APPLICATION FOR INCLUSION OF ARTESUNATE/AMODIAQUINE FIXED DOSE COMBINATION TABLETS IN THE WHO MODEL LISTS OF ESSENTIAL MEDICINES
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1. Summary statement of the proposal for inclusion

Malaria is an important cause of death and illness in children and adults in tropical countries. *P. falciparum* is responsible for virtually all of the estimated 700,000 to 2.7 million deaths per year that occur predominantly (75%) in African children (1).

The WHO recommends combinations of antimalarials for the treatment of *P. falciparum* uncomplicated malaria, to counter the threat of resistance of *P. falciparum* to monotherapies, and to improve the treatment outcome (2).

Artemisinin-based combination therapies (ACTs) are now generally considered as the best current treatment for uncomplicated *P. falciparum* malaria (2) and are more and more widely used. By June 2008 (the latest information available to WHO), all except 4 countries and territories worldwide (Cape Verde, Dominican Republic, French Guyana and Swaziland) had adopted ACT as the first line treatment for *P. falciparum*.

We propose that the artesunate/amodiaquine fixed dose combination tablets (doses of 25mg/67.5 mg, 50mg/135 mg and 100mg/270 mg artesunate/amodiaquine respectively) be registered in the WHO Model Lists of Essential Medicines as a fixed dose combination therapy for the treatment of uncomplicated *P. falciparum* malaria, especially in paediatric patients.

The development of this drug was initiated by the FACT project (Fixed dose Artesunate Combination Therapy) that began in 2002 under the umbrella of Médecins Sans Frontières (and then the non-profit product development organisation DNDi) in coordination with TDR (the UNICEF-UNDP-World Bank-WHO’s Special Programme for Research and Training in Tropical Diseases). The objective of the FACT project was to develop a fixed dose combination of artesunate-amodiaquine that would improve patient compliance and would be made available to all countries with low rates of resistance to amodiaquine. In 2004, Sanofi-Aventis teamed up with the FACT partners to bring its expertise in industrial, preclinical and clinical development, to optimize the quality of the drug and to expedite its availability.

Rationale on the proposed formulation:

1- The artesunate/amodiaquine fixed dose combination was formulated to ensure that patients take both drugs together in the right dose, with a particular attention paid to paediatric needs (dose ratio, age-adapted strengths, optimized pharmaceutical form…). The WHO considers patient adherence to treatment as a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence (3). As mentioned in the WHO guideline for registration of fixed dose combination medicinal products (3), the development of fixed dose combinations is becoming increasingly important from a public health perspective, for an optimal treatment of malaria and for the prevention of drug resistance. Fixed dose combinations simplify treatment regimens, improve patient adherence and facilitate the implementation of interventional programs.
2- There are currently no paediatric artesunate-containing drug products or paediatric artesunate-containing combined therapies listed in the WHO Model Lists of Essential Medicines \(^{(4,5)}\) for uncomplicated malaria.

3- The artesunate/amodiaquine fixed dose combination was developed to provide to all patients with doses as close as possible to 4 mg/kg/day and 10 mg/kg/day for artesunate and amodiaquine, respectively \(^{(6)}\). Dosing recommendations were made for four consecutive body weight and age ranges that are predicted to result in the lowest possible proportion of over or under dosing.

5- The artesunate/amodiaquine fixed dose combination was developed to reduce the number of tablets that should be administered per day: one artesunate/amodiaquine tablet per day is recommended for children between 4.5kg and 36 kg and 2 tablets per day for adults. Three different dosages depending on body weight and age ranges are available as shown in the table below.

<table>
<thead>
<tr>
<th>Body weight ranges (age ranges)</th>
<th>Co-blistered tablets of artesunate and amodiaquine</th>
<th>Fixed dose combination artesunate / amodiaquine bilayer tablet</th>
<th>artemether lumefantrine combination tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4.5kg to &lt; 9 kg (2 to 11 months)</td>
<td>½ tablet of amodiaquine ½ tablet of artesunate per day for 3 days</td>
<td>1 tablet (25mg artesunate/67.5 mg amodiaquine) per day for 3 days</td>
<td>Between 5kg-10kg 6 tablets over 3 days</td>
</tr>
<tr>
<td>≥9kg to &lt;18kg (1 to 5 years)</td>
<td>1 tablet of amodiaquine 1 tablet of artesunate per day for 3 days</td>
<td>1 tablet (50mg artesunate/135 mg amodiaquine) per day for 3 days</td>
<td>Between 10kg-15kg 6 tablets over 3 days</td>
</tr>
<tr>
<td>≥18kg to &lt;36kg (6 to 13 years)</td>
<td>2 tablets of amodiaquine 2 tablets of artesunate per day for 3 days</td>
<td>1 tablet (100mg artesunate/270 mg amodiaquine) per day for 3 days</td>
<td>Between 18-25 kg 12 tablets over 3 days</td>
</tr>
<tr>
<td>≥ 36kg (14 years and above)</td>
<td>4 tablets of amodiaquine 4 tablets of artesunate per day for 3 days</td>
<td>2 tablets (100mg artesunate/270 mg amodiaquine) per day for 3 days</td>
<td>Above 35 kg 24 tablets over 3 days</td>
</tr>
</tbody>
</table>

6- The artesunate/amodiaquine fixed dose combination is formulated and packaged to guaranty the stability of the active ingredient even under tropical conditions. Packaged in aluminium/aluminium blisters, the current shelf-life of the tablets is now 36 months, when stored below 30°C in the original container. Further to 36 months stability results, the extension of shelf-life, from 24 to 36 months, received the WHO positive opinion in August 2010.

**Rationale on the proposed dosage form:**
Liquid formulations are considered as the most appropriate formulations for younger children (below 8 years of age) if the dose volume, the palatability and the stability are satisfactory. As artesunate is not stable in solution, a reconstituted liquid formulation stable for 3 days under tropical conditions could not be envisioned.

However, based on the criteria of the EMEA/CHMP/PEG/194810/2005 guideline “Formulations of choice for the paediatric population” (7), the artesunate / amodiaquine solid oral dosage forms (tablets) present several features of interest:

- for the paediatric population under 6 years:
  - Tablets can be dissolved in water before administration. They can be considered as soluble tablets because they disintegrate in water in less than 3 minutes in accordance with the European Pharmacopoeia,
  - Tablets can also be crushed and administered with water.

- for the paediatric population over 6 years:
  - no particular issue was documented regarding the acceptability by children of the taste, smell or texture of the tablets,
  - feedback from clinical investigators did not evidence any issue for administration to children whatever their age. The fixed dose combination is very easy to administer in children because only one daily tablet is needed,
  - the tablets are small: 10 mm diameter for toddlers and 13 mm for children. They can be easily swallowed. And as for younger children they can also be dissolved in water or crushed and administered with water.

- for the paediatric population in general:
  - Children are unlikely to tolerate repeated administration of medicines which are uncomfortable, painful or stressful. The present tablets allow a dose regimen and mode of administration in accordance with this aim,
  - a simple dosage regimen [once a day dosing facilitating patients’ compliance and therefore diminishing risks of treatment failure and development of parasite resistance],
  - there are no excipients such as preservatives, sweeteners, fillers, solvents, colouring agents or coating material that should cause adverse effects in children,
  - knowing how bodyweight cannot always be easily assessed in field conditions, this drug can be prescribed based on either body weight or on age. The doses of artesunate and amodiaquine for the fixed dose combination were selected based on a study recently published in the WHO Bulletin. Demographic data of over 88,000 African children and adults, including malaria patients, were used to select 4 different presentations based on age and weight. The artesunate/amodiaquine doses that were selected are expected to provide the lowest possible risks of over- and under-dosage

- for the parent/caregiver, ease, convenience and reliability of administration, through:
  - convenient presentations: a single Alu/alu blister of 3 tablets (one tablet once a day for three days up to 13 years of age (35kg)) or a single Alu/alu blister of 6
tablets (2 tablets once a day for three days from 14 years of age (36kg and above)),
- better stability, accuracy of dosing and improved portability over liquid formulations,
- minimal dosage frequency,
- one dosage form fits the full range of paediatric patients.

- for procurement and distribution:
  - Solid dosage forms such as fixed dose combinations facilitate the logistics of procurement and distribution compared to liquid forms (in terms of weight/volume) or to loose combinations (in terms of quantities).
  - Packaged in Alu/Alu blisters the product is stable up to 36 months.

Proof of efficacy and safety:

Amodiaquine is listed in WHO Model Lists of Essential Medicines (16th edition March 2009 and 2nd edition Children March 2009)\(^{(4,5)}\) and should preferably be used as part of combination therapy. Likewise artesunate is listed in the same lists.

The clinical efficacy and safety of the artesunate amodiaquine combination is supported by 15 studies.

- **Five studies** were performed with a theoretical 2.5 *artesunate/amodiaquine dose ratio* (free combination) based on monotherapy and weight adjusted posology (amodiaquine 10mg/kg/day and artesunate 4 mg/kg/day);
- **Ten studies** with a 3.1 dose ratio based on age adjusted posology (co-blisters ratio);
- **Two pivotal studies** (Burkina Faso study and ATAQ EASY multinational study) with the optimized dose ratio 2.7 (dose-ratio of the fixed-dose combination).

The table below details the number of patients exposed to the three artesunate-amodiaquine dose ratios.

**Extent of exposure (based on safety dataset)**

<table>
<thead>
<tr>
<th>Weight adjusted posology</th>
<th>Coarsucam(^{TM})</th>
<th>Age adjusted posology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose ratio 2.5</td>
<td>Dose ratio 2.7</td>
<td>Dose ratio 3.1</td>
</tr>
<tr>
<td>5 safety and efficacy studies</td>
<td>2 efficacy and safety study</td>
<td>10 safety and efficacy studies</td>
</tr>
<tr>
<td>N= 2,691</td>
<td>N=1,003</td>
<td>N=3,016</td>
</tr>
</tbody>
</table>

The efficacy and safety of the fixed dose combination was confirmed in a study performed in Burkina Faso (see also section 10 for more details). A 3 days treatment of the fixed dose combination (25/67.5 mg) was evaluated in a randomised, controlled, open-label, parallel-group study, versus a loose combination (AS+AQ= Arsumax\(^{®}\) + Flavoquine\(^{®}\)) of the individual drugs, in children with malaria attack due to *P. falciparum*. The primary study...
The objective was to show the non-inferiority in terms of efficacy of the fixed combination amodiaquine/artesunate (AS/AQ) compared to both drugs given as a loose combination (AS+AQ). For this study, a total of 750 children with an age range from 6 months up to 5 years inclusive, with body weight of at least 5 kg were included.

