemether/lumefantrine oral suspension:

Body weight	**Number of millilitres**		
	1° day	**2° day**	**3° day**
5 kg	7 ml	7 ml	7 ml
7,5 kg	10 ml	10 ml	10 ml
10 kg	14 ml	14 ml	14 ml
15 kg	20 ml	20 ml	20 ml

This is an average dosing scheme but when considered necessary the dose may be increased depending on the severity of the case and the clinical situation of the patient.

Precautions and contra-indications: Artemether/lumefantrine oral suspension is contraindicated in individuals hypersensitive to artemether and lumefantrine. Therefore, there are no strict contra-indications for the use of artemether in children.
Nevertheless, no correlation has been found between QTc interval prolongation and plasma concentrations of lumefantrine, caution is advised to patients who are taking drugs that are know to prolong the QT interval, such as certain antibiotics (macrolides, fluoroquinolones, imidazole) or who are predisposed to cardiac arrhythmias.
It is advisable not to use drugs during pregnancy but in view of the high risk of malaria during pregnancy for mother and foetus, the responsible physician may consider it essential, as in the case of cerebral malaria, to treat a pregnant woman. It is recommended that this drug is only administered if the expected benefits outweigh the potential risks.
Artemether/lumefantrine oral suspension should not be taken during breastfeeding. Due to the long elimination half-life of lumefantrine, it is recommended that breast-feeding should not start until at least one week after stopping an artmether/lumefantrine combination treatment.

Drug interactions: Specific negative drug-drug interactions were not seen. Artemether potentialises the antimalarial activity of other antimalarials.
As grapefruit juice retards the metabolism of some antimalarials, it would be better not to drink grapefruit juice while taking Artemether:lumefantrine oral suspension.

Overdose: In case of overdose, emergency symptomatic treatment in a specialised facility is required, which should include ECG and kaliemia monitoring.

Side effects: With artemether virtually no side effects have been seen. Laboratory abnormalities such as a slight rise in transaminases and a decrease in reticulocyte count are rare and transient. A lowering of sinus frequency without causing ECG changes has been noticed. At high doses transient abdominal pain, tinnitus and diarrhoea have been described but a causal relationship in unclear.
Some antimalarials as halofantrine and quinine can influence the ECG pattern. Attention should be made to patients previously treated with those antimalarials. A reasonable period should be taken in account before to start a treatment with lumefantrine combinations.
Sometimes it could be possible that rash, a common side effect, occurs. Check this with your doctor. Sometimes the following common side effects can occur: trouble of sleeping, nausea, vomiting, diarrhoea, coughing. They need medical attention when persisting.

Resistance and recrudescence: Resistance of *plasmodia* to artemether has not yet been observed. It is unlikely to occur in view of the specific mechanism of action which is very cytotoxic for the *Plasmodia* (opening of the peroxide bridge). An apparent resistance is sometimes seen but is mainly due to multiple broods of plasmodia developing at different times in the same patient. In controlled studies recrudescence does not exceed 10%. In case of recrudescence (real or apparent) a new complete treatment for three days is advisable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics: Both compounds, artemether and lumefantrine, have their own action site in the malarial parasite. The presence of the endoperoxide bridge in artemether, generating singlet oxygen and free radicals which are very cytotoxic to the plasmodia, appears to be essential for antimalarial activity. Morphological changes of the parasitic membranes induced by artemether have been described as being the result of free-radical action. lumefantrine interferes more in the polymerisation processes.
Other in vitro tests suggest that both cause a marked diminution of nucleic acid synthesis. Inhibition of protein synthesis as the basic mechanism of action is suggested in studies which showed morphological changes in ribosomes as well as in the endoplasmic reticulum.
Although, Artemether acts essentially as a blood schizonticide, artemether/lumefantrine oral suspension did clear gametocytes in comparative clinical trials.

