APPLICATION FOR INCLUSION OF ARTEMETHER 20mg/1ml FOR INTRAMUSCULAR ADMINISTRATION IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN

Generic name: Artemether 20mg/ml solution for intramuscular injection

Trade name: Artesiane® 20

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Information to be included with an application for inclusion

1. Summary statement of the proposal for inclusion

Intravenous quinine has been the drug of choice to treat severe or cerebral malaria in most malaria endemic countries all over the world. However, in some rural areas intravenous administration is not preferred because of the high risk of infection. Alternative treatments, such as intramuscular artemether are necessary to overcome this problem. In view of its good performance and of the simplicity of its administration by intramuscular injection, artemether appears to be an excellent alternative for treatment of severe malaria and cerebral malaria in rural areas where facilities for intravenous administration may not yet be optimal (poor medical facilities). Apart from this, since the introduction of the artemisinin in the mid nineties artemether in oil for intramuscular injection has become popular. WHO recognised the importance of the artemisinin derivatives and placed artemether 80mg/ml (adult dose) for intramuscular use on its essential drug list. Unfortunately, paediatric formulations were not available and accurate dosing with the adult formulation of 80 mg/ml is difficult.

For years, Dafra has been preparing artemether intramuscular injectables with miglyol as carrier solvent. Miglyol is a short chain fatty acid (C_6-C_{10}) which is rapidly hydrolyzed from the glycerol moiety and taken up by the blood. This makes that the artemether will be released rapidly from the site of injection and adequate drug levels are built up much faster than with arachis oil preparations, used in most other available intramuscular formulations. Moreover, apart from the adult formulation of 80 mg/ml artemether solved in miglyol for intramuscular injection (Artesiane® 80), a paediatric formulation of 20 mg/ml artemether solved in miglyol for intramuscular injection (Artesiane® 20) was developed to overcome the accurate dosing difficulties.

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 solution for intramuscular injection contains an antimalarial drug with the INN name artemether dissolved in fractionated coconut oil. In the public market the product is known under the brand name Artesiane® 20 and under the generic name Artemether 20 mg/1ml solution for intramuscular injection.

5. Dosage form or strength proposed for inclusion

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.

5.2. The paediatric formulation

Name	Formula	FUNCTION	REFERENCE

ACTIVE PRINCIPLE

β-artemether	**20,00 mg**	**Active principle**	**Int. Pharm**

OTHER COMPONENTS

Fractionated coconut oil (medium chain triglycerides, miglyol) qs ad	1,00 ml	solvent	PhEur
Nitrogen	QS	Inert atmosphere	PhEur

As Refined coconut oil (miglyol) is a fluid with relatively high viscosity, the ampoules are filled as to ensure an extractable volume of 1.00-1.15ml: the nominal fill volume is 1.1ml

5.3. Stability of the formulation

Testing at ambient conditions

Artemether ampoules are stored at room temperature (15 - 25°C) and at atmospheric humidity. The results show that the product is stable for at least 36 months. The impurities present in the finished product are due to the impurities of the starting material.

Testing at accelerated conditions

The study of accelerated degradation (45°C and 75% R.H.) shows that there is no degradation of the active ingredient. The finished product characteristics remain within the specified limits. This result proves that there is no degradation of the active ingredient in tropical areas (zone IV).

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 solution for intramuscular injection is manufactured under licence by Rotexmedica GmbH, Bunsenstrasse 4, D-22946 Trittau, Germany 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. Miglyol, fractionated coconut oil, is manufactured by SASOL Germany GmbH, Standort Witten, Arthur-Imhausen Str 92, D-58453 Witten.

6.2. History of the product

At the beginning of the 1990s the Chinese Authorities and Rhone-Poulenc Rorer signed an agreement to develop intramuscular artemether indicated for the treatment of malaria caused by all forms of Plasmodium including severe malaria caused by multiple drug resistant strains and to market the product, Paluther®, in the malaria endemic countries. Together with the company the products has been bought by the pharmaceutical group Sanofi aventis. Preclinical and clinical studies confirmed the importance of the drug in the curative treatment of severe malaria due to Plasmodium falciparum, or when resistance to other antimalarial

drugs is suspected. The outcome of these new trials was the recognition that i.m. artemether is at least as efficient as quinine. (Helenport and Roche, 1998) The importance of artemisinin and its derivatives was also recognised by the WHO Expert Committee on Essential Drugs. As a consequence, artemether 80 mg/ml as an intramuscular injectable formulation was added to the WHO Complementary Model list of Essential Medicines as a reserve antimalarial for the treatment of severe falciparum malaria resistant or suspected of being resistant to quinine (WHO, 1996). Artemether intramuscular injection was marketed in African and Asian countries. In the revision of March 2007 artemether intramuscular was listed as a real essential medicine. Unfortunately, paediatric formulations are not available and accurate dosing with the adult formulation of 80 mg/ml to treat small children is difficult. Moreover, most artemether intramuscular formulations, like Paluther®, use arachis oil (Kunming pharmaceutical factory, Kunming, Republic of China) as carrier solvent to solve the active antimalarial artemether. This causes some pharmacokinetic problems. Arachis oil is a long chain fatty acid (C18-C20), which is known to cause delayed release of the included compounds, much the same as sesame oil. A single intramuscular (i.m.) injection of 3.2 mg/ kg artemether solved in arachis oil was reported to give variable absorption kinetics probably related to drug formulation characteristics (Mithwani *et al.*). Furthermore, other investigators found that intramuscular artemether solved in arachis oil was absorbed very slowly in patients with acute malaria (Silamut *et al.*).

For years, Dafra has been preparing artemether i.m. injectables with miglyol as carrier solvent to overcome the variable absorption kinetics. Miglyol is a short chain fatty acid (C_6-C_{10}) which is rapidly hydrolyzed from the glycerol moiety and taken up by the blood. This makes that the artemether will be released rapidly from the site of injections and adequate drug levels are built up much faster than with arachis oil preparations. Initially, Dafra Pharma developed artemether 80 mg/ml in the early nineties and brought it on the market in several African and Asian countries. However, Dafra Pharma noticed the difficulties of accurate dosing with this preparation in small children and as a result they started the development of a paediatric formulation of artemether 20 mg solved in 1 ml miglyol for intramuscular injection in 1996. Marketing started in 1998 and the first registrations were obtained in 1999. At this moment Artesiane® 20 is registered in 28 countries.

6.3. International availability and production capacity

The current maximal production capacity is 1 million paediatric ampoules per month (12 million ampoules per year). Dependent on the quantities needed the product can be scaled

up to 24 million ampoules per year ore more when needed. There is no restriction on the availability of the raw active material artemether and on the availability of fractionated coconut oil.

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

Artemether solution for intramuscular injection must be listed as an example of the pharmacotherapeutic group antimalarial medicines for curative treatment of severe falciparum malaria.