The dosage was adapted to body weight. For the youngest children, the fixed-dose combination tablets were either crushed or dissolved in water.

For the primary analysis PCR-corrected parasitological cure rates at Day 28 were similar in both treatment groups in all datasets. The upper bound of the 90% confidence interval for the difference in PCR-corrected parasitological cure rates (AS+AQ-AS/AQ) was always <0.05, thus demonstrating the non-inferiority of AS/AQ compared to AS+AQ. Analysis of PCR-corrected parasitological cure rates at Day 28 in the mPP dataset provides an assessment of the treatment efficacy when it is actually taken. In this dataset, efficacy rates of both the tested drugs are above the limit fixed in the 2006 WHO recommendations for efficacy of new treatments (95%), namely 96.01% for AS+AQ and 95.74% for AS/AQ.

The incidence of general adverse events was consistent with what can be expected for young patients presenting with malaria. In particular, it is difficult to assign reports of fatigue, nausea, vomiting to the study drugs, the malaria infection itself or to concomitant conditions. Based on what is known of artesunate and amodiaquine safety profile, no unexpected adverse events occurred.

In addition, a multinational, randomised, comparative, single blind Phase III trial was carried out in Cameroon, Madagascar, Mali, and Senegal, in order to assess the non inferiority of the fixed dose combination (25/67.5 mg and 50/135 mg) versus artemether/lumefantrine fixed dose combination (ATAQ EASY study) (see also section 10 for more details).

The primary objective was the comparison of artesunate/amodiaquine tablets one daily intake with artemether/lumefantrine (two daily intakes). A total of 941 patients, including 433 children under 5 years of age, weighing at least 10 kg, were included. Of these patients, 1 discontinued the study before treatment initiation. Therefore 940 patients were treated. The dosage was adapted to bodyweight. For the youngest children, the tablets were either crushed or dissolved in water.

Adequate Clinical and Parasitological cure Rates (ACPR) in the Intent-To-Treat (ITT) population on Day 28 after PCR correction were 95.2% in the artesunate amodiaquine fixed-dose combination one daily dose group and 95.5% in the artemether/lumefantrine group.

Statistical analyses performed in both ITT and PP populations demonstrated the non-inferiority of administering artesunate amodiaquine fixed-dose combination one daily intake versus artemether/lumefantrine, in terms of clinical and parasitological efficacy on D28. The non inferiority of administering Coarsucam™ 1 daily intake versus Coartem® was also confirmed in the subpopulation of children of less than 5 years.

The data of ATAQ EASY study are publicly available on [clinicalstudyresults.org](http://www.clinicalresults.org/drugdetails/?sort=inn.inn_name&page=3&drug_id=3995).

All the reports related to this study have been evaluated by the WHO prequalification program ([http://healthtech.who.int/pq](http://healthtech.who.int/pq)).
**Rationale on cost:**

The cost of Artemisinin-based Combination Therapies has decreased significantly over the past few years and has now reached a point where the main determinant of cost is the price of the active ingredient, i.e. the artemisinin derivative itself. The pharmaceutical dosage form for paediatric patients is the same than the one for adults. The paediatric formulation is homothetic to the adult formulation and is manufactured with the same equipment. This ensures production and cost viability for these paediatric formulations.

This is the first fixed dose combination of artesunate and amodiaquine. On the public market, the only fixed dose combination which is comparable to artesunate/amodiaquine is artemether/lumefantrine.

Sanofi-Aventis has developed a program that makes drugs available through both the public and private distribution channels to reach all population segments:

- On the private market, the whole sale price for the artesunate/amodiaquine fixed dose combination is 2.3 € (around 3 USD)

  Public tenders prices fluctuate over time. However, based on the latest tender prices, artesunate/amodiaquine fixed dose combination with a “no profit-no loss” approach, the average cost of a full treatment is about 0.54 USD. For the pediatric patients (from 6 months to 13 years of age) the average cost of a full treatment is 0.38 USD (see also section 12).

**Quality:**

- Each active ingredient manufacturer is declared GMP compliant by the local authorities, Sanofi-Aventis’ Maphar finished product manufacturing site was inspected by the WHO prequalification inspection team on January 2008 and on February 2009. Each time, it was found to be compliant with WHO GMP ([http://healthtech.who.int/pq/](http://healthtech.who.int/pq/))
- Sanofi-aventis artesunate/amodiaquine fixed dose combination was approved by the WHO Prequalification Programme on October 14, 2008.

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

Not relevant

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

DNDi: Drug for Neglected Diseases Initiative
1, Place Saint Gervais
CH-1201 Geneva-Switzerland
4. International Non-proprietary Name (INN, generic name) of the medicine

Artesunate / amodiaquine tablet is a fixed dose combination of two antimalarial drugs artesunate (INN) and amodiaquine (INN).

5. Dosage form or strength proposed for inclusion

5.1. Chemical characteristics

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (Artemisia annua). The chemical mechanism of action of artesunate has been widely studied and appears well established. The artesunate endoperoxide’s bridge is split by heme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

Amodiaquine is a synthetic amino 4-quinoline antimalarial. Its activity is characterized by a schizonticidal action on all Plasmodium species. Therefore it is used to treat acute illnesses by destroying intraerythrocytic forms. The chemical mechanism of action of amino 4-quinoline derivatives against Plasmodium is not yet completely known. It is nonetheless accepted that these derivatives, one of which is amodiaquine, penetrate the infected red blood cells in a specific way and prevent the parasite from polymerizing heme into an insoluble product called hemozoin, leading to parasite death.

5.2. The formulation proposed for inclusion:

Artesunate (AS) plus amodiaquine (AQ) is one of the three WHO-recommended ACTs to treat uncomplicated P. falciparum malaria in Africa. Both artesunate and amodiaquine are part of the WHO Model lists of Essential Medicines (4,5).

The artesunate/amodiaquine fixed dose combination was formulated to ensure that patients take both drugs together in the right dose, with a particular attention paid to paediatric needs (dose ratio, age-adapted strengths, optimized pharmaceutical form…). The WHO considers patient adherence to treatment is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is
probably a very important contributor to adherence (3). As mentioned in the WHO guideline for registration of fixed dose combination medicinal products (3), the development of fixed dose combinations is becoming increasingly important from a public health perspective, for an optimal treatment of malaria and for the prevention of drug resistance. Fixed dose combinations simplify treatment regimens, improve patient adherence and facilitate the implementation of interventional programs.

The artesunate/amodiaquine fixed dose combination was developed to provide doses as close as possible to 4 mg/kg/day and 10 mg/kg/day for artesunate and amodiaquine respectively (WHO’s recommendations, see also section 9.4).

The rationale for the selected artesunate and amodiaquine doses is based on study results published in the WHO Bulletin (6). Demographic data of over 88,000 African children and adults, including malaria patients, were used to select 4 different presentations based on age and weight. The artesunate/amodiaquine doses that were selected are expected to provide the lowest possible risks of over- and under-dosage (see also section 9.4), whether dosage is based on the patient’s age or on his/her weight.

The artesunate/amodiaquine fixed dose combination was developed to reduce the number of tablets that should be administered per day: one artesunate/amodiaquine tablet per day is recommended for children between 4.5 kg and 36 kg and 2 tablets per day for adults. Three different dosages depending on body weight and age ranges are available for children, and one for adolescents and adults as shown in the table hereafter.
Artesunate/amodiaquine tablets are available as round bilayer tablets: one layer is yellow colored, the other one is white to slightly yellow, with score line, engraved on one side “AS” and on the other side “25”, “50” or “100” depending of the concerned strength.

The tablets contain a fixed combination of the two active substances -artesunate and amodiaquine- with respective doses of 25, 50 and 100 mg for artesunate and 67.5, 135 and 270 mg for amodiaquine (base):
- 25mg/67.5 mg for treatment of children between 2 and 11 months of age (≥ 4.5 kg to < 9 kg),
- 50mg/135 mg for treatment of children between 1 and 5 years of age (≥ 9 kg to < 18 kg),
- 100mg/270 mg for treatment of children (and adults) over 6 years of age (≥ 18 kg).

Liquid formulations are considered as the most appropriate formulation for younger children (below 8 years old) if the dose volume, the palatability and the stability are satisfactory. As artesunate is not stable in solution, it was not possible to consider a reconstituted liquid formulation of artesunate-amodiaquine that would be stable for 3 days under tropical conditions.