Pharmacokinetics: Orally administered artemether is rapidly absorbed reaching therapeutic levels within 60-90 minutes. Artemether is metabolized in the liver to the demethylated derivative dihydroartemisinin (DHA). The elimination is rapid, with a T1/2 of 2-4 hours. DHA, being a potent anitmalarial itself, has a T1/2 of about 2-4 hours. The degree of binding to plasma proteins varied markedly according to the species studied. The binding of artemether with plasma protein in man is about 50%. Radioacivity distribution of artemether was found to be equal between cells and plasma.
The absorption of lumefantrine is highly influenced by lipids and food intake (from 10% by fasten to 100% at normal diet). Therefore parents should be encouraged to give the medication with some fatty food as soon as it can be tolerated.
Lumefantrine is N-debutylated in human liver microsomes. This metabolite has 5 to 8 fold higher antiparasitic effects than lumefantrine. Lumefantrine is found to be highly protein

bound (95%). The elimination half-life in malaria-attaint patients will be 4 to 6 days. Lumefantrine and his metabolites are found in bile and faeces.
Breastfeeding: Data on excretion in breast milk are not available for humans.

PHARMACEUTICAL PARTICULARS

List of excipients:
Saccharose.
Avicel CL 611
Citric acid
Xanthan gum
Methyl-p-hydroxybenzoate
Propyl-p-hydroxybenzoate
Coconut flavour
Silicium Oxide Colloidal anhydrous

Special precautions for storage
Artemether/lumefantrine oral suspension vials should be stored at room temperature. In a closed vial the powders are stable for 3 years and once the oral suspension has been made up, it is stable for at least 14 days. Longer conservation is not recommended.

Marketing authorisation holder
Dafra Pharma nv/sa
Slachthuisstraat 30/7
2300 Turnhout
Belgium

16.References

1993

Petras JM et al (1993) Brain induced injury in Rattus rattus by the antimalarial drug arteether (AE): a neuroanatomical and neuropathological analysis. *Anatomical Record. 237 (Suppl.1): 95.2.*

1994

Brewer TG, Peggins JO, Grate SJ, Petras JM, Levine BS, Weina PJ, Swearengen J, Heiffer MH, Schuster BG (1994) Fatal neurotoxicity of arteether and artemether . *American Journal of Tropical Medicine and Hygiene, 51: 251-259.*

1995

Genovese RF, Petras JM, Brewer TG (1995) Arteether neurotoxicity in the absence of deficiency in behavioral performance in rats. *Annals of Tropical Medicine and Parasitology, 89: 447-449.*

1997

von Seidlein L, Jaffar S, Pinder M, Haywood M, Snounou G, Gemperli B, Gathmann I, Royce C, Greenwood B (1997) Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. *J Infect Dis., 176(4): 1113-6.*

1998

Hatz C, Abdulla S, Mull R, Schellenberg D, Gathmann I, Kibatala P, Beck HP, Tanner M, Royce C (1998) Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat acute falciparum malaria in Tanzanian children aged 1-5 years. *Trop Med Int Health, 3(6): 498-504.*

McGready R, Cho T, Cho JJ, Simpson JA, Luxemburger C, Dubowitz L, Looareesuwan S, White NJ, Nosten F (1998) Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. *Trans R Soc Trop Med Hyg., 92(4): 430-3.*

Tan-ariya P, Na-Bangchang K, Ubalee R, Thanavibul A, Thipawangkosol P, Karbwang J (1998a) Pharmacokinetic interactions of artemether and pyrimethamine in healthy male Thais. *Southeast Asian J Trop Med Public Health, 29(1): 18-23.*

Tan-ariya P, Ubalee R, Na-Bangchang K, Karbwang J (1998b) Plasma containing artemether-pyrimethamine has ex vivo blood schizonticidal activity against Plasmodium falciparum. *Southeast Asian J Trop Med Public Health, 29(2): 213-24.*

van Agtmael MA, Van Der Graaf CA, Dien TK, Koopmans RP, van Boxtel CJ (1998) The contribution of the enzymes CYP2D6 and CYP2C19 in the demethylation of artemether in healthy subjects. *Eur J Drug Metab Pharmacokinet., 23(3): 429-36.*

van Vugt MV, Brockman A, Gemperli B, Luxemburger C, Gathmann I, Royce C, Thra Slight, Looareesuwan S, White NJ and Nosten F (1998) Randomized Comparison of Artemether-Benflumetol and Artesunate-Mefloquine in Treatment of Multidrug Resistant Falciparum Malaria. *Antimicrobial Agents and Chemotherap,y Vol. 42, No. 1: 135-139.*

von Seidlein L, Bojang K, Jones P, Jaffar S, Pinder M, Obaro S, Doherty T, Haywood M, Snounou G, Gemperli B, Gathmann I, Royce C, McAdam K, Greenwood B (1998) A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. *Am J Trop Med Hyg., 58(5): 638-44.*