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 risk of severe falciparum malaria developing is greatest among young children, 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 et al., 2006; Krishna *et al.*, 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) for treatment of uncomplicated malaria. (WHO 2001a and 2006). However, in cases of complicated severe malaria monotherapy is still the standard.. At present, quinine remains the drug. For nearly 400 years quinine has been the principal drug used to treat severe malaria and at present it remains the drug of choice for the treatment of severe complicated malaria in most parts of the world. Despite its long history of efficacy, quinine has significant limitations. Even with prompt administration, case-fatality rates in severe malaria often exceed 20%. (Anstey *et al.*, 2006)
Moreover, it should always be given initially by intravenous infusion and should be replaced by oral administration of an ACT as soon as the patient is capable of swallowing. Intravenous therapy has many risks and should therefore only be performed by trained personnel under medical supervision, using proper equipment. In some rural areas, where medical facilities are poor, intravenous administration is not preferred because of the high risk of secondary infection. Alternative treatments, such as intramuscular artemether, are necessary to overcome this problem. Data indicate that the efficacy of intravenous quinine and intramuscular artemether are similar under hospital conditions. However, the more complicated dosing regimen of IV quinine and the accompanying need to monitor both cardiac function and glucose levels make IM artemether the drug of choice for management of severe malaria in most epidemic situations because quinine use is impractical in most areas with poor medical facilities. (WHO, 2003)

9. Treatment details

9.1. Method of administration

The drug is given by intramuscular injection in the gluteal muscle. Aseptic conditions must be respected when injecting artemether.

9.2. Dosage

The dosage depends on the severity of the case and the clinical state of the patient. Formulations for intramuscular injection of artemether are mostly used in case of severe malaria, but also in case of patients showing gastro-intestinal problems.
In general 3.2 mg/kg body weight is administered as one single injection (loading dose) on the first day, followed by a maintenance dose of: 1,6 mg/kg body weight administered as one

single injection during the following four days. Treatment can however also be continued by oral artemisinin-based combination therapies.

9.3. Duration

A full course therapy of five days is essential in order to avoid recrudescence.
In severe malaria it may be necessary to increase the loading dose and to prolong treatment for seven days if parasitaemia is not cleared during the first few days.

9.4. WHO treatment guidelines

Formulation advised by the WHO are ampoules of injectable solutions for intramuscular injection containing 80 mg artemether in 1 ml oil solution for adults or 40 mg artemether in 1 ml for paediatric use. The advised dosage is 3.2 mg/kg body weight as a loading dose followed by half that dose (1,6 mg/kg) during the following four days given in the anterior thigh (WHO, 2006). As soon as the patient is capable of swallowing then treatment can be continued by an oral artemisinin-based combination therapy.

10. Summary of comparative effectiveness and evidence on safety in a variety of clinical settings

10. 1. Studies in Asia

Non-comparative trials with im artemether as a single agent

Thirty-three female patients suffering from acute uncomplicated falciparum malaria were treated with intramuscular artemether (160 mg (day1) followed by 80 mg or in case of low body weight 3.2/kg (day 1) followed by 1.6 mg/kg/dose) for 5 days during May-October 1990. Thirty-one patients had completed the 28-day follow-up. The cure rate was 90.3% (28/31). The geometric mean of parasitemia was 17,378/microliters (range 640-234,720). The mean fever (FCT) and parasite clearance time (PCT) were 41.8 and 49.4 hours, respectively. Mild and transient adverse effects like pain at the injection sites, vomiting, dizziness, abdominal pain, palpitation and diarrhoea were experienced in eleven patients but may in part be due to symptom complex of malaria. In conclusion, artemether proves to be effective and safe. (Bunnag *et al.*, 1993)

Myint & Tin Shwe (1986) examined 30 patients with falciparum malaria who were treated with intramuscular artemether (200 mg initial dose, followed by 100 mg every 12 h for 4 doses (total dose = 600 mg)). Control patients were treated with standard doses of chloroquine (4 patients), quinine (2 patients) and sulfadoxine / pyrimethamine (2 patients). It was shown in this study that the patients who were treated with artemether had a rapid initial response with mean fever and parasite clearance times of 18 and 29 h, respectively. These parameters were claimed to be faster than those obtained from chloroquine, quinine and sulfadoxine-pyrimethamine. At the 28-day follow-up 23 patients were seen. There were 4 patients with reappearance of asexual parasites in peripheral blood smear, the cure rate was calculated to be 83 %. However, re-infection can not be excluded in these relapsing patients. One patient had abscess on the site of artemether injection, 7 had bradycardia as was shown during ECG examination. No other laboratory abnormality was noted.

Bhattacharya *et al.* (1997) treated 154 patients suffering from acute attack of moderate to severe malaria caused by Plasmodium falciparum with 480 mg artemether, administered intramuscularly in six equally divided doses at 12 hour intervals. Results showed a rapid parasite clearance. Mean parasite clearance time was found to be 23.65 ± 1.57 hours. Mean fever clearance time was 35.28 ± 1.7 hours. Adverse drug events were mild and self-limiting. Recrudescence rate among the patients followed up was 4.55%.

An open clinical trial was conducted in Indonesia by Sharma *et al.* (1999). 30 patients of severe falciparum malaria with heavy parasitaemia were treated with artemether administered as 80 mg intramuscular injection twice on first day and then single dose of 80 mg intramuscular on 2nd to 5th day. The trial could be completed in 28 patients and two patients expired. All patients became afebrile by the 4th day with fever clearance time approximately 31.92 +/- 15.30 hr. Twenty-five patients (83.33%) became parasite free by 5th day with mean parasite clearance time approximately 47.04 +/- 19.95 hr. Deranged liver function and renal profile was observed in 63% and 50% patients respectively. Two patients, who died had very high degree of parasitaemia (50% and 16%) with cerebral malaria. One died due to multiorgan failure and other due to massive hematemesis and shock. No significant side effects were noted. This pilot study demonstrated that intramuscular artemether is a useful addition to antimalarial drugs in this erea of multidrug resistant P. falciparum malaria showing high clinical potency with virtually no side effect.

Dose ranging trials and experiments with alternative dosing schedules

Bunnag *et al.* (1992) carried out a comparative study of two dosage regimens of artemether, ie 480 mg and 600 mg total dose given over 5 days in uncomplicated and severe falciparum malaria. 167 patients were included in the study, 61 with acute uncomplicated falciparum malaria and 106 with severe malaria. All patients showed a good initial response. The difference in total dose had no effect on the parasite or fever clearance time. However, the severity of the disease did have some influence of these times. The parasite clearance time and fever clearance time from either regimen of uncomplicated malaria were significantly faster than those of severe malaria ($p < 0.005$ and $= 0.05$, respectively). The cure rate seems to have some correlation with the amount of drug given and severity of the disease. The cure rates in uncomplicated malaria were 84 and 92%, respectively, for 480 mg and 600 mg. In severe malaria the cure rates dropped to 65 and 76%, respectively, for 480 and 600 mg. The authors conclude that artemether can be considered as an alternative antimalarial for multiple drug resistant falciparum malaria. However, the cure rate of severe falciparum malaria in this study is not considered satisfactory in areas with multiple drug resistant falciparum malaria.