However, based on the EMEA/CHMP/PEG/194810/2005 guideline “Formulations of choice for the paediatric population” (7), the artesunate/amodiaquine solid oral dosage forms (tablets) present several features of interest:

<table>
<thead>
<tr>
<th>Body weight range (age range)</th>
<th>Co-blistered tablets of artemesunate and amodiaquine</th>
<th>Fixed dose combination: artemesunate and amodiaquine bilayer tablet</th>
<th>artemether lumefantrine combination tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4.5kg to &lt; 9 kg (2 to 11 months)</td>
<td>½ tablet of amodiaquine 1/4 tablet of artemesunate per day for 3 days</td>
<td>1 tablet (25 mg artesunate/67.5 mg amodiaquine) per day for 3 days</td>
<td>Between 5kg-10kg 6 tablets over 3 days</td>
</tr>
<tr>
<td>≥9kg to &lt;18kg (1 to 5 years)</td>
<td>1 tablet of amodiaquine 1 tablet of artesunate per day for 3 days</td>
<td>1 tablet (50 mg artesunate/135 mg amodiaquine) per day for 3 days</td>
<td>Between 10kg-15kg 6 tablets over 3 days, Between 15-18 kg 12 tablets over 3 days</td>
</tr>
<tr>
<td>≥18kg to &lt;36kg (6 to 13 years)</td>
<td>2 tablets of amodiaquine 2 tablets of artesunate per day for 3 days</td>
<td>1 tablet (100 mg artesunate/270 mg amodiaquine) per day for 3 days</td>
<td>Between 18-25 kg 12 tablets over 3 days, Between 25-35 kg 18 tablets over 3 days</td>
</tr>
<tr>
<td>≥ 36 kg (14 years and above)</td>
<td>4 tablets of amodiaquine 4 tablets of artesunate per day for 3 days</td>
<td>2 tablets (100 mg artesunate/270 mg amodiaquine) per day for 3 days</td>
<td>Above 35 kg 24 tablets over 3 days</td>
</tr>
</tbody>
</table>
• for the paediatric population under 6 years:
  - Tablets can be dissolved in water before administration. They can be considered as soluble tablets because they disintegrate in water in less than 3 minutes in accordance with the European Pharmacopoeia (see table below),

<table>
<thead>
<tr>
<th>Batch number</th>
<th>0001</th>
<th>0002</th>
<th>0002</th>
<th>0003</th>
<th>0005</th>
<th>0006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength artesunate/amodiaquine</td>
<td>50/135mg</td>
<td>25/67.5mg</td>
<td>50/135mg</td>
<td>25/67.5mg</td>
<td>50/135mg</td>
<td>25/67.5mg</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>58s</td>
<td>46s</td>
<td>40s</td>
<td>31s</td>
<td>41s</td>
<td>35s</td>
</tr>
</tbody>
</table>

  - Tablets can also be crushed and administered with water.

In the two pivotal studies (Burkina Faso and "ATAQ EASY”), 666 children below 5 years old were treated with the ASAQ fixed-dose combination. Actual tablet administration method was not recorded in the study Case Report Form. The number of patients who received crushed or dissolved tablets is therefore not available. However, with additional information provided by investigators, it can be estimated that more than 400 children received the fixed-dose combination tablets either crushed or dissolved in water.

• for the paediatric population over 6 years:
  - no particular issue was documented regarding the acceptability by children of the taste, smell or texture of the tablets,
  - feedback from clinical investigators did not evidence any issue for administration to children whatever their age. The fixed dose combination is very easy to administer in children because only one daily tablet is needed,
  - the tablets are small: 10 mm diameter for toddlers and 13 mm for children. They can be easily swallowed. And they can also be dissolved in water or crushed and administered with water.

• for the paediatric population in general:
  - Children are unlikely to tolerate repeated administration of medicines which are uncomfortable, painful or stressful. The present tablets allow a dose regimen and mode of administration in accordance with this aim,
  - a simple dosage regimen [once a day dosing facilitating patients’ compliance and therefore diminishing risks of treatment failure and development of parasite resistance],
  - there are no excipients such as preservatives, sweeteners, fillers, solvents, colouring agents or coating material that should cause adverse effects in children.
• for the parent/caregiver, ease, convenience and reliability of administration, through:
  - convenient presentations: a single Alu/alu blister of 3 tablets (one tablet once a day for three days up to 13 years of age (35kg)) or a single Alu/alu blister of 6 tablets (2 tablets once a day for three days from 14 years of age (36kg and above)),
  - specific color-coded packaging for each age range,
  - better stability, accuracy of dosing and improved portability over liquid formulations,
  - minimal dosage frequency,
  - one dosage form fits the full range of paediatric patients,
  - knowing how bodyweight cannot always be easily assessed in field conditions, this drug can be prescribed based on either body weight or on age.

• for procurement and distribution:
  - Solid dosage forms such as fixed dose combinations facilitate the logistics of procurement and distribution compared to liquid forms (in terms of weight/volume) or to loose combinations (in terms of quantities).
  - Packaged in Alu/Alu blisters the product is stable up to 36 months

5.3. Stability of the formulation

The Sanofi-Aventis artesunate/amodiaquine fixed dose combination is formulated and packaged to guarantee the stability of the active ingredients even under tropical conditions. Packaged in aluminium/aluminium blisters, the approved shelf-life of the tablets is now 36 months.

Further to 36 months stability results, the extension of shelf-life, from 24 to 36 months, received the WHO positive opinion in August 2010.

The manufacturer recommends that the drug is stored below 30°C in the original package.

6. International availability – sources, if possible manufacturers

6.1. Sources and manufacturers

The fixed dose combination of artesunate/amodiaquine is manufactured by Sanofi-Aventis Pharma in its manufacturing plant: MAPHAR Laboratories, km 7, Route de Rabat-Aïn Sebaâ Casablanca, Morocco.

Maphar Laboratories has the capacity to produce the three dosage strengths according to Good Manufacturing Practice (GMP) and in sufficient quantities to meet expected needs. It was inspected by a WHO prequalification inspection team on January 2008 and on February 2009. Each time, it was found to be compliant with WHO GMP.
Amodiaquine is manufactured at:

IPCA Laboratories Limited
89 A-B, 90-91
Industrial Estate, Pologround
Indore
India

or by IPCA Laboratories Limited
Sejavta
Ratlam, Pin: 457 002
India

Artesunate is manufactured at:

KNOLL/ABBOTT LIESTAL LTD
Oristalstrasse 65
4410 Liestal
Switzerland

or by Sanofi-Aventis S.p.A.
Garessio site
Via R. Lepetit, 142
12075 – Garessio
Italy

Each active ingredient manufacturer is certified as GMP compliant by their local authorities.
As there is no patent covering this artesunate/amodiaquine fixed dose combination, the reference Marketing Authorization will enable third parties to submit applications for generic versions of this product.

6.2. History of the product

In January 2006, “the WHO requested pharmaceutical companies to end the marketing and sale of “single-drug” artemisinin malaria medicines, in order to prevent malaria parasites from developing resistance to this drug. The use of single-drug artemisinin treatment – or monotherapy- hastens development of resistance by weakening but not killing the parasite. When used correctly in combination with other antimalarial drugs in artemisinin Combination Therapies (ACTs), artemisinin is nearly 95% effective in curing malaria and the parasite is highly unlikely to become drug resistant. ACTs are currently the most effective medicine available to treat malaria.(...)Additionally, to anticipate and prevent the onset and spread of drug resistance in the long term, WHO urges the global malaria research community and the pharmaceutical industry to rapidly invest in the design of the next generation of antimalarial drugs (11).

Sanofi-Aventis had, for several years, undertaken an active policy of ACT development, based on artesunate and on amodiaquine, to provide, as recommended by the WHO, the simultaneous administration of at least two blood antimalarial drugs, with independent modes of action and different intraparasitic biochemical targets.
Sanofi-Aventis registered initially Arsucam®, a co-blister presentation, containing both artesunate and amodiaquine tablets. Arsucam® was marketed for approximately four years by Sanofi-Aventis in sub-Saharan Africa, until 2007.

Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to ACT. But when combinations are provided as two separate drugs, there is a risk that patients take only one of the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of failure and development of resistance. Fixed dose combinations combine two drugs into one tablet, instead of separate tablets, to ensure that the patients take both drugs together in the right dose. The WHO considers that patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence \(^\textit{1}\). From a public health perspective, an important approach to addressing the management of malaria has included the development of fixed dose combination of individual components administered together in one dosage form. Fixed dose combinations simplify treatment regimens, improves patient adherence and facilitates the implementation of interventional programs.

Based on these recommendations, work was undertaken by sanofi aventis to develop a fixed dose combination of artesunate and amodiaquine, with optimised tablet strengths designed to maximize the proportion of patients, and in particular young children, predicted to receive appropriate doses of amodiaquine and artesunate, based on their bodyweight.

In parallel, work on a similar approach was also initiated by the FACT project (Fixed dose Artesunate Combination Therapy) that began in 2002 under the umbrella of Médecins Sans Frontières (and then the non-profit product development organisation DNDi) in coordination with TDR (the UNICEF-UNDP-World Bank-WHO’s Special Programme for Research and Training in Tropical Diseases). The objective of the FACT project was to develop a fixed dose combination of artesunate-amodiaquine that would improve patient compliance and would be made available to all countries with low rates of resistance to amodiaquine. In 2004, Sanofi-Aventis teamed up with the FACT partners to bring its expertise in industrial, preclinical and clinical development, to optimize the quality of the drug and to expedite its availability.

### 6.3. International availability and production capacity

Effective malaria treatments are often not accessible to those who need it, because of their price, inappropriate distribution channels or lack of information. Sanofi aventis has developed a comprehensive program, called Impact Malaria that aims at mobilizing the expertise and resources of a major pharmaceutical manufacturer against malaria.

To support the pharmaceutical development and the industrial manufacture of the fixed dose combination, sanofi aventis chose its manufacturing site in Morocco, in accordance with its “Access to Medicines” policy to manufacture in the “South” products for the “South”, so as to help local employment and favour technology transfers. This site has well-developed industrial equipment, with a high level of technology, thanks to a major investment program,
that began in 2000 and allowed the plant to reach appropriate quality levels required for the development of international projects.

To allow the manufacture of the fixed dose combination, the registration file was first submitted in Morocco on December 7, 2005 and the Marketing/Manufacturing Authorisation was granted on February 1, 2007.

Following this initial registration, several endemic countries have then granted local Marketing Authorisation. These countries are: Benin, Burkina Faso, Burundi, Cameroon, Centraafican Republic, Chad, Congo, Côte d’Ivoire, Democratic Republic of Congo, Gabon, Ghana, Guinea, Kenya, Madagascar, Mali, Mauritania, Morocco, Mozambique, Niger, Nigeria, Senegal, South Sudan, Tanzania, Togo, Uganda, Zambie and Zanzibar.

Registration procedures are ongoing in a couple of other African countries: Malawi, Sierra Leone.

In parallel, on February 23, 2007, Sanofi-Aventis submitted the fixed dose combination dossier to the World Health Organisation, as part of the pre-qualification registration program concerning Artemisinin based antimalarial products.