World Health Organization (1998). The use of artemisinin and its derivatives as anti-malarial drugs. Report of a WHO Informal Consultation 10-12 June 1998. (WHO/MAL/98.1086.)

1999

Baune B, Furlan V, Taburet AM, Farinotti R (1999) Effect of selected antimalarial drugs and inhibitors of cytochrome P-450 3A4 on halofantrine metabolism by human liver microsomes. *Drug Metab Dispos., 27(5): 565-8.*

Hassan Alin M, Björkman A, Wernsdorfer WH (1999) Synergism of benflumetol and artemether in Plasmodium falciparum. *Am J Trop Med Hyg., 61(3): 439-45.*

Looareesuwan S, Wilairatana P, Chokejindachai W, Chalermrut K, Wernsdorfer W, Gemperli B, Gathmann I, Royce C (1999) A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute Plasmodium falciparum malaria in Thailand. *Am J Trop Med Hyg., 60(2): 238-43.*

van Agtmael, Gupa V, van der Wosten TH, Rutten JP, van Boxtel CJ (1999) Grapefruit juice increases the bioavailability of artemether. *Eur J Clin Pharmacol., 55(5): 405-10.*

Van Vugt MV, Wilairatana P, Gemperli B, Gathmann I, Phaipun L, Brockman A, Luxemburger C, White NJ, Nosten F, Looareesuwan S (1999) Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant Plasmodium falciparum malaria. *Am J Trop Med Hyg., 60(6): 936-42.*

White NJ,van Vugt M, Ezzet F (1999) Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. *Clin Pharmacokinet., 37(2): 105-25.*

World Health Organization (1999). WHO Informal Consultation on clinical neurological investigations required for patients treated with artemisinin compounds and derivatives. (TDR/TDF/99.1.)

2000

Bakshi R, Hermeling-Fritz I, Gathmann I, Alteri E (2000) An integrated assessment of the clinical safety of artemether-lumefantrine: a new oral fixed-dose combination antimalarial drug. *Trans R Soc Trop Med Hyg., 94(4): 419-24.*

Bindschedler M, Lefevre G, Ezzet F, Schaeffer N, Meyer I, Thomsen MS (2000) Cardiac effects of co-artemether (artemether-lumefantrine) and mefloquine given alone or in combination to healthy volunteers. *European Journal of Clinical Pharmacology, 56: 375-381*.

Kshirsagar NA, Gogtay NJ, Moorthy NS, Garg MR, Dalvi SS, Chogle AR, Sorabjee JS, Marathe SN, Tilve GH, Bhatt AD, Sane SP, Mull R and Gathmann I (2000) A randomized, double-blind, parallel-group, comparative safety, and efficacy trial of oral co-artemether vs oral chloroquine in the treatment of acute uncomplicated *P. falciparum* malaria in adults in India. *Am Soc Trop Med Hyg., 62(3): 402-408.*

Price RN (2000). Artemisinin drugs: novel antimalarial agents, Expert Opinion on Investigatory Drugs, 9: 1815-1827

van Vugt M, Looareesuwan S, Wilairatana P, McGready R, Villegas L, Gathmann I, Mull R, Brockman A, White NJ, Nosten F (2000) Artemether-lumefantrine for the treatment of multidrug-resistant falciparum malaria. *Trans R Soc Trop Med Hyg., 94(5): 545-8.*

World Health Organization (2000a). The use of Essential Drugs. Ninth Report of the WHO Expert Committee (including the revised Model List of Essential Drugs) WHO Technical Report Series No.895.