Karbwang *et al.* (1994) randomised 28 male Thai patients with severe falciparum malaria to receive either artemether for a 5 (300 mg initial dose followed by 100 mg for another 4 days) or a 7 days regimen (160 mg initial dose, followed by 80 mg daily for another 6 days). Thirteen patients received a 5 day regimen and 15 received 7 day regimen. The follow-up period was 28 days. The median values of parasite and fever clearance times in the 5 and 7 days regimens were 52 vs 60 hours, and 85 vs 68 hours, respectively. There were 8 and 4 patients, respectively who had recrudescence during days 15 to 25. The cure rates were 38% (95% CI = 14-68%) and 73% (95% CI - 50-96%), respectively for 5 and 7 day regimens. None died in either group. No patients in either group had neurological sequelae after recovery of consciousness. Clinically adverse effects in either group were transient pain at the site of injection. No drug related biochemical or ECG changes were noted in either group. The duration of treatment is the determinant of the cure rate; however, the duration of even 7 days still resulted in high recrudescence rate.

Comparison of artemether im with quinine

Myint & Shwe (1987) treated 31 pairs of patients with complicated falciparum malaria (with anaemia, jaundice, raised blood urea, hyperpyrexia or more than 2% of erythrocytes parasitized) with artemether (200mg as initial dose, followed by 100 mg every 12h for 4

doses) or quinine. All patients in the artemether group survived but 2 of those treated with quinine died. Fever clearance time and parasite clearance time of patients treated with artemether were significantly shorter than in the quinine-treated group. One patient who failed to respond to quinine within 72 h was saved with artemether. Follow-up of the patients showed that 9 of 23 (39.1%) recrudesced on day 28 in the artemether group. In the quinine group the recrudescence rate was 9% (2 of 22). Hence artemether may be considered as one of the drugs of choice for severely ill patients; it may even be better than quinine. There were no serious signs or symptoms of drug toxicity, no changes in ECG were found in any of the patients treated with artemether.

Karbwang *et al.* (1992) randomly allocated 26 patients with severe falciparum malaria to be treated with quinine or artemether. Twelve patients received quinine at the standard dose and fourteen patients received artemether intramuscularly at a total dose of 640 mg over 7 days. The patients were kept in the hospital for at least 7 days. The survival rates were 93% and 58% in artemether and quinine groups, respectively ($p = 0.052$ at 95% confidence, using Fisher's exact test). The parasite and fever clearance times, and the time taken to gain consciousness in cerebral malaria patients were not significantly different between the two groups. Adverse effects in the quinine group consisted of dizziness and vertigo which were reported by 4 patients. No adverse effects were noticed in the artemether group.

Karbwang *et al.* (1995) randomly allocated 102 patients with severe falciparum malaria (92 males and 10 females) to receive either the standard regimen of quinine infusion (52 cases) or intramuscular artemether (50 cases). Artemether gave a better survival rate (87.2% vs. 63.3%) and parasite clearance time (54 vs. 78 h) than quinine. Fever clearance times (79 h vs. 84 h) and time to recovery of consciousness (48 h in both groups) were comparable. The most common adverse effect in patients treated with quinine was tinnitus. Two patients had severe hearing impairment which resolved within 1 week after the end of treatment. Mild, transient pain was noted at the injection site of artemether but no abscess formed. QTc wave prolongation was seen in most patients receiving quinine; however, no arrhythmia was observed despite the high concentration of quinine in some patients who had received quinine before admission. Complications developed in 7 survivors in each treatment group. No patient in the artemether group had neurological sequelae after recovery of consciousness, but 2 in the quinine group had left facial palsy and one had a myasthenia gravis-like syndrome. No patient died with complications in he artemether group, but 7 died with pulmonary complications in the quinine group.

Tran *et al.* (1996) conducted a randomized, double-blind trial in 560 adults with severe falciparum malaria. Two hundred seventy-six received intramuscular quinine dihydrochloride (20 mg/kg body weight followed by 10 mg/kg every eight hours), and 284 received intramuscular artemether (4 mg per kilogram followed by 2 mg per kilogram every eight hours). Both drugs were given for a minimum of 72 hours. There were 36 deaths in the artemether group (13 %) and 47 in the quinine group (17 %; P = 0.16; relative risk of death in the patients given artemether, 0.74; 95 % confidence interval, 0.5 to 1.11). The parasites were cleared more quickly from the blood in the artemether group (mean, 72 vs. 90 hours; P < 0.001); however, in this group fever resolved more slowly (127 vs. 90 hours, P < 0.001), the time to recovery from coma was longer (66 vs. 48 hours, P = 0.003), and the hospitalization was longer (288 vs. 240 hours, P = 0.005). Quinine treatment was associated with a higher risk of hypoglycemia (relative risk, 2.7; 95 % confidence interval, 1.7 to 4.4; P < 0.001), but there were no other serious side effects in either group.

An open-label, randomized, controlled trial was conducted by (Seaton *et al.*, 1998) to compare the safety and efficacy of intramuscular artemether (a loading dose of 3.2 mg/kg, followed by 1.6 mg/kg daily for 4 days) and intravenous quinine (a loading dose of 20 mg quinine dihydrochloride/kg, followed first by 10 mg/kg every 8 h, each injection taking 4 h, for at least 48 h, and then oral quinine for a total of 7 days) in the management of strictly defined severe/complicated malaria in Melanesian adults. Four (12%) of the 33 patients who enrolled and completed follow-up died (one of the 15 who received artemether and three of the 18 who received quinine). Overall, cerebral malaria was uncommon (6%) whilst jaundice was common (76%). The time taken to clear 50% of parasites was less in those treated with artemether (median = 8 h; range = 2-24 h) than in the patients given quinine (median = 14 h; range = 2-25 h; P = 0.05). Temperature defervescence was also quicker in those treated with artemether (median = 32 hours; range = 20-112 h) than in those in the quinine group (median = 48 h; range = 28-88 h; P = 0.034). Hypoglycaemia was not observed in any patient treated with artemether but complicated therapy in 11 (79%) of the 14 patients given quinine who had not had pre-treatment spontaneous hypoglycaemia. No serious adverse effects were attributable to artemether. The Plasmodium falciparum infections observed during the 1 month of follow-up, in three patients who had received artemether and two who had been given quinine, were probably due to recrudescence. Plasmodium vivax parasitaemias were also observed during follow-up, in one or two patients in each treatment group. Artemether

appeared to be safe in Melanesian adults and was found to be as effective as intravenous quinine in the treatment of severe or complicated falciparum malaria.

A randomized controlled trial was undertaken by Faiz *et al.* (2001) to compare the effectiveness of intramuscular artemether and parenteral quinine in the treatment of cerebral malaria in adults in Bangladesh. 51 patients received artemether and 54 patients received quinine. In the group treated with artemether 39 patients recovered, 9 patients died and 3 patients had neurological sequelae. In the group treated with quinine 43 patients recovered, 10 patients died and 1 patient had neurological sequelae (no significant difference with artemether group). Artemether treatment was associated with relatively quicker PCT 52.1 ± 33.3 h but slower FCT 58 ± 15.6 h compared with quinine (PCT = 60.7 ± 39 h and FCT = 47 ± 31.5 h). Fever and parasite clearance times were not significantly different in the two treatment groups ($p > 0.05$). In the patients treated with artemether the coma resolution time CRT was significantly slower in comparison of that of the quinine group (74.2 ± 51.8 h versus 53.4 ± 36 h, $p < 0.05$). Adverse reactions like vomiting and diarrhoea were similar in both groups while convulsions and neuropsychiatry side effects were more common with artemether than with quinine. No significant ECG changes were found in either of the two groups. These study results suggest that treatment with artemether is as effective as parenteral quinine in the treatment of cerebral malaria in adults.