Sanofi-aventis fixed dose combination was approved by the WHO prequalification program on October 14, 2008.

Further to recent investments, the maximal total capacity has been scaled up to more than 100 millions treatments (blisters) per year (all strengths).

There is no restriction on the availability of the active ingredients. Sanofi-aventis produce artesunate in its own plant in Garessio (Italy) based on secured supply of artemisisin.

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

Artesunate/amodiaquine fixed dose combination tablets are proposed to be listed in the WHO Model Lists of Essential Medicines (Adults and Children) within the pharmacotherapeutic group “antimalarial medicines for curative treatment”, subdivision 6.5.3 antimalarial medicines – curative treatments.

In this group, the only combination therapy listed, in the March 2009 16th edition EML and March 2009 2nd edition EML for children, is artemether + lumefantrine (20mg/120mg) combination tablets.

The Sanofi-Aventis artesunate/amodiaquine fixed dose combination can be prescribed to children with bodyweight as low as 4.5 kg, and only requires one artesunate/amodiaquine tablet per day for children between 4.5 kg and 36 kg. Importantly, knowing how bodyweight cannot always be easily assessed in field conditions, this drug can be prescribed based on either body weight or on age. The table below compares dosing regimens for the artesunate-amodiaquine co-blister and fixed dose presentations to the artemether-lumefantrine fixed dose combination.

<table>
<thead>
<tr>
<th>Body weight range (age range)</th>
<th>Co-blistered tablets of artesunate and amodiaquine</th>
<th>Fixed dose combination artesunate and artemether lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/ 67.5 mg, 50 mg/ 135 mg and 100 mg/270 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Artesunate / Amodiaquine, Fixed dose combination 17/57
<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Amodiaquine/Bayer Tablet</th>
<th>Combination Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4.5kg to &lt;9 kg</td>
<td>½ tablet of amodiaquine</td>
<td>Between 5kg-10kg</td>
</tr>
<tr>
<td>(2 to 11 months)</td>
<td>½ tablet of artesunate</td>
<td>6 tablets over 3 days</td>
</tr>
<tr>
<td></td>
<td>per day for 3 days</td>
<td></td>
</tr>
<tr>
<td>≥9kg to &lt;18kg</td>
<td>1 tablet of amodiaquine</td>
<td>Between 10kg-15kg</td>
</tr>
<tr>
<td>(1 to 5 years)</td>
<td>1 tablet of artesunate</td>
<td>6 tablets over 3 days</td>
</tr>
<tr>
<td></td>
<td>per day for 3 days</td>
<td></td>
</tr>
<tr>
<td>≥18kg to &lt;36kg</td>
<td>2 tablets of amodiaquine</td>
<td>Between 18-25 kg</td>
</tr>
<tr>
<td>(6 to 13 years)</td>
<td>2 tablets of artesunate</td>
<td>12 tablets over 3 days</td>
</tr>
<tr>
<td></td>
<td>per day for 3 days</td>
<td></td>
</tr>
<tr>
<td>≥36kg (14 years and above)</td>
<td>4 tablets of amodiaquine</td>
<td>Above 35 kg</td>
</tr>
<tr>
<td></td>
<td>4 tablets of artesunate</td>
<td>24 tablets over 3 days</td>
</tr>
<tr>
<td></td>
<td>per day for 3 days</td>
<td></td>
</tr>
</tbody>
</table>

The artesunate/amodiaquine fixed dose combination simplifies treatment regimens, can improve patient adherence and can facilitate the implementation of interventional programs.

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

Malaria is an important cause of death and illness in children and adults in tropical countries. Mortality currently estimated at over a million people per year, has risen in recent years, probably due to increasing resistance to antimalarial medicines\(^{(2)}\). *P. falciparum* is responsible for virtually all of the estimated 700,000 to 2.7 million deaths per year that occur predominantly (75%) in African children\(^{(1)}\). The World Health Organization (WHO) has decreed that prompt and effective treatment is a key element of a successful strategy to control malaria.

In recent years, Chinese scientists isolated a very potent and effective anti-malarial drug out of the plant *Artemisia Annua*, known as artesmin. Artemisin and its derivatives are very potent and effective anti-malarial drugs (Heemskerk W et al, 2006\(^{(12)}\), Krishna S, 2004\(^{(12)}\) and WHO, 2006\(^{(2)}\)) and for patients with *P.falciparum* malaria resistant to the common antimalarial drugs, the use of artesmin and its derivatives is essential (WHO, 2000b\(^{(14)}\), 2001a, b\(^{(15)}\),\(^{(16)}\)).

The importance of artesminin and its derivatives was recognised by the WHO Expert Committee on Essential Drugs (WHO 2000a\(^{(17)}\)). 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 treatment failures in the development of resistances.
As a result, the WHO recommended the use of artemisinin-based Combination Therapies (ACT). ACT 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) there are generally well-tolerated (Heemskerk W et al, 2006 (15); Krishna S, 2004 (16) and WHO 2001a (15) and 2006(2)). At present, only the ad hoc combinations of artemesin with mefloquine (MQ), amodiaquine (AQ), chloroquine (CQ) or sulfadoxine-pyrimethamine (SP) were widely used operationally in areas of multidrug resistant P. falciparum malaria. However, fixed dose combinations of artemisinin derivatives should have operational advantages since they should be easier to use will provide greater compliance in the target populations than ad hoc combinations (WHO, 2001a and b (15)(16)).
CURRENT USE AND RATIONALE OF THE FIXED DOSE COMBINATION

DEVELOPMENT

The WHO recommends combinations of antimalarials for the treatment of *P. falciparum* uncomplicated malaria, to counter the threat of resistance of *P. falciparum* to monotherapies, and to improve treatment outcome (3). The WHO actively encourages malaria-endemic countries to adopt Artemisinin-based combination therapy (ACT), and many of them are starting to do so. By June 2008 (the latest information available to WHO), all except 4 countries and territories worldwide (Cape Verde, Dominican Republic, French Guyana and Swaziland) had adopted ACT as the first line treatment for *P. falciparum*.

The artesunate-amodiaquine fixed dose combination is an ACT, which consists, as recommended by the WHO, in the simultaneous administration of two blood antimalarial drugs; artesunate and amodiaquine with independent modes of action and different intraparasitic biochemical targets.

Both artesunate and amodiaquine are already registered and available on the market of endemic countries for this indication and are frequently and widely used in the clinic, individually and in combination with each other and with other compounds. Artesunate has been marketed in Africa for 10 years and in Asia for 15 years and can be considered as an active substance with a well-established use in endemic countries. Amodiaquine has been on the market for about 60 years and can be considered as an active substance with a well-established use. Amodiaquine is listed in WHO Model Lists of Essential Medicines (EML revised March 2009 and EML for children March 2009) and should be used in combination with artesunate for the treatment of *P. falciparum* malaria. Likewise artesunate is listed in the same lists, and has to be used in combination with amodiaquine, mefloquine or sulfadoxine/pyrimethamine.

The drugs used in combination should theoretically have similar pharmacokinetics and pharmacodynamics, no adverse pharmacological interaction, and no additional toxicity. With the current artemisinin based combinations, the pharmacology characteristics are different in that the artesunate acts quickly and has a very short half-life, and the companion drugs act more slowly but have longer half-lives. The latter ensures that the companion drugs act for long enough to kill the remaining parasites and those parasites are never exposed to artesunate alone. In this way, artesunate is protected.

Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to ACT. But when combinations are provided as two separate drugs, there is a risk that patients take only one of the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of failure and development of resistance. Fixed dose combinations combine two drugs into one tablet, instead of separate tablets, to ensure that the patients take both drugs together in the right dose. The WHO considers that patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision, and that co-formulation is probably a very important contributor to adherence (3).

As mentioned in the WHO guideline for registration of fixed dose combination medicinal products (3), the development of fixed dose combinations is becoming increasingly important.
from a public health perspective. Fixed dose combination simplifies treatment regimens, improves patient adherence and facilitates the implementation of interventional programs.

**TARGET POPULATION AND RATIONALE ON THE RATIO/DOSE**

The target population is linked to the indication: treatment of uncomplicated cases of malaria due to \textit{P. falciparum} strains, which are susceptible to amodiaquine as well as to artesunate.

**Rationale on the ratio/dose**

Three artesunate amodiaquine dose ratios were tested in clinical trial and two of them are already widely used:

- **a theoretical 2.5 dose ratio**, based on monotherapy and \textit{weight adjusted posology}. This dose ratio comes from the 2006 WHO guidelines recommendation based on patients’ bodyweight: 10mg/kg/day for amodiaquine and 4 mg/kg/day for artesunate. These recommandations are difficult to implement in “real life” situations, because patients’ weight is not available and AS and AQ presentations do not enable precise dosing adaptation to bodyweight.

- **a 3.1 dose ratio**, based on \textit{age adjusted posology}. It could be obtained by using marketed artesunate amodiaquine co-blisters available in 2006 (AQ 153 mg base tablets and AS 50 mg tablets and according to the dosing schedule recommended by the 2006 WHO guidelines.

- **the optimized dose ratio 2.7**, that could be obtained by the proposed fixed dose combination. The optimal tablet strength design for an age-based dosing regimen of artesunate amodiaquine as a fixed-dose combination have been determined, using a novel approach by modelling currently available, relevant, weight-for-age data from malaria endemic African countries (as published in Bulletin of WHO, December 2006, 84(12), 956-965). This dataset is referred to as malaria weighted anthropometric reference (MWAR) dataset. This methodology allows the design of practical regimens that maximize the proportions of patients receiving acceptable drug doses that should be safe and efficacious (see section 9.4).

Tablets containing 25, 50 and 100 of artesunate combined respectively with 67.5, 135 and 270 mg of amodiaquine were chosen because this dose ration gave the lowest risk of amodiaquine overdosing.

The amodiaquine/arteresunate ratio (2.7) of the artesunate amodiaquine fixed-dose combination ASAQ lies between the dose ratios of widely marketed loose combinations or co-blisters presentations (respectively 2.5 and 3.1). This ratio was confirmed to be consistent with the WHO Global Malaria Program treatment guidelines (appendix 1).
9. Treatment details

9.1. Method of administration

Oral use
The tablets should be swallowed with water.
For administration to the youngest children (below 6 years old), the tablets can be dissolved in water before administration. The tablets can also be crushed and administered with water.