World Health Organization (2000b). Report of 20th Expert Committee on Malaria. WHO Technical Report Series No.892.

2001

Lefevre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I, Mull R, Bakshi R (2001) A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum malaria in Thailand. *Am J Trop Med Hyg., 64(5-6): 247-56.*

World Health Organization (2001a). Antimalarial drug combination therapy. Report of a WHO Techical Consultation. 4-5 April 2001. (WHO/CDS/RBM/2001.35.)

World Health Organization (2001b). The use of antimalarial drugs . Report of a WHO Informal Consultation 13-17 November 2000. (WHO/CDS/RBM/2001.33.)

2002

Bindschedler M, Lefevre G, Degen P, Sioufi A (2002) Comparison of the cardiac effects of the antimalarials co-artemether and halofantrine in healthy participants. *Am J Trop Med Hyg., 66(3): 293-8.*

Lefevre G, Carpenter P, Souppart C, Schmidli H, Martin JM, Lane A, ward C, Amakye D (2002a) Interaction trial between artemether-lumefantrine (Riamet®) and quinine in healthy subjects. *J Clin Pharmacol., 42: 1147-1158*

Lefevre G, Carpenter P, Souppart C, Schmidli H, McClean M, Stypinski D (2002b) Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet®)with concomitant administration of ketoconazole on healthy subjects. *Br J Clin Pharmacol., 54(5): 485-92*

2003

Krudsood S, Chalermrut K, Pengruksa C, Srivilairit S, Silachamroon U, Treeprasertsuk S, Kano S, Brittenham GM, Looareesuwan S (2003) Comparative clinical trial of two-fixed combinations dihydroartemisinin-napthoquine-trimethoprim (DNP) and artemether-lumefantrine (Coartem/Riamet) in the treatment of acute uncomplicated falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health, 34(2): 316-21.*

Kouame KJ, Houenou YA, Kouakou YG (2003) Comparative study of Artemether suspension monotherapy in 2 different regimes with a combination suspension containing artemether-lumefantrine for the treatment of simple childhood malaria in Abidjan, Ivory Coast. Report available at Dafra Pharma nv.

Omari AA, Preston C, Garner P (2003) Artemether-lumefantrine for treating uncomplicated falciparum malaria. *Cochrane Database Syst Rev. (2):CD003125. Update of: Cochrane Database Syst Rev. 2002; (3):CD003125.*

2004

Fogg C, Bajunirwe F, Piola P, Biraro S, Checchi F, Kiguli J, Namiiro R, Musabe J, Kyomugisha A, Guthmann JP (2004) Adherence to a six-dose regimen of Artemether-Lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Uganda. *Am. J. Trop. Med. Hyg., 71(5), 525-530.*

Krishna S, Uhlemann AC, Haynes RK (2004) Artemisinins: mechanisms of action and potential for resistance. *Drug Resist Updat., 7(4-5):233-44*

Mayxay M, Khanthavong M, Lindegardh N, Keola S, Barends M, Pongvongsa T, Yapom R, Annerberg A, Phompida S, Phetsouvanh R, White NJ, Newton PN (2004) Randomized comparison of chloroquine plus sulfadoxine-pyrimethamine versus artesunate plus mefloquine versus artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in the Lao People's Democratic Republic. *Clin Infect Dis., 39(8):1139-47. Epub 2004 Sep 27.*

Omari AA, Gamble C, Garner P (2004) Artemether-lumefantrine for uncomplicated malaria: a systematic review. *Trop. Med. and Int. Health, vol 9(2), 192-199.*

Stohrer JM, Dittrich S, Thongpaseuth V, Vanisaveth V, Phetsouvanh R, Phompida S, Monti F, Christophel EM, Lindegardh N, Annerberg A, Jelinek T (2004) Therapeutic efficacy of artemether-lumefantrine and artesunate-mefloquine for treatment of uncomplicated Plasmodium falciparum malaria in Luang Namtha Province, Lao People's Democratic Republic. *Trop Med Int Health,. 9(11):1175-83.*

Tall A, Raharimalala LA, Lepere JF, Receveur MC, Baur F, Rabarijaona LP, Randrianarivelojosia M, Macarry A, Roussin C, Roussin JM, Robert V, Ariey F (2004) Efficacy of artemether-lumefantrine treatment in patients with acute uncomplicated Falciparum malaria in Mayotte, a French collectivity of the Comoros Archipelago. *Parasit,e 11(3):325-8.*

Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W (2004) Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. *Eur J Pharmacol., 484(1):41-8*.