Comparison of artemether im with other antimalarials

In a small 6-patient trial in patients suffering from multi drug-resistant falciparum malaria IM artemether (160mg on d1, followed by 80mg/d for 4 days) produced a 100% cure rate. Pain at the injection site with injectable artemether preparations was reported by some patients (Bunnag *et al.,* 1991).

One hundred and seventy five Vietnamese adults with severe and complicated malaria admitted to a rural district hospital were entered into an open randomized comparative study by Ha *et al.* (1997). 4 treatment regimens based on artemisinin and its derivatives were compared: intramuscular (i.m.) artemether, artemisinin suppositories, artesunate (i.m.) and intravenous Artesunate. The median fever clearance time ($P = 0.13$) was respectively 48 h (95% confident interval [CI] 38-58 h), 42 h (95% CI 36-48 h), 36 h (95% CI 30-42 h) and 30 h (95% CI 18-42 h) in. The respective median parasite clearance times were 30 h (95% CI 26-34 h), 30 h (95% CI 24-36 h), 24 h (95% CI 15-33 h), and 24 h (95% CI 15-33 h) ($P = 0.30$); the median times for recovery of consciousness were 47 h (95% CI 31-63 h), 24 h (95% CI

18-30 h), 30 h (95% CI 18-42 h), and 24 h (95% CI 4-44 h) (P = 0.18); and the mortality rates were 11.1%, 17.6%, 10.2% and 16.6%, respectively (P = 0.64). There was no significant difference in efficacy between the 4 treatments.

Looareesuwan *et al.* (2002) compared the antimalarial efficacy of intramuscular (i.m.) artemotil with intramuscular artemether in Thai patients with acute uncomplicated falciparum malaria.. METHODS: Two different artemotil dose regimens: 3.2 mg kg-1 on day 0 and 1.6 mg kg-1 on days 1-4 (treatment A1) and 3.2 mg kg-1 on day 0 and 0.8 mg kg-1 on days 1-4 (treatment A2) were compared in three groups of 20-22 patients with standard i.m. artemether treatment: 3.2 mg kg-1 on day 0 and 0.8 mg kg-1 on days 1-4 (treatment R). The mean PCT for each of the two artemotil treatments (52 and 55 h, respectively) was significantly longer than for artemether (43 h). The 95% CI for the difference A1 vs R was 0, 16 h (P=0.0408) and for difference A2 vs R it was 2, 19 h (P=0.0140). FCT was similar for the three treatments. The incidence of RI ranged from 5 out of 19 for treatment A2 to 3 out of 20 for treatment R. Safety assessment, including neurological and audiometric examinations showed no clinically relevant findings. Adverse events before and during treatment included headache, dizziness, nausea, vomiting and abdominal pain. These are characteristic of acute malaria infections and resolved during treatment. Both treatments were safe and effective in the treatment of acute uncomplicated P. falciparum malaria.

Krudsood *et al.* (2003) prospectively studied 803 Thai patients admitted to the Bangkok Hospital for Tropical Diseases to assess the safety, tolerability and effectiveness of treatments for strictly defined P. falciparum malaria. Patients were assigned to one of five treatment groups: (group 1) a 5-day course of intravenous artesunate in a total dose of 600 mg (group 2) intravenous artesunate as in group 1 followed by mefloquine, 25 mg/kg, (group 3) a 3-day course of intramuscular artemether in a total dose of 480 mg; (group 4) intramuscular artemether as in group 3 followed by mefloquine, 25 mg/kg and (group 5) intravenous quinine, 200 mg/kg given in divided doses over seven days followed by oral tetracylcine, 10 mg/kg, for 7 days. When patients could take oral medications, the parenteral antimalarials were administered as oral agents. There were no major adverse effects observed with any of the five treatment regimens. With all regimens, 95 to 100% of the patients survived. Mean parasite clearance times were more rapid with the artemisinin regimens (53 to 62 hours) than with quinine (92 hours). The mean fever clearance times with intravenous artesunate (80 to 82 hours) were about a day shorter than those with intramuscular artemether (108 hours) or intravenous quinine (107 hours). Mefloquine reduced the recrudescence rate from 24 to 5%

with intravenous artesunate but from 45 to 20% with intramuscular artemether; recrudescence was 4% with quinine and tetracycline. A dose and duration of therapy greater than those in this study are needed for optimal therapy with intramuscular artemether.

Karunajeewa *et al.* (2006) compared artesunate suppositories (n = 41; 8 to 16 mg/kg of body weight at 0 and 12 h and then daily) with intramuscular (i.m.) artemether (n = 38; 3.2 mg/kg at 0 h and then 1.6 mg/kg daily) in an open-label, randomized trial with children with severe Plasmodium falciparum malaria in Papua New Guinea. One suppository-treated patient with multiple complications died within 2 h of admission, but the remaining 78 recovered uneventfully. Compared to the artemether-treated children, those receiving artesunate suppositories had a significantly earlier mean PCT50 (9.1 versus 13.8 h; P = 0.008) and PCT90 (15.6 versus 20.4 h; P = 0.011). Mean time to per os status was similar for each group. One child in the i.m. artemether group developed abdominal pain, diarrhoea, nausea, and anorexia on days 2 to 4, and another artemether-treated child developed late fever on day 3. In all of these cases, symptoms were mild, their onset was after parasite and fever clearance and resolution occurred spontaneously within 1 to 3 days. In severely ill children both treatments were effective and safe.

Studies using artemether im combination therapies

Plasmodium falciparum in south-east Asia currently is highly resistant to chloroquine and sulfadoxine-pyrimethamine. Mefloquine used to be the chemosuppressant drug of choice in areas with chloroquine resistance. However, sensitivity to this drug has recently decreased in South-East Asia, and there is no suitable single alternative drug. However, enhanced cure rates with the well-tolerated combination artemether / mefloquine have been obtained in several thousands of patients recruited by a large number of investigators:

As the recrudescence rate after artemether treatment is high, Shwe *et al.* (1988) studied the effects of the a artemether / mefloquine combination in 30 pairs of patients with complicated Plasmodium falciparum malaria (with anaemia, hyperpyrexia, jaundice or more than 5% of erythrocytes parasitized). Patients with cerebral signs and symptoms were excluded. One group of patients was treated with oral mefloquine (750 mg) and artemether (600 mg by injection, 200 mg initially and 100 mg every 12 h). The second group of patients was treated with quinine (10 mg/kg orally every 8 h for 7 d). All patients were admitted to hospital for 7 d and examined subsequently on days 14, 21 and 28. All those treated with mefloquine plus

artemether survived and their parasite clearance time and fever clearance time were significantly shorter than those of patients receiving quinine. 2 patients treated with quinine died. There was no recrudescence in any patient of either group. There were no serious clinical toxicity or ECG changes in the artemether-mefloquine group.