9.2. Dosage

The dosage of artesunate and amodiaquine is:
- 4 mg/kg (range 2 to 10 mg/kg) body weight of artesunate and
- 10 mg/kg (range 7.5 to 15 mg/kg) body weight of amodiaquine base
once daily for 3 days.

<table>
<thead>
<tr>
<th>Weight range (approximate age range)</th>
<th>1st day of treatment</th>
<th>2nd day of treatment</th>
<th>3rd day of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4.5kg to &lt; 9 kg (2 to 11 months)*</td>
<td>25 mg AS</td>
<td>25 mg AS</td>
<td>25 mg AS</td>
</tr>
<tr>
<td></td>
<td>67.5 mg AQ</td>
<td>67.5 mg AQ</td>
<td>67.5 mg AQ</td>
</tr>
<tr>
<td>≥9kg to &lt;18kg (1 to 5 years)*</td>
<td>50 mg AS</td>
<td>50 mg AS</td>
<td>50 mg AS</td>
</tr>
<tr>
<td></td>
<td>135 mg AQ</td>
<td>135 mg AQ</td>
<td>135 mg AQ</td>
</tr>
<tr>
<td>≥18kg to &lt;36kg (6 to 13 years)*</td>
<td>100 mg AS</td>
<td>100 mg AS</td>
<td>100 mg AS</td>
</tr>
<tr>
<td></td>
<td>270 mg AQ</td>
<td>270 mg AQ</td>
<td>270 mg AQ</td>
</tr>
<tr>
<td>≥36kg (14 years and above)*</td>
<td>200 mg AS</td>
<td>200 mg AS</td>
<td>200 mg AS</td>
</tr>
<tr>
<td></td>
<td>540 mg AQ</td>
<td>540 mg AQ</td>
<td>540 mg AQ</td>
</tr>
</tbody>
</table>

* if a weight-age mismatch occurs, dosing should be weight-based
AS : artesunate
AQ : amodiaquine

9.3. Duration

The daily dose must be repeated during 3 consecutive days.
9.4. WHO treatment guidelines

WHO’s 2006 treatment guidelines on the use of artesunate/amodiaquine (2) recommends two dosing regimens for artesunate plus amodiaquine (AS + AQ):

1. Recommendation based on patients’ body weight is: 4 mg/kg/day for AS and 10 mg/kg/day for AQ given once a day for 3 days. This amounts to an AQ/AS = 2.5 based on each monotherapy recommended dosing regimen. These recommendations are difficult to implement in “real life” situations, because patients’ weight is not available and AS and AQ presentations do not enable precise dosing adaptation to bodyweight.

2. Recommendation based on presentations of AS and AQ available in 2006 (AQ 153 mg base tablets and AS 50 mg base tablets).

The dosing schedule after-specified illustrates this recommendation, which amounts to a 3.1 AQ/AS ratio.

<table>
<thead>
<tr>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>5-11 months</td>
</tr>
<tr>
<td>≥ 1-6 years</td>
</tr>
<tr>
<td>≥ 7-13 years</td>
</tr>
<tr>
<td>&gt; 13 years</td>
</tr>
</tbody>
</table>

The amodiaquine/artesunate ratio (2.7) of the artesunate amodiaquine fixed-dose combination ASAQ lies between the dose ratios of widely marketed loose combinations or co-blister presentations (respectively 2.5 and 3.1). This ratio was confirmed to be consistent with the WHO Global Malaria Program treatment guidelines (appendix 1).

The rationale of the selected 2.7 dose ratio of artesunate and amodiaquine in the fixed dose combination is based on study results recently published in the WHO Bulletin (6).

Weight-based dosing in malaria endemic countries is challenging because functioning weighing scales are scarce and access to formal health services is limited. Thus, the majority of malaria treatments are dosed based on the patient’s age. Cognisant of this practice, the WHO has both age and weight-based recommendations for the commonly used antimalarial drugs. However age/weight correlation is usually based on non-African population data.

The optimised tablet strength and blister design for an age-based dosing regimen of artesunate/amodiaquine as a fixed dose combination have been determined, using a novel approach by modeling currently available, relevant, weight-for-age data from malaria endemic African countries (6). This dataset is referred to as malaria weighted anthropometric reference (MWAR) dataset (88,000 African children and adults). This methodology allows the design of practical regimens that maximize the proportions of patients receiving acceptable drug doses that should be safe and efficacious.

The strategy of simplicity over dose accuracy demanded a definition of acceptable dosing ranges for both drugs. The dosing ranges for artesunate and amodiaquine were:
- artemesunate: 2 to 10 mg/kg (5 fold), reflecting its tolerability and, therefore, wide therapeutic index.
- amodiaquine: 7.5 to 15 mg/kg (2 fold). There was less flexibility with AQ, thus, AQ determined the final dosing and age categories.

Two conventions were adopted:
- select age groups with an approximate doubling in median bodyweight, and
- double the drug dose per age category.
These conventions led to selecting five age groups: (1) 0-1 months (4.2 kg), (2) 2-11 months (6.9 kg), (3) 1-6 years (13.3 kg), (4) 7-13 years (25.6 kg), and (5) ≥ 14 years (58.0 kg).

The model predicted that virtually all patients in each age category would receive a therapeutic dose of artemesunate. Tablets containing 25 and 100 mg were chosen because this dose gave the lowest risk of overdosing: 1 in 10,000 patients would receive more than 10 mg/kg/day and 1 in 1000 patients less than 2 mg/kg/day. The same rationale applied to the choice of the amodiaquine dosage (67.5 and 270 mg). The higher degree of under-dosing associated with the 67.5 and 270 mg tablets was considered less critical because the profound parasiticidal effect of artemesunate reduces substantially the parasite biomass leaving a small number of parasites to be killed by the amodiaquine.

This tablet strength, 67.5 mg for paediatric tablets and 270 mg for adult tablets (2.7 dose ratio) lead to 81.9% of patients within the therapeutic range (10.0% below and 8.2% above). The 2.7 ASAQ dose ratio was eventually chosen because it is associated with the lowest risk of AQ overdosing.

The convention of selected five age groups which had an approximate doubling in median bodyweight in this database, eventually conducted to change the age range; children 6 years old have to be treated with tablets containing 270 mg of amodiaquine instead of 153 mg amodiaquine with the coadministration treatment.

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

The clinical efficacy and safety of the artemesunate/amodiaquine combination is supported by 15 studies:
- Five studies were performed with a theoretical 2.5 artemesunate/amodiaquine dose ratio (free combination) based on monotherapy and weight adjusted posology (amodiaquine 10 mg/kg/day and artemesunate 4 mg/kg/day),
- Ten studies with a 3.1 dose ratio based on age adjusted posology (co-blister ratio),
- Two pivotal studies (Burkina Faso and ATAQ EASY multinational study) with the optimized 2.7 dose ratio (dose ratio of the fixed-dose combination).

List of the studies

<table>
<thead>
<tr>
<th></th>
<th>2.5 ratio</th>
<th>3.1 ratio</th>
<th>2.7 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDR study 1</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study A</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
The table below details the number of patients exposed to the three artesunate-amodiaquine dose ratios.

Extent of exposure (based on safety dataset)

<table>
<thead>
<tr>
<th>Weight adjusted posology</th>
<th>Coarsucam™</th>
<th>Age adjusted posology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>Dose ratio</td>
<td>Dose ratio</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>3.1</td>
</tr>
<tr>
<td>5 safety and efficacy studies</td>
<td>2 efficacy and safety study</td>
<td>10 safety and efficacy studies</td>
</tr>
<tr>
<td>N= 2,691</td>
<td>N=1,003</td>
<td>N=3,016</td>
</tr>
</tbody>
</table>

The different studies are described hereafter.

Co-administration of both artesunate and amodiaquine presented independently

The development of artesunate/amodiaquine co-administration was based on the results of studies initiated within the framework of the WHO/TDR antimalarial program whereby the efficacy and safety of several combinations of the artemisinin derivative artesunate (AS) with chloroquine (CQ), amodiaquine (AQ), sulfadoxine-pyrimethamine (SP) and mefloquine (MQ) were assessed (17).

The effective dose regimen of the AS+AQ combination was established through a clinical program established as follow:

- WHO/TDR Studies

3 randomized, double-blind studies conducted in children with uncomplicated *P. falciparum* malaria in 3 African countries; Senegal, Gabon and Kenya, (representing different forms of malaria transmission and patterns of drug resistance but where amodiaquine was expected to be efficacious (19)) as part of the WHO/TDR program. These 3 studies, which are referred to as WHO/TDR studies no 1, 2 and 3, compared the efficacy and safety of the artesunate (AS) plus amodiaquine (AQ) combination (4 mg/kg/day of AS and 10 mg/kg/day of AQ for consecutive 3 days) to AQ (Camoquin™) alone (10 mg/kg/day for 3 days) plus placebo (for double-blind conditions to be met). The AS+AQ
combination was composed of Arsumax® and Camoquin™ and is therefore referred to as the Arsumax®+Camoquin™ combination.

Study n°1: was conducted in Senegal (Casamance region) where malaria transmission is seasonal (July-November) and the entomological inoculation rate is 25/person-year. Chloroquine resistance is high (50-68%), and AQ (30mg/kg total) has a 14-day parasitological efficacy of 61%.

Study n°2: was conducted in Gabon where a rate of Chloroquine resistance of 53% was recently reported (18). In the Lambarene area, malaria transmission is hyperendemic and perennial and the entomological inoculation rate is 50/person-year. The 28-day AQ (25mg/kg total) parasitological efficacy was of 91% in 1994.

Study n°3: was conducted in southern Kenya (Entasopia and Migori) where malaria transmission is seasonal (May-July). The 14-day efficacy of AQ before the start of the study was 63% in Entasopia and 97% in Migori.

These 3 randomized double blind studies were carried out in a total of 941 children up to 10 years of age with body weight of at least 5 kg. All patients had uncomplicated malaria characterized by P.falciparum monoinfection with parasite counts ranging from at least 1000/µl to less than 200 000/µl and a history of fever during the past 24 hours. The demographic and pathological profile of the patients was well defined, and similar in the 3 studies, thus allowing assessing whether the efficacy of the drug regimen which was used (weight-adjusted Arsumax®+Camoquin™ versus Camoquin™ + placebo) was reproducible in all 3 countries (Senegal, Gabon and Kenya).

The results (table below) convincingly demonstrated the superiority of the efficacy of Arsumax®+Camoquin™ over that of Camoquin™ alone in the treatment of uncomplicated P.falciparum malaria. Even though the parasitological response rates at Day 14 and Day 28 were not significantly different between groups in Senegal, response rates with the combination in this country were only a close second to those in Gabon as illustrated in Figure 1. The lack of difference between the 2 groups in the Mlomp area of Senegal may be due to the efficacy of AQ remaining high in this area. It must be noted that parasitemia decreased more quickly in the presence of Arsumax® in Senegal as well as in Gabon and Kenya. The most obvious beneficial effect of the adjunction of Arsumax® to Camoquin™ was seen in Kenya. However, response rate at Day 28 with the combination was only 68.3%, probably due to the low mean age of the studied children population (only 2.7 years) and the relative lack of acquired immunity in such a young population, or possibly because of a higher incidence of AQ resistance.

**WHO/TDR studies results table**

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Study</th>
<th>AQ alone*</th>
<th>AS+AQ*</th>
<th>Δ [95% CI] or OR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cures at Day 14†</td>
<td>No. 1 Senegal</td>
<td>147/157(94)</td>
<td>148/160(93)</td>
<td>-1.1% [-6.7; 4.5]</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>No. 2 Gabon</td>
<td>86/96(90)</td>
<td>92/94(98)</td>
<td>8.3% [1.5; 15.1]</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Artesunate / Amodiaquine, Fixed dose combination 25 mg/ 67.5 mg, 50 mg/135 mg and 100 mg/270 mg
<table>
<thead>
<tr>
<th></th>
<th>No. 3 Kenya</th>
<th>140/188 (74)</th>
<th>175/192 (91)</th>
<th>16.7% [9.3; 24.1]</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cures at Day 28† (PCR uncorrected)</td>
<td>No. 1 Senegal</td>
<td>123/156 (79)</td>
<td>130/159 (82)</td>
<td>2.9% [-5.9; 11.7]</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>No. 2 Gabon</td>
<td>70/98 (71)</td>
<td>80/94 (85)</td>
<td>13.7% [2.2; 25.2]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>No. 3 Kenya</td>
<td>75/183 (41)</td>
<td>123/180 (68)</td>
<td>27.3% [17.5; 37.2]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cures at Day 28‡ (PCR corrected)</td>
<td>No. 2 Gabon</td>
<td>77/98 (79)</td>
<td>85/94 (90)</td>
<td>11.9% [1.8; 21.9]</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>No. 3 Kenya</td>
<td>98/183 (54)</td>
<td>144/180 (80)</td>
<td>26.4% [17.2; 35.7]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 1 - PCR-Uncorrected Efficacy Response Rates in WHO/TDR Studies
Gametocyte carriage rose in the Camoquin™ group in all 3 countries. Compared with Camoquin™, Arsumax®+Camoquin™ reduced gametocyte carriage on Days 7, 14 and 21 in all 3 countries; the difference between groups was statistically significant on Day 7 and Day 14 in Kenya and of borderline significance on Day 14 in Senegal [Figure 2].

**Figure 2 - Gametocyte Carrier Rate in WHO/TDR Studies**
Implementation study:

Subsequently, the same Arsumax®+Camoquin™ drug regimen (4 mg/kg/day of AS and 10 mg/kg/day of AQ for 3 consecutive days) was used for 2 consecutive seasons in Senegal as first-line treatment of uncomplicated malaria in South-Western Senegal. Again, this combination proved highly effective in conditions resembling routine use.

In the implementation study conducted in Casamance (Senegal), the 624 patients treated over the 2 consecutive transmission seasons of Year 2000 and Year 2001 were recruited among a mixed population of children and adults, although a majority of patients were children as shown by mean ages, 11 years for year 2000 and 10 years for year 2001 (for the 253 Arsumax®-treated patients). All selected patients in this open-label implementation study had fever or history of fever and microscopically confirmed \textit{P. falciparum} malaria. Thus, overall, they were included according to criteria similar to those of the patients of the WHO/TDR. This type of field study permitted to confirm the efficacy of the weight-adjusted Arsumax®+Camoquin™ treatment in less contingent conditions in a large number of patients over 2 seasons.

This open-label study with Arsumax®+Camoquin™ was carried out in Mlomp (Senegal) like the WHO/TDR Study No. 1. Although not meant to be a comparative study, it comprised a smaller group of patients treated with Camoquin™ alone. Efficacy rates at Day 28 during both seasons was similar in the 2 treatment groups, although slightly higher than in the WHO/TDR study: 95.8% with a 95% CI of [92.2; 98.1] and 94% [90.7; 96.4] during Years 2000 and 2001 for Arsumax®+Camoquin™, respectively, and 92.5% [81.8; 97.9] and 95.7% [85.5; 99.5] for Camoquin™ alone, respectively. These data confirm the lack of difference between the 2 groups and the good results of either treatment seen in that region of Senegal in the more rigorous methodological conditions of the WHO/TDR study.
Artesunate/amodiaquine co-blister Phase III Studies

While the antimalarial efficacy of the Arsumax®+Camoquin™ combination had been clearly demonstrated, coprescribing separate marketed products, i.e., Arsumax® and Camoquin™ or Flavoquine® was economically unaffordable for the African Health Authorities and not practical to implement as such. The ARSUCAM® coblisters containing both AS and AQ tablets were developed to provide the antimalarial combination as a low-price, age-adjusted, easy-to-use dosage forms for children up to 6 years of age, children in the 7-13 years age range and for patients 14 years and over, respectively.

Eight Phase III studies were conducted with ARSUCAM® cob blister. Among them, 6 studies were carried out in different regions of Senegal as part of the National Malaria Control Program (NMCP) (20). They include:

- Study A, conducted in Bougoula Hameau in Mali (where a steady increase in the prevalence of *P. falciparum* resistance to chloroquine has been documented) was a randomized, blinded study comparing 3 treatments: ARSUCAM®, SP+Arsumax® and Arsumax® alone, conducted in a total of 752 patients with age ranging from 0.6 years to 38 years. Of those, 252 were treated with weight-adjusted ARSUCAM®. Inclusion criteria were similar to those described for the WHO/TDR patients, except that patients showing infection with *Plasmodium Species* (not only those with *P. falciparum* infection) could be included. However, efficacy results are reported only for those with *P. falciparum* infection.

- Study B, conducted in Niakhar, Central Senegal where malaria transmission is markedly seasonal (July-December), was a randomized, single-blind study comparing 3 combinations: ARSUCAM®, SP+Arsumax® and SP+AQ, conducted in a total of 706 patients with age ranging from 10 to 71 months (i.e., approximately 1 to 6 years). Of those, 341 were treated with age-adjusted ARSUCAM®. Inclusion criteria were similar to those described for the WHO/TDR patients. This Phase 3 study mostly differs from the other Phase 3 studies on ARSUCAM® in that it was conducted in a rather large number of young children only.

- Open-label studies C and D of ARSUCAM® were conducted in two districts of Senegal, Guediaweye (where chloroquine resistance rate was 30% in 2002) and Podor (where periods of heavy transmission of malaria can be observed and where malaria is hypo-to-mesoendemic (inoculation rate of 5/person-year)).
Studies C, D, E, F, G and H were conducted in a total mixed population of 1136 children and adults among whom 462 were treated with age adjusted ARSUCAM®. Among the ARSUCAM® patients, 87 were aged 5 years or less. Again, inclusion/exclusion criteria for these patients with uncomplicated *P. falciparum* monoinfection were similar to those used in the previously described studies.

Altogether, the baseline malarial characteristics of the patients of all clinical trials included in this application were similar: patients were all treated for uncomplicated malaria due to a monoinfection with *P. falciparum*, with counts of at least 1000/µL of blood, fever, mild-to-moderate anemia and no danger signs or severe malaria. Gametocytemia was not always specified, except for the 3 WHO/TDR studies and Study A. However, changes in the percentages of gametocyte carriers during a 28-day follow-up period were well described in the 3 WHO/TDR studies as well as in Studies A and B.

As presented in table below, efficacy results with ARSUCAM® in all Phase 3 studies were consistent with or even better than those obtained in the WHO/TDR studies with Arsumax®+Camoquin™.
### Response Rates in Phase 3 Studies with ARSUCAM®

<table>
<thead>
<tr>
<th>Study</th>
<th>A</th>
<th>B</th>
<th>C, D, E, F, G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Mali</td>
<td>Senegal</td>
<td>Senegal</td>
<td>Comoros Union</td>
</tr>
<tr>
<td>Number of patients in ARSUCAM® group</td>
<td>237</td>
<td>341</td>
<td>360&lt;sup&gt;a&lt;/sup&gt;</td>
<td>102</td>
</tr>
<tr>
<td>Primary efficacy endpoint</td>
<td>Clinical and parasitological efficacy at Day 28</td>
<td>Clinical and parasitological efficacy at Day 28</td>
<td>Clinical and parasitological efficacy at Day 28</td>
<td>Clinical and parasitological efficacy at Day 14</td>
</tr>
<tr>
<td>Results (uncorrected)</td>
<td>81.0%</td>
<td>ACPR (Day 28): 87.2%</td>
<td>ACPR (Day 28): 97.5%</td>
<td>ACPR (Day 14): 98.0%</td>
</tr>
<tr>
<td>Parasitological failure after PCR</td>
<td>1%</td>
<td>1.5%</td>
<td>PCR not available</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

ACPR = accurate clinical and parasitological response; PCR = polymerase chain reaction

<sup>a</sup> all patients of the ARSUCAM® group in Studies C, D, E, F, G pooled

In Study A, the uncorrected response rate of 81% with ARSUCAM® was lower than that observed with the SP+AS bitherapy. However, after PCR correction, both bitherapies gave nearly complete (99.1%) or complete (100%) ACPR rate [figure 3]. The proportion of gametocyte carriers, of 6% at baseline decreased to less than 1% on Day 28 in the ARSUCAM® group. A similar pattern was seen in the other 2 groups. Fever decreased faster in the ARSUCAM® group compared to the SP+AS group and the AS5 group (5% febrile patients on Day 1 versus 9% and 13% in the SP+AS and AS5 groups, respectively; p <0.001), although it was nearly absent in all groups on Day 3.

![Figure 3 - Uncorrected Adequate Clinical and Parasitological Response Rate in Study A](image)

**Figure 3 - Uncorrected Adequate Clinical and Parasitological Response Rate in Study A**

The lower response rate in Study B is probably not clinically significant compared with results in the other studies. However, a polymerase chain reaction (PCR) check could be performed on 28 of the 36 patients with parasitemia on Day 28. As only 3
of the 28 patients for whom pair (Day 0 and Day 28) of PCR results were available, an extrapolated correction assessed the failure rate at 1.5%, which is a PCR-corrected response rate of 98.5%, similar to that in the other Phase 3 studies. Response rates on Day 28 with the comparators SP+AQ and SP+AS were 97.2% and 89.7%, respectively [figure 4], although no PCR correction was available for these groups. The proportion of gametocyte carriers was not significantly different between the 3 groups, but was consistently lower in the ARSUCAM® group on Days 7, 14 and 28.

![Figure 4 - Adequate Clinical and Parasitological Response Rates in Study B](image)

**Figure 4 - Adequate Clinical and Parasitological Response Rates in Study B**

**Altogether, the data of Studies A and B demonstrate that ARSUCAM® is at least as effective as the SP+AQ or SP+AS bitherapy and more effective than Arsumax® alone for 5 days in children and adults.**

In Studies C (district of Guediawaye), D (district of Podor), E (district of Richard-Toll), F (district of Kaolack), and G (district of Velingara) pooled together, ARSUCAM® (N = 360) provided, at Day 28, a response rate of 97.5% which was similar to the response rate with Artequin® (98.0%, N = 145), AQ+SP (98.8%, N = 161), Coartem® 4 doses (82.9%, N = 140) and Coartem® 6 doses (100%, N = 29) [see also figure 5]. Parasitological and fever clearances were rapid with percentages of febrile patients and parasite carriers of 1% and 5% at Day 2, respectively, and of 0% for both parameters at Day 3.
Parasitological clearance was also similar in all treatment groups, with 100% clearance obtained on Day 3. In Study C, the proportion of gametocyte carriers decreased steadily from 5.3% at Day 0 to 0% at Day 28, results consistent with those in WHO/TDR studies. In terms of response by study site, most of the failures (36/38, including 9 with ARSUCAM®) were reported in the district of Kaolack, and all failures but 1 were late treatment failures (LTF) occurred between Day 21 and Day 28. According to this author, some of the LTFs could be reinfections after Day 20. Kaolack is an important crossway between Gambia and Guinea, a fact that may increase transmission and the risk of reinfection.

Similarly consistent results were obtained in Study H carried out in the Comoros Union where efficacy response rate (ACPR rate) was 98% for ARSUCAM® (N = 102), 99% for AS+SP (N = 104) and 96% for CQ+SP (N = 95) [Figure 6].
WHO/TDR studies, as well as Study B with ARSUCAM®, were carried out in children population only. Results convincingly demonstrated (i) the superiority of the Arsumax®+Camoquin™ over Camoquin™ alone and (ii) the high response rate following ARSUCAM® (even before PCR correction). Other ARSUCAM® Phase 3 studies were carried out in a mixed population of patients (although mostly youngsters). In studies A and H, however, separate analyses were reported for the whole population and for children aged 5 years or less, i.e., in patients possibly more susceptible to infection because of a low level of immunity. In Study A, no difference was seen in efficacy rate on Day 14 between the lower age group (≤5 years) and the upper age group (>5 years). Likewise, in Study H, efficacy rate was similar in the <5-year-old group and in the whole study group (all ages combined). Altogether, the data demonstrate that the efficacy of artesunate amodiaquine combination covers all age groups.

No apparent clinically significant efficacy differences could be detected for the weight-adjusted Arsumax®+ Camoquin™ or the age-adjusted ARSUCAM® combinations across the countries (Senegal, Gabon, Kenya, Comoros Union) or across the Senegalese districts (Guediawaye, Podor, Richard-Toll, Kaolack, Velingara) where the clinical trials took place, even if failures (not PCR corrected) were seen in Kaolack district where the risk of reinfection may be specially high.

- Phase 4 ATOL study with Arsucam®

This multicenter, open, randomized study was conducted in Senegal and Cameroun, and compared Arsucam® once a day to Arsucam® twice a day. The main objective was to demonstrate the non-inferiority of Arsucam®, as a single dose intake versus two daily.

316 patients (adults and children weighing more than 10 kg) were included; 161 in the Arsucam® once-a-day group and 155 in the twice-a-day group. The primary endpoint was the adequate response to treatment on D14 (WHO definition).

The adequate responses to treatment were similar for the 2 treatments regimens, and approaching 100% before and after PCR analysis on D14 (99.4% on the one daily dose group and 99.3% in the two daily doses group). The statistical analysis conducted on the ITT and PP populations demonstrated the non-inferiority of administering Arsucam® as 2 daily intakes versus a single daily intake, in terms of clinical and parasitological efficacy on D14. Parasite clearance was comparable in the 2 treatment groups. Approximately 70% of patients showed negative parasitaemia on D2 and approximately 90% on D3. Arsucam® treatment was well tolerated during the study. Main reported adverse events were gastrointestinal disorders (2.5%) and pruritus (2.5%). The 2 treatment regimens showed similar safety profiles.

- Efficacy of artesunate and amodiaquine presented as a fixed dose combination

Burkina Faso study(21)
This was a randomised, controlled, open-label, parallel-group study comparing the efficacy and safety of artesunate-amodiaquine tablets (25/67.5 mg and 50/135 mg) over 3 subsequent days to an almost equivalent dose regimen of the individual drugs administered together (AS+AQ= Arsumax® + Flavoquine®), in children with malaria attack due to *P.falciparum*.

The study was carried out in Burkina Faso, in a rural area located 120 km from Ouagadougou, where a high level of transmission can be observed during the rainy season (from July to December).

A total of **750 children with ages ranging from 6 months up to 5 years inclusive**, with body weight of at least 5 kg were included. All patients had uncomplicated malaria characterized by *P. falciparum* mono-infection with parasite counts of at least 1000/µL and fever (uncorrected axillary temperature ≥ 37.5°C) at Day 0. Causes for exclusion were: signs of severe malaria, underlying diseases, allergy to drugs, intake of amodiaquine within 7 days prior to inclusion or intake of artemisin derivates within 3 days prior to inclusion, completed treatment with anti-malarial drugs within 7 days prior to inclusion (except chloroquine), and ongoing antibiotic treatment with drugs with anti-malarial activity (e.g. cotrimoxazole, tetracyclines, macrolides). The dosage was adapted to body weight. For the youngest children, the fixed dose combination tablets were either crushed or dissolved in water.

**Primary endpoint**

Since the ITT dataset stringently managed missing data as treatment failures, the event rate (cure rate) could be less than that on which the sample size was based and that could lead to a power less than 90%. For this reason, the Per-Protocol (PP) dataset was the primary analysis dataset.

For the primary analysis in the PP dataset, the PCR-corrected parasitological cure rates at D28 were the same (92.1%) in both treatment groups (2 sided 90% CI = [-0.03 ; 0.03]).

In the modified Per-Protocol (mPP) dataset (excluding patients spitting out/repeatedly vomiting), the PCR-corrected parasitological cure-rates at day 28 were 95.7% for the fixed-dose combination versus 96.0% for the loose combination (2 sided 90% CI = [-0.02 ; 0.03]).

With a pre-set non inferiority delta of 5%, the analysis of clinical as well as parasitological data demonstrated the non inferiority of the fixed-dose artesunate and amodiaquine combination compared to separate drugs administered concomitantly in children aged 6 months to 5 years. It also confirmed a satisfactory level of efficacy of the combination of artesunate and amodiaquine for the treatment of *Plasmodium falciparum* malaria in children aged 6 months to 5 years.

In this study, around 95% of the patients received crushed tablets.
ATAQ EASY Study

This phase III study aimed to validate the efficacy and safety of ARTESUNATE/AMODIAQUINE tablets (25/67.5mg and 50/135 mg) in comparison with artemether/lumefantrine fixed-dose combination, and to define the optimal dosage regimen (1 or 2 daily intakes per day) for the treatment of uncomplicated *Plasmodium falciparum* malaria. The primary objective was the comparison of ARTESUNATE/AMODIAQUINE tablets one daily intake with artemether/lumefantrine (two daily intakes).

This was a multinational, randomized, comparative, observer-blinded study, conducted in patients presenting with uncomplicated *Plasmodium falciparum* malaria. The trial was performed at five different sites in four countries: Senegal (2 sites), Mali, Cameroon, and Madagascar.

Overall, 941 patients (children and adults) were enrolled. Of these patients, 1 discontinued the study before treatment initiation. Therefore, 940 patients were treated. The dosage was adapted to body weight. For the youngest children, the tablets were either crushed or dissolved in water.