2005

Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Diamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL (2005) Effect of Artemether-Lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. *PLos Medicine, vol 2(11); e330.*

Davis TME, Karunajeewa HA, Filett K (2005) Artemisinin-based combination therapies for uncomplicated malaria. *MJA, vol 182(4), 181-185.*

Falade C. Makanga M, Premji Z, Ortmann CE, Stockmeyer M, Ibarra de Palacios (2005) Efficacy and safety of artemether-lumefantrine (Coartem®) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria. *Trans. Roy. Soc. Trop. Med. Hyg 99, 459-467.*

Hutagalung E, Paiphun L, Ashley EA, McGready R, Brockman A, Thwai KL, Singhasivanon P, Jelinek T, White NJ, Nosten FH (2005) A randomized trial of artemether-lumefantrine vs mefloquine – artesunate for the treatment of uncomplicated multi-drug resistant *Plasmodium falciparum* on the western border of Thailand. *MJ, 4:46.*

Jima D, Tesfaye G, Medhin A, Kebede A, Argaw D, Babaniyi O (2005) Safety and efficacy of artemether-lumefantrine in the treatment of uncomplicated falciparum malaria in Ethiopia. *East Afr. Med. J 82(8), 385-386.*

Koram KA, Abuaku B, Duah N, Quashie N (2005) Comparative efficacy of antimalarial drugs including ACTs in treatment of uncomplicated malaria among children under 5 years in Ghana. *Acta Trop., 95(3), 194-203.*

Martensson A, Stromberg J, Sisowath C, Msellem MI, Pedro Gil J, Montgomery SM, Olliaro P, Ali AS, Bjorkman A (2005) Efficacy of Artesunate Plus Amodiaquine vs that of Artemether-Lumefantrine for the treatment of uncomplicated childhood *Plasmodium falciparum* Malaria in Zanzibar, Tanzania. *Clin. Inf. Dis., 41: 1079-86.*

Mutabingwa TK, Anthony D, Heller A, Hallett R, Ahmed J, Drakeley C, Greenwood BM, Whitty CJM (2005) Amodiaquine alone, amodiaquine + sulfadoxine-pyrimethamine, amodiaquine + artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomised effectiveness trial. *Lancet, vol 365, 1474-1480.*

Omari AA, Gamble C, Garner P (2004) Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. *Cochrane Database Syst Rev. (4):CD005564.*

van den Broek IV, Maung UA, Peters A, Liem L, Kamal M, Rahman M, Rahman MR, Bangali AM, Das S, Barends M, Faiz AM (2005) Efficacy of chloroquine + sulfadoxine-pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat Plasmodium falciparum malaria in the Chittagong Hill Tracts, Bangladesh. *Trans. Roy. Soc. Trop. Med. Hyg., 99, 727-735.*

Zurovac D, Ndhlovu M, Rowe AK, Hamer DH, Thea DM, Snow RW (2005) Treatment of paediatric malaria during a period of drug transition to artemether-lumefantrine in Zambia: cross sectional study. *BMJ, 331(7519), 706-7.*

2006

Alecrim MG, Lacerda MV, Mourao MP, Alecrim WD, Padilha A, Cardoso B, Boulos M (2006) Successful treatment of Plasmodium falciparum malaria with a six-dose regimen of artemether-lumefantrine vs quinine-doxycycline in the western amazon region of Brazil. *Am. J. Trop. Med. Hyg., 74(1), 20-25.*

Bukirwa H, Yeka A, Kamya MR, Talisuna A, Banek K, Bakyaita N, Rwakimari JB, Rosenthal PJ, Wabwire-Mangen F, Dorsey G, Staedke SG (2006) Artemisinin combination therapies for treatment of uncomplicated malaria in UgandaUganda Malaria Surveillance Project, Kampala, Uganda. *PLoS Clin Trials., 1(1):e7. Epub 2006 May 19.*

Chanda P and Hawela M (2006) Assessment of therapeutic efficacy of antimalarials in children under five years in the sentinel districts of Zambia in 2005 transmission season. Draft report.