An open study of artemether combined with mefloquine was conducted by Shwe *et al.* (1989) in the Tharawaddy Civil Hospital in 1988. 13 cerebral malaria patients were recruited in the study. The regimen was oral mefloquine (750 mg) and artemether (600 mg by injection, 200 mg initially and 100 mg every 12 h). Mefloquine was given via an intragastric tube. All patients survived. No recrudescence was detected in any of the patients.

141 cases of strictly defined cerebral malaria were recruited for the study published by Win *et al.* (1992) of three regimens: (1) intramuscular artemether plus oral mefloquine, (2) intravenous artesunate plus oral mefloquine, and (3) intravenous quinine (with or without an initial loading dose) plus oral tetracycline. The overall mortalities in each group were 14%, 8.3% and 34.3% respectively. The average parasite clearance time was 27.30 ± 19.62 hours in regimen 1, 41.84 ± 17.55 hours in regimen 2, and 47.30 ± 21.95 hours in regimen 3. No recrudescence was observed in regimens 1 and 2, but 12.1% recrudesced in the third. No serious side-effects were noticed in any group. It was concluded that artemether and artesunate were superior to quinine in reducing the mortality and the recrudescence rate in severe falciparum malaria.

The efficacy and safety of the combination artemether / mefloquine was also confirmed by Shwe & Hla (1992) who compared the effect of this combination with the efficacy of quinine in 35 patients with complicated falciparum malaria including 5 patients with cerebral malaria. All patients treated with the artemether-mefloquine combination survived and all were free from toxic effects of the drugs. Three patients on quinine therapy died. The mortality rate was 8.5%. The mean parasite clearance time of patients treated with artemether plus mefloquine was significantly shorter than those treated with quinine but there was no significant difference in the mean fever clearance of the two groups of patients. There was no recrudescence with artemether and mefloquine; the recrudescence rate was 5.5% with quinine. The study showed that the artemether-mefloquine combination is superior to quinine for the treatment of patients with complicated falciparum malaria, including cerebral malaria.

Other combinations have also been used with variable success:

Naing *et al.* (1988) treated 29 male patients with a combination of 200 mg artemether (Single intramuscular dose), 1500 mg sulfadoxine and 75 mg pyrimethamine (orally). The mean parasite clearance time was 106.7 ± 48.7 h. Side effects were few and self-limiting. 13 of 29 patients had recrudescences before day 28; as all the patients were living in towns, reinfection was unlikely. This parasite clearance time was longer than that in patients treated with artemether alone (600 mg total dose), and the recrudescence rate was higher. The authors do not recommend this scheme for patients in areas where sulfadoxine/pyrimethamine resistance is already established.

10.2 Studies in Africa

Non-comparative trials with im artemether as a single agent

Kombila *et al.* (1995) evaluated the efficacy and tolerance of artemether administered intramuscularly twice daily (1.6 or 3.2 mg/kg/day) in 47 children (mean age 2.4 years old) suffering from mild (n = 28) or severe (n = 19) attacks of Plasmodium falciparum malaria. Parasites were eliminated in all patients in a mean of 47.7 +/- 9.8 hours. The time to eradication was not significantly affected by the dose, prior administration of an anti-malarial agents to treat the attack or the severity of the attack. There were two cases of clinical and parasitological regression, on days 14 and 21. There were no deaths. The neurological symptoms of severity resolved in 48 hours in most cases. Local and systemic tolerance was excellent.

The clinical efficacy of intramuscular artemether was studied in 144 children suffering from severe non cerebral malaria by Sowunmi & Oduola (1996a). Fifty-three children with chloroquine-resistant and 27 children with sulfadoxine-pyrimethamine-resistant falciparum malaria were also studied. Pre-treatment parasitaemia was cleared by 24 h after commencement of treatment in more than 95% of the patients in all groups. The parasite and fever clearance times were 35.4 ± 8.0 and 18.6 ± 6.3 h respectively, in children suffering from severe non cerebral malaria 36.3 ± 7.9 and 15.6 ± 3.8 h, respectively, in the chloroquine-resistant and 36.8 ± 8.8 and 16.5 ± 4.2 h, respectively, in the sulfadoxine-pyrimethamine-resistant groups. The cure rate in all groups on day 14 was 100%. Side effects following

treatment were minimal and comprised pain with mild tenderness at site of injection in two children and bradycardia, on the second or third day of treatment, in another two patients. In another study by the same authors, a 100% cure rate was seen in 32 patients in which treatment with one or more courses of chloroquine, amodiaquine, sulphadoxine-pyrimethamine and erythromycin given alone or in combination failed to eradicate malaria (Sowunmi & Odulola 1997).

Comparison of artemether im with quinine

In the preliminary study of moderately severe malaria by White *et al.* (1992), 30 Gambian children were randomised in pairs to receive either intramuscular artemether (4 mg/kg loading dose followed by 2 mg/kg daily) or intramuscular chloroquine 3.5 mg base/kg every 6 h. Both drugs were well tolerated and rapidly effective. The times to parasite clearance were significantly shorter in the artemether recipients (mean 36.7 [SD 11.3] vs 48.4 [16.8] h, p less than 0.05). 43 children with severe malaria were then randomised to receive intramuscular treatment with the same regimens of artemether (n = 21) or chloroquine (n = 22) as used in the preliminary study. 8 children (19%) died. There were no significant differences between the two groups in the clinical, haematological, biochemical, or parasitological measures of therapeutic response in survivors and there was no evidence of local or systemic toxicity.

The efficacy of artemether administered intramuscularly for the treatment of Plasmodium falciparum malaria was compared to quinine in an open randomized trial including 54 patients in eastern Sudan, where chloroquine resistance is common (Elhassan *et al.*, 1993). The artemether treatment (5 d intramuscular regimen) was effective and the drug was well tolerated. All patients had cleared the parasitaemia and were free of symptoms 48 h after initiation of treatment. The parasite clearance time was comparable in patients receiving artemether and quinine. No side effect was reported by patients receiving artemether. No recrudescence was seen in 21 patients treated with artemether who completed 28 d follow-up. In the quinine group 3 of 18 patients had recrudescences, or possibly reinfections, on days 14, 21 and 28.

Taylor *et al.* (1993) compared artemether treatment with standard quinine treatment in Malawian children with cerebral malaria. 65 unconscious children were randomly allocated to intravenous quinine (n = 37) or intramuscular artemether (n = 28) treatment. The two groups were well matched for various prognostic features. Median parasite clearance times were

shorter in the artemether group (28 vs 40 h in the quinine group, p = 0.0002). Coma resolution times were also shorter with artemether than with quinine (8 vs 14 h, p = 0.01).

Cerebral malaria has a mortality rate of 10 to 30 % despite treatment with parenteral quinine, a situation that may worsen with the spread of quinine resistance. van Hensbroek *et al.* (1996) conducted a randomized, unblinded comparison of intramuscular artemether and intramuscular quinine in 576 Gambian children with cerebral malaria. The primary end points of the study were mortality and residual neurologic sequelae. Fifty-nine of the 288 children treated with artemether died in the hospital (20.5 %), as compared with 62 of the 288 treated with quinine (21.5 %). Among the 418 children analyzed at approximately five months for neurologic disease, residual neurologic sequelae were detected in 7 of 209 survivors treated with artemether (3.3 %) and 11 of 209 survivors treated with quinine (5.3 %, P = 0.5). After adjustment for potential confounders, the odds ratio for death was 0.84 (95 % confidence interval, 0.53 to 1.32) in the artemether group, and for residual neurologic sequelae, 0.51 (95 % confidence interval, 0.17 to 1.47). There were fewer local reactions at the injection site with artemether than with quinine (0.7 % vs. 5.9 %, P = 0.001).

Murphy *et al.* (1996) have compared the efficacy of intramuscular artemether (3.2 mg/kg loading dose followed by 1.6 mg/kg daily) versus intravenous quinine (20 mg/kg loading dose followed by 10 mg/kg every 8 h) as treatment for cerebral malaria in children with coma and Plasmodium falciparum parasitaemia in an open randomized clinical trial in Kenya. Both drugs were well tolerated and no significant adverse effect was observed. Parasite clearance times (50% and 90%) were shorter in patients treated with artemether (median times [h], with interquartile ranges in brackets, were: 50%, 7.3 [4.2-12.4] vs. 15.5 [9-22]; 90%, 16.9 [13.2-25] vs. 28.5 [22-35]; P < 0.0001). The total mortality in 160 children with cerebral malaria was 16.25%, with no overall significant difference between the 2 treatment groups. The frequency of neurological sequelae and clinical recovery times were similar in both treatment groups. We conclude that there would currently be no advantage in replacing quinine with artemether for the treatment of cerebral malaria in African children.

Taylor *et al.* (1998) compared IM artemether and IV quinine in the treatment of cerebral malaria in African childrenin an open, randomized trial. Data from 83 artemether recipients and 81 quinine recipients were reported. Overall mortality rates and coma resolution times were not significantly different in the two treatment groups but parasite and fever clearance times were significantly more rapid in the artemether recipients. Analyses which took into

account the possible confounding variables did not significantly alter the findings of these unadjusted analyses.

A study was carried out by Fargier *et al.* (1999) to compare intramuscular artemether (3.6 mg/kg on the first day and 1.6 mg/kg for the following 4 days) and intravenous quinine (1.6 mg/kg for the first 4 hours and 8 mg every 8 hours for the next 3 days) for management of severe falciparum malaria in adults and adolescents in Cameroon. 84 patients were included; 40 in the artemether group and 44 in the quinine group. Findings showed that artemether was more effective than quinine with regard to total clearance of parasitemia, 90 p. 100 clearance, and fever control and that it was as effective with regard to 50 p. 100 clearance and recovery of consciousness. In view of its good performance and of the simplicity of its administration by intramuscular injection, artemether is an excellent alternative for treatment of severe malaria and cerebral malaria.

The efficacy of a 5-day treatment with intramuscular artemether (3.2-mg/kg loading dose followed by 1.6 mg/kg daily) was compared to that of the standard 7-day treatment with quinine (20-mg/kg loading dose followed by 10 mg/kg every 8 h) in a randomised clinical trial including 103 children aged 12-60 months with cerebral malaria between 1994 and 1996 (Olumese *et al.*, 1999). No statistical difference of immediate efficacy was found between the two treatments. There were 11 (20%) deaths in the artemether group and 14 (28%) in the children who received quinine. The respective artemether versus quinine median fever clearance times (h) were 39 (interquartile ranges [IQ] 30-54) vs. 48 (IQ 30-60), and parasite clearance 42 (IQ 24-60) vs. 36 (IQ 30-48). However, one patient who received artemether had a recrudescence on day 14, which was successfully treated with sulphadoxine-pyrimethamine. Times to recovery from coma were 24 h (IQ 18-45) and 33 h (IQ 19-57), respectively. The occurrence of transient neurological sequelae including motor disabilities, cortical blindness, and afebrile seizures was also similar in the two groups. No adverse reactions to the two drugs were recorded during the study period. Artemether intramuscular is a safe and effective treatment of cerebral malaria in children.

Adam *et al.* (2002) compared with an open randomized controlled clinical trial the efficacy of intramuscular artemether with that of intravenous quinine in the treatment of Sudanese children with severe falciparum malaria. Forty one male and female children were enrolled; 21 allocated to artemether and 20 to quinine. The mean +/- (SD) fever clearance time was 30.5 +/- (20.9) hours in the artemether group, while it was 18.0 +/- (8.1) hours in the quinine group; the difference was highly significant (P=0.02). The mean parasite clearance time was

shorter in the artemether group than in the quinine group, but it was not statistically significant, (16.0 vs. 22.4 hours; p>0.05). In comatose patients (three in the artemether group, three in the quinine group) the time of recovery from coma was significantly shorter in artemether group than in quinine group (12.5 vs. 20.16 hours; P<0.05). In the quinine group, one patient died and one patient developed hypoglycaemia. No serious adverse events were detected in the group treated with artemether. The results obtained show that artemether can be used as safe and effective alternative drug for the treatment of children with severe falciparum malaria in the wake of the growing resistance to quinine in Sudan.

Comparison of artemether im monotherapy with other antimalarials

Walker *et al.* (1993), and Salako *et al.* (1994a) compared the efficacy of intramuscular artemether against intramuscular sulfadoxine-pyrimethamine in an open randomized study in children with severe but uncomplicated malaria. Parasite clearance time and fever clearance time were faster with artemether. The parasitological clearance on day 14 was 100% for artemether and 98% for sulfadoxine-pyrimethamine, but 8 patients in the artemether group and 1 in the other group had a recrudescence of parasitaemia. There was no toxic reaction of note in either group.

Intramuscular artemether was compared with intramuscular sulfadoxine-pyrimethamine in Nigerian children with moderately severe malaria requiring parenteral therapy (Salako *et al.* 1994b). Artemether produced significantly shorter parasite and fever clearance times but a higher parasite recrudescence rate than sulfadoxine-pyrimethamine. There was no significant difference in their initial parasitological cure rates: 100% for artemether, 98% for sulfadoxine-pyrimethamine. In a separate study intramuscular artemether was compared with intravenous quinine in children with cerebral malaria. There was no significant difference between the 2 drugs in parasite and fever clearance times, time to regain consciousness, or recrudescence rate. There was an overall mortality of 16.7%, with 12% in the artemether group and 21% in the quinine group. Artemether was well tolerated. There was no abnormal change in haematological and biochemical features monitored and there was no adverse clinical reaction.

Studies of artemether im in combination with other antimalarials

The efficacy of intramuscular artemether given for 5 days and a single oral dose of mefloquine, 25 mg/kg/body-weight, was evaluated in 84 children with uncomplicated

Plasmodium falciparum hyperparasitaemia (> 5% parasitized erythrocytes) by Sowunmi *et al.* (1996b). Follow-up was for 14 days in the artemether group and 28 days in the mefloquine group. Artemether produced a significantly higher parasite reduction at 24 hours [mean 90.6 vs 63.3%, 95% confidence interval 10.7-43.9] and significantly shorter parasite clearance time [mean 38.4 vs 49.3 hours, 95% confidence interval 5.5-16.3] than mefloquine. Fever clearance times were similar, presumably because of the use of an antipyretic in both treatment groups. Cure rate was 98% with artemether on day 14 and 100% with mefloquine on day 28. One child in the artemether group who had recurrence of parasitaemia on day 14 responded promptly to mefloquine with clearance of parasitaemia and fever at 24 hours. Although both drugs were well tolerated, mefloquine produced more episodes of abdominal pain with or without diarrhoea and vomiting. These results suggest that both drugs are effective in uncomplicated Plasmodium falciparum hyperparasitaemia in children from an endemic area of south-west Nigeria.

Falade *et al.* (2007) compared two dose forms of artemisinin derivatives, dihydroartemisinin suppository and intramuscular artemether, in Nigerian children 6 months to 10 years of age with moderately severe malaria for which oral therapy was not appropriate. Children were randomly allocated to receive three daily doses of dihydroartemisinin or artemether followed by a single oral dose of sulfadoxine-pyrimethamine on the third day of both treatment regimens and were monitored for parasitological and clinical response for a period of 14 days. Patients were encouraged to continue follow-up until day 28., Mean parasite and fever clearance times were similar in both groups. Fever clearance times were 23.0 ± 17.3 and 18.7 ± 10.2 for artemether and dihydroartemisinin respectively (p= 0.50). Parasite clearance times were 32.5 ± 14.3 and 31.4 ± 17.7 for artemether and dihydroartemisinin respectively. Days 14 and 28 parasitological cure rates were 100% (34 of 34) and 96.2% (25 of 26) versus 96.2% (25 of 26) and 91.7% (22 of 24) for children treated with dihydroartemisinin and artemether, respectively. In conclusion, both treatment regimens were efficacious and well tolerated.

10.3 Conclusion

A multitude of clinical trials of various design types including several thousands of patients shows that artemether IM is a very efficacious and safe agent in the treatment of Plasmodium falciparum infections resistant to other antimalarials in both adults and in children. Artemether has been in use as a curative antimalarial for more than a decade. Artemether has no preventive properties. The drug rapidly eradicates the parasites and provides quick relief

from the signs and symptoms associated with moderate to severe malaria and malaria-induced coma.

11. Safety, tolerability, precautions and contraindications

Safety and tolerability issues were already mentioned in the studies described in the section above.

- **Specific studies looking at organ specific assessment**

In animals, high doses of intramuscular artemether have been shown to cause selective damage to brain stem centres involved predominantly in auditory processing and vestibular reflexes. Also a prolongation of QT interval corrected for rate (QTc) on electrocardiograms (ECGs) with bizarre ST-T segment changes were seen. (Brewer *et al.*, 1994 and Nontprasert *et al.*, 2002). However these findings and there interpolation to the risk in man and limitations in clinical use are discussed by Dayan AD (1989). Evaluation of the risk to man must be based on conventional assessment of active doses in animals versus those employed in the treatment of cerebral malaria. They argue that in the case of artemether intramuscular injection there is no reason to anticipate a particular risk of conventional regimes employing up to artemether 3-6mg/kg/d for a few days.

Neuropathological assessment in humans

Hien TT *et al.* (2003) examined the brainstems of adults who died after treatment with high dose artemether or quinine for severe falciparum malaria for evidence of a pattern of selective neuronal damage. Neuropathological findings were similar in recipients of quinine (n=15) and artemether (n=6; total artemether doses received 4-44 mg/kg). No evidence was recorded for artemether-induced neurotoxic effects.

Cardiological assessment in humans

The effect of intramuscular artemether (intramuscular loading dose of 160 mg, followed by 80 mg daily for another 6 doses), in comparison with that of quinine (intravenous infusion of loading dose of 20 mg/kg, followed by 10 mg/kg 8 hourly for 7 days), on the electrocardiograph of severe falciparum malaria patients were investigated in 102 Thai patients (92 males, 10 females) admitted to Pra Pokklao Hospital, Chantaburi, southeast of

Thailand. Fifty patients (19 with quinine and 31 with artemether) were eligible for ECG analysis. In the group with intramuscular artemether, 17 cases had tachycardia prior to artemether treatment. QTc prolongation and non-specific T-wave change were found in 2 and 6 cases. One patient had RBBB and second degree AV-block on Day 1, but returned to normal on Day 2. No other dysrhythmia or other significant changes in ECG tracing which would suggest any effect of artemether on cardiovascular system were observed. (Karbwang *et al.*, 1997)

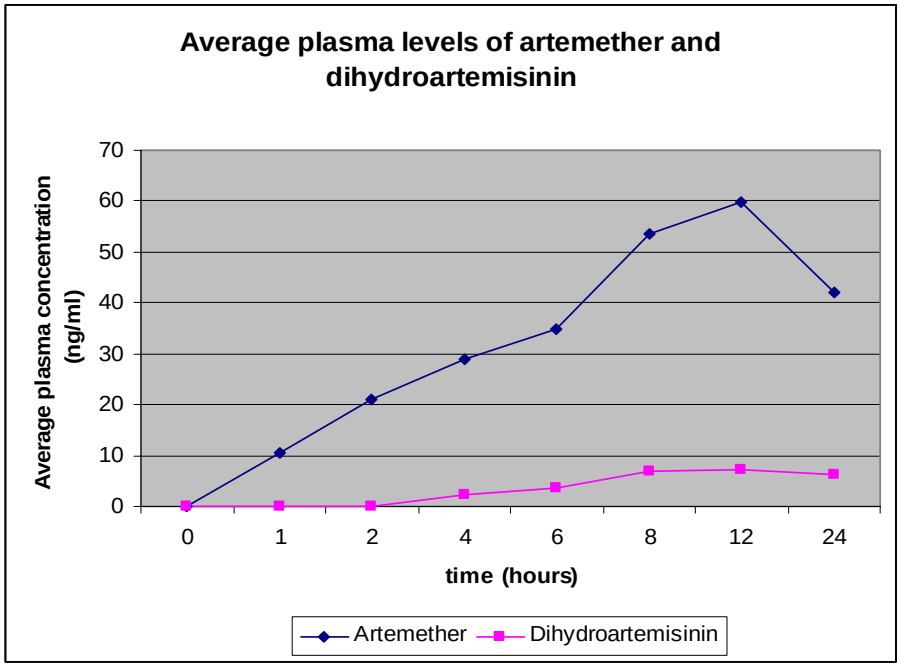
- **Pharmacokinetic study conducted by Dafra Pharma**

To 11 patients with non-complicated malaria, a single dose of intramuscular formulation of artemether solved in miglyol (Artesiane®) (4 mg/kg) was administered. Blood samples were withdrawn over a 24 hour period, at 0, 1, 2, 4, 6, 8, 12 and 24 hours. The blood plasma levels of artemether and its principal metabolite dihydroartemisinin were determined by LC-MS.

Table: Plasma levels of artemether and dihydroartemisin (± SD)

Timepoint	Artesiane®	
	Artemether (ng/ml)	DHA (ng/ml)
t = 0	0.0	0.0
t = 1	10.6 ± 5.5	0.0
t = 2	20.9 ± 12.9	0.0
t = 4	28.9 ± 23.6	2.3 ± 7.7
t = 6	34.8 ± 24.5	3.7 ± 9.1
t = 8	53.7 ± 37.5	6.9 ± 13.1
t = 12	59.8 ± 34.9	7.1 ± 13.4
t = 24	42.2 ± 16.7	6.1 ± 10.6

Within one hour, therapeutic levels of artemether and of dihydroartemisinin (IC50-limit reported to be 0.3-1.8 ng/ml respectively) were obtained. The Cmax values for Artemether and Dihydroartemisinin were 59.8 (18 – 128) ng/ml and 7.0 (0.1 – 40) ng/ml respectively. The Tmax for both compounds was 12 ± 2 hours. Therapeutic levels were maintained throughout the observed 24-hour period. No serious adverse events occurred.



- **Precautions and contraindications**

None are known.

- **Drug interactions**

Specific untoward drug interactions have not been found. Potentialisation of other antimalarial drugs is a common feature. Loading dose of Artemether followed by other antimalarial drugs have shown strong beneficial potentialisation effects.

- **Effects on the ability to drive or operate machinery**

None are known.

- **Overdose**

No cases of artemether overdose have been reported so far.

- **Use in pregnancy and lactation**

Not applicable because artemether solution 20mg/1ml for intramuscular injection is for paediatric use only.

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

Cost per treatment dose Artesiane® 20:

Pack of 10 ampoules artemether 20 mg/1 ml (miglyol) = 3.62 USD

- Treatment child 5 kg:

  5 ampoules van 0.362 USD

  1.81 USD

- Treatment child 10 kg:

  6 ampoules van 0.362 USD

  2.71 USD

Cost per treatment dose Paluther®:

Pack of 6 ampoules artemether 40 mg/1 ml (arachis oil) = 8.6 USD

- Treatment child 5 kg:

  5 ampoules van 1.43 USD

  7.15 USD

- Treatment child 10 kg:

  5 ampoules van 1.43 USD

  7.15 USD

→ More expensive and the artemether is solved in arachis oil which leads to variable and slow absorption kinetics.

Cost per treatment dose intravenous quinine dihydrochloride:

Pack of 100 ampoules of 2 ml containing quinine dihydrochloride 300mg/1ml = 15 USD

- Treatment child 5 kg:

  6 ampoules van 0.15 USD

  0.90 USD

- Treatment child 10 kg:

  6 ampoules van 0.15 USD

  0.90 USD

→ Cheaper but in some rural areas, where medical facilities are poor, intravenous administration is not preferred because of the high risk of secondary infection.

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

Export declaration from Belgium: 1418ED2F12

Has been granted a marketing authorization in the following 28 African countries: Angola, Benin, Burkina Faso, Burundi, Cambodia, Cameroun, Ivory Coast, Gabon, Ghana, Gyunée Conackry, Kenya, Malawi, Mali, Mauretania, Mozambique, Myanmar, Niger, Nigeria, Congo Brazzaville, République Centrafricaine, République Démocratique du Congo, Senegal, Sierra Leone, Tanzania, Tchad, Togo, Ouganda and Zambia.

14. Availability of pharmaceutical standards

Pharmacopeal standards for artemether have been established by WHO (International Pharmacopoeia, 4th Edition, 2006).

15. Proposed text for the WHO Model Formulary

SUMMARY OF PRODUCT CHARACTERISTICS

Name of the medicinal product

Artesiane® 20, Artemether (INN Name) 20 mg/1 ml solution for intramuscular injection

Presentation

Artemether 20 mg/1 ml ampoules. Clear glass ampoules containing β-Artemether 20 mg in a 1 ml solution of fractionated coconut oil. The solution is sterile and colourless.

CLINICAL PARTICULARS

Therapeutic indications

Artemether 20 mg/1 ml is indicated for the treatment of malaria caused by all forms of *Plasmodium* including severe malaria caused by multiple drug resistant strains of *P. falciparum.*

Dose and method of administration

For INTRAMUSCULAR use only

Formulations for intramuscular injection of Artemether are mostly used in case of severe malaria, but also in case of patients showing gastro-intestinal problems. The dosage depends on the patients' weight, the severity of the case and the clinical condition of the patient.

Loading dose: administered as one single injection.

Children → 3,2 mg/kg body weight on the first day.

Maintenance dose: administered as one single injection.

Children → 1,6 mg/kg body weight during the following four days.

Treatment can however also be continued by oral Artemisinin-based combination therapies (ACT), if the patient's condition does not require injections.

Note: a) A full course therapy of five days is essential in order to avoid recrudescence.

b) In severe malaria it may be necessary to increase the loading dose and to prolong treatment for seven days if parasitaemia is not cleared during the first few days.

Precautions and contra-indications

Contra-indications: Hypersensitivity to the active substance (this has not been seen so far) or to any of the excipients.

Warnings: In cerebral malaria and complicated malaria, general supporting therapy is usually required.

Drug interactions: Specific untoward drug interactions have not been found. Potentialisation of other antimalarial drugs is a common feature. Loading dose of Artemether followed by other antimalarial drugs have shown strong beneficial potentialisation effects.

Side effects: At the therapeutic dose there are very few side-effects. There are reports on laboratory abnormalities, i.e. a decrease in reticulocyte count, a transient increase in transaminases and ECG changes (lowering of sinus heart rate, but effects on conduction or on repolarisation have not been observed). At high doses, transient abdominal pain, diarrhoea and tinnitus was reported.

Resistance and recrudescence: Resistance of *Plasmodia* to Artemether has not been observed. It is also unlikely to occur in view of the specific mechanism of action which is very cytotoxic for the *Plasmodia* (opening of a 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 3 %. In case of recrudescence (real or apparent) a new complete treatment for five days is advisable.

Precautions: Do not exceed the prescribed dose. In case of overdosage, symptomatic treatment in a specialized unit is recommended. The administration of several times the therapeutic dose was not reported to give serious side effects.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics: β-Artemether acts essentially as a blood schizonticide. The presence of the endoperoxide bridge (generating singlet oxygen and free radicals) appears to be essential for antimalarial activity. 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. Morphological changes of the parasitic membranes induced by Artemether have been described, being the result of free-radical action. Other in vitro tests suggest that β -Artemether causes a marked diminution of nucleic acid synthesis.

Pharmacokinetics: Intramuscular β -Artemether is rapidly absorbed reaching therapeutic levels within the first hour. Cmax is obtained within 4-6 hours. It is metabolized in the liver to the demethylated derivative dihydroartemisinin. The elimination is rapid, with a T1/2 of 1-3 hours. Dihydroartemisinin, being a potent antimalarial itself, has a similar T1/2 of. The degree of binding to plasma proteins varied markedly according to the species studied. The binding of β -Artemether with plasma protein is of the order of 50 %. Distribution of radioactive-labelled β -Artemether was found to be equal between cells and plasma.

PHARMACEUTICAL PARTICULARS

List of excipients

Artemether 20 mg/1 ml solution for injection also contains purified coconut oil (miglyol)

Special precautions for storage

Artemether 20 mg/ml ampoules should be protected from light and stored at room temperature below 30°C. Keep out of reach and sight of children. They have a shelf-life of 3 years.

Package Quantities

Pack of 10 ampoules artemether 20 mg/1 ml

Marketing authorisation holder

Dafra Pharma nv/sa, Slachthuisstraat 30/7, 2300 Turnhout, Belgium

Manufacturer

ROTEXMEDICA GmbH, Bunsenstrasse 4, 22946 Trittau, GERMANY

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