Adequate Clinical and Parasitological cure Rates (ACPR) in the Intent-To-Treat (ITT) population on Day 28 after PCR correction were 95.2% in the artesunate amodiaquine fixed-dose combination one daily dose group (n=310) and 95.5% in the artemether lumefantrine group (n=311). They were 94.9% in the artesunate amodiaquine fixed-dose combination two daily doses group (n=315). Results calculated in the per protocol (PP) population were 98.9% in the artesunate amodiaquine fixed-dose combination one daily dose group (n=283) and 98.6% in the artemether lumefantrine group (n=289). ACPR was 100% in the artesunate amodiaquine fixed-dose combination two daily doses group (n=285). Statistical analyses performed in both ITT and PP populations demonstrated the non-inferiority of administering artesunate amodiaquine fixed-dose combination one daily intake versus artemether lumefantrine, in terms of clinical and parasitological efficacy on D28 (2 sided 90%CI= [-0.03; 0.03] in the ITT population; = [-0.02; 0.01] in the PP population).

In children less than 5 years, ACPR in the ITT population on day 28 after PCR correction were 94.4% (n=143) in the artesunate amodiaquine fixed-dose combination one daily dose group and , 93.7% (n=142) in the artemether lumefantrine group with a 90% confidence interval for the difference between Coartem – artesunate amodiaquine FDC of [-0.06;0.04]. In the PP population ACPR on D28 were 98.5% (n=134), and 97% (n=133) with a 90% confidence interval of [-0.0526;0.0181], respectively. Because the superior limits of the CI was inferior to the non-inferiority delta 5% (respectively 0.04 in ITT population and 0.0181 in PP population), statistical analyses performed in both ITT and PP populations demonstrated the non-inferiority of administering artesunate amodiaquine fixed-dose combination one daily intake versus artemether lumefantrine, in terms of clinical and parasitological efficacy on D28.

The non-inferiority of administration of artesunate amodiaquine fixed-dose combination two daily intakes versus artemether lumefantrine and artesunate amodiaquine fixed-dose combination one daily intake was also demonstrated, in terms of clinical and parasitological efficacy on D28 (respectively two sided 90%CI:[-0.02 ; 0.04] and [-0.03 ; 0.03] for ITT population and [-0.03 ; 0.00] and [-0.03 ; 0.00] for PP population).

On D14, adequate responses to treatment after PCR correction were obtained for the 3 treatment regimens in both ITT and PP populations. In the ITT population 96.4% in the artesunate amodiaquine one intake, 95.9% in the artesunate amodiaquine two intakes, 97.4% in the artemether lumefantrine ; In the PP population, respectively 100.0%, 100.0% and 99.7%.

Approximately 35% of patients showed negative parasitaemia on D1 and around 99% on D3 without any significant difference between treatment groups at each time point.

A favourable evolution of baseline symptoms was observed for the 3 patient groups during the study.

In summary, the administration of artesunate amodiaquine fixed-dose combination dispensed into 1 or 2 daily intakes was non-inferior to artemether lumefantrine in terms of clinical and parasitological efficacy. No age or centre effect was observed regarding efficacy of study treatments.
Conclusions on the Efficacy of the fixed dose combination
The analysis of clinical as well as parasitological data of the Burkina Faso study clearly demonstrated the non-inferiority of the fixed artesunate and amodiaquine combination compared to both drugs administered concomitantly. It also confirmed a satisfactory level of efficacy of the combination of artesunate and amodiaquine for the treatment of *Plasmodium falciparum* malaria in children aged 6 months to 5 years (<18 kg).

The efficacy rate of both treatments in the most clinically meaningful population (mPP dataset) is superior to the 2006 WHO limit of 95% of PCR corrected ACPR level recommended in this target population.

It is well known that children under five years of age represent the most difficult population to treat because of their lack of immunity against malaria.

In the ATAQ EASY study it was demonstrated that, the administration of artesunate/amodiaquine fixed-dose combination dispensed into 1 or 2 daily intakes was non-inferior to artemether lumefantrine in terms of clinical and parasitological efficacy.

11. Summary of comparative evidence on safety

11.1. Safety and tolerability

More than 2,500 patients were treated and evaluated in the 5 clinical trials using the free combination (ratio 2.5); approximately 3,000 patients were treated and evaluated in the 9 clinical trials using a 3.1 dose ratio (co-blister). 1,003 patients were treated and evaluated in the 2 pivotal studies using the fixed-dose combination (ratio 2.7).

Overall exposure by age group is provided in the table below:

<table>
<thead>
<tr>
<th>Age group</th>
<th>Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 years</td>
<td>&gt;1,850</td>
</tr>
<tr>
<td>6-13 years</td>
<td>&gt;2,119</td>
</tr>
<tr>
<td>≥ 14 years</td>
<td>&gt;1,890</td>
</tr>
</tbody>
</table>

719 patients up to 38 years of age and exposed to 2.5 dose ration,
From 4 studies are excluded from this table,
Because the exposure by age group data is not available.

In the 2 pivotal studies, about 30% of treated patients experienced adverse reactions. Most of the reported adverse events were similar to symptoms usually seen during malaria attack.

The **most frequent adverse reactions** observed were:
- anorexia, abdominal pain, nausea, asthenia, somnolence, insomnia and cough (see hereafter).

The **most serious adverse reactions** observed were:
- asthenia, anaemia and vertigo.

The type and frequencies of all adverse events observed from the 2 pivotal studies are summarised hereafter:

The adverse events are ranked under body-system and frequency using the following convention: very common: ≥1/10; common: ≥ 1/100 to <1/10; uncommon: ≥ 1/1000 to <
1/100; rare : ≥1/10,000 to < 1/1000; very rare : < 1/10,000; not known : cannot be estimated from the available data.

<table>
<thead>
<tr>
<th>Class-organ</th>
<th>Frequency</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Bronchitis acute, gastroenteritis, oral candidiasis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Anorexia, insomnia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hallucination</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Ocular icterus</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Arrhythmia, bradycardia</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Common</td>
<td>Cough</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Common</td>
<td>Nausea, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Diarrhoea, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Pruritus, rash, face oedema, skin disorders</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Oedema peripheral, pyrexia</td>
</tr>
</tbody>
</table>

The following adverse reactions have been reported with amodiaquine, especially at higher doses and/or during prolonged treatment:

- Blood and lymphatic system disorders: cases of leucopenia and neutropenia (agranulocytosis),
- Nervous system disorders: rare neuromyopathy,
- Eye disorders, varying in type and severity: transient accommodation disorders, corneal opacifications regressive once treatment is stopped, very rarely, irreversible retinopathy justifying specialist ophthalmic attention,
- Hepato-biliary disorders: severe cases of sometimes fatal hepatitis,
- Skin and subcutaneous disorders: slate-grey pigmentation, notably affecting the fingers and mucous membranes.

In published literature data, generated mostly during post-approval use of amodiaquine and/or artesunate, additional types of events have been reported. Since frequency estimates are highly variable across the studies, no frequencies are given for these events. For some of these events, it is unclear whether they are related to amodiaquine/артесунате or occur as a result of the underlying disease process: headache, dizziness, cold, flu, rhinitis, shivering, sore throat, splenomegaly, convulsion, jaundice and allergic reaction.

11.2. A Risk Management Plan for ASAQ fixed-dose combination
Clinical data on the efficacy and safety of the artesunate-amodiaquine association (loose association and co-blister presentation) is available from over 8,000 patients. Clinical data on the ASAQ fixed-dose combination is, at present, available from approximately 1,000 patients. However, Sanofi-aventis and DNDi see it as part of their responsibility to ensure that appropriate documentation is made available on ASAQ safety and effectiveness (linked to the possible emergence of resistances, real life conditions, treatment compliance, etc). The sanofi-aventis’ pharmacovigilance system, in compliance with current rules and regulations will include ASAQ.

In addition it was decided to set up a proactive “ASAQ deployment monitoring plan” to provide good quality safety and effectiveness data on ASAQ when used in real-life conditions. This monitoring plan includes a variety of proactive studies, each providing different type of data. These studies will be performed in countries of West, Central and east Africa, with various malaria transmission patterns which together will provide a comprehensive picture of ASAQ safety and effectiveness.

- randomized, comparative, longitudinal studies:
  These studies’ primary objective is to document the efficacy, effectiveness and safety of repeated administration of ASAQ compared with artemether-lumefantrine fixed dose combination in cohorts of patients followed-up for 2 years. A comparative design will also facilitate the distinction between adverse events related to malaria itself and those related to treatments.

- ASAQ implementation studies:
  These studies will provide data on the impact of ASAQ deployment on parasite amodiaquine resistance markers and in vivo effectiveness over time, as well as on its safety in “real life” conditions.

- A large scale comparative safety study in patients over 6 years of age.
  This population was chosen to enable the collection of subjective adverse events (e.g. nausea, headache, tiredness, etc.), that is not possible in younger children.

- Investigator-sponsored trials:
  These studies are “investigators-sponsored trials”, usually comparative efficacy and safety clinical trials, for which sanofi-aventis provides ASAQ and will have access to efficacy and safety data.

All projects sponsored by sanofi-aventis and DNDi within the “ASAQ deployment monitoring plan” are set up in close cooperation with National Malaria Control Programs and collected data will be presented at defined time points to independent Data safety Monitoring Boards. Local pharmacovigilance agencies will also be involved in implementation studies.

In addition, sanofi-aventis submitted (April 2009) to the WHO Department of Medicines Policy and standards, a document that describes all these activities that are included in the “ASAQ deployment monitoring plan” that meets the requirements of the EMEA CHMP Guideline on Risk Management Systems for Medicinal Products for Human use (November 20, 2005).

11.3. Use in pregnancy and lactation
Pregnancy:
Malaria is known to be particularly hazardous during pregnancy. The benefits and risks of therapy with artesunate amodiaquine fixed-dose combination to mother and foetus must be assessed by the prescriber.

The safety of amodiaquine in pregnant women has not been conclusively established, although many years of experience with the drug have not indicated any teratogenicity. Data on a limited number of exposed pregnant women do not indicate any adverse effect of artemisinins on pregnancy or on the health of the foetus/newborn child. Animal data indicate a limited embryotoxic effect at doses of 6 mg/kg/day or more.

During 1st trimester of pregnancy, artesunate amodiaquine fixed-dose combination should not be used unless clearly necessary e.g. if treatment is life-saving for the mother, and if another antimalarial is not suitable or not tolerated.

During 2nd or 3rd trimesters of pregnancy, artesunate amodiaquine fixed-dose combination may be used with caution