Chanda P, Hawela M, Kango M, Sipilanyambe N (2006) Assessment of the therapeutic efficacy of a paediatric formulation of artemether-lumefantrine (Coartesiane) for the treatment of uncomplicated Plasmodium falciparum in children in Zambia. *Malar J., 5:75.*

Fanello CI, Karema C, van Doren W, Van Overmeir C, Ngamije D, D'Alessandro U (2006) A randomised trial to assess the safety and efficacy of artemether-lumefantrine (Coartem((R))) for the treatment of uncomplicated Plasmodium falciparum malaria in Rwanda. *Trans R Soc Trop Med Hyg. [Epub ahead of print]*

Guthmann JP, Cohuet S, Rigutto C, Fortes F, Saraiva N, Kiguli J, Kyomuhendo J, Francis M, Noel F, Mulemba M, Balkan S (2006) High efficacy of two artemisinin-based combinations (artesunate + amodiaquine and artemether + lumefantrine) in Caala, Central Angola. *Am J Trop Med Hyg., 75(1):143-5.*

Heemskerk W, Schallig H, de Steenhuijen Piters B (2006) The World of artemisinin in 44 questions. (http://smartsite.kit.nl/net/KIT_Publicaties_output/showfile.aspx?a=tblFiles&b=FileID&c=FileName&d=TheFile&e=879).

Lesaffre E, Garcia Zattera MJ, Kackou H, Bissangéné E, Penali L, Ameye C and Jansen FH (2006) Relative advantages of various Artesunate based Combination Therapies (ACT's): A meta-analysis. Submitted for publication AJTMH.

Makanga M, Premji Z, Falade C, Karbwang J, Mueller EA, Andriano K, Hunt P, De Palacios PI (2006) Efficacy and safety of the six-dose regimen of artemether-lumefantrine in pediatrics with uncomplicated Plasmodium falciparum malaria: a pooled analysis of individual patient data. *Am J Trop Med Hyg., 74(6):991-8.*

Meremikwu M, Alaribe A, Ejemot R, Oyo-Ita A, Ekenjoku J, Nwachukwu C, Ordu D, Ezedinachi E (2006) Artemether-lumefantrine versus artesunate plus amodiaquine for treating uncomplicated childhood malaria in Nigeria: randomized controlled trial. *Malar. J., 5:43.*

Mohamed AO, Eltaib EH, Ahmed OA, Elamin SB, Malik EM (2006) The efficacies of artesunate-sulfadoxine-pyrimethamine and artemether-lumefantrine in the treatment of uncomplicated, Plasmodium falciparum malaria, in an area of low transmission in central Sudan. *Ann Trop Med Parasitol., 100(1):5-10.*

Mulenga M, Van Geertruyden JP, Mwananyanda L, Chalwe V, Moerman F, Chilengi R, Van Overmeir C, Dujardin JC, D'Alessandro U (2006) Safety and efficacy of lumefantrine-artemether (Coartem(R)) for the treatment of uncomplicated Plasmodium falciparum malaria in Zambian adults. *Malar J., 5:73.*

Omari AA, Gamble C, Garner P (2006) Artemether-lumefantrine (four-dose regimen) for treating uncomplicated falciparum malaria. *Cochrane Database Syst Rev. (2):CD005965.*

Salah MT, Faroug M, Magzoub MM, Adam I (2006) Efficacy of artemether-lumefantrine (Co-Artesiane®) suspension in the treatment of uncomplicated P. falciparum malaria among children under 5 years in eastern Sudan. *Tropical Journal of Pharmaceutical Research, 5 (1): 551-555.*

World Health Organization (2006). Guidelines for the treatment of Malaria. (WHO/HTM/MAL/2006.1108). (http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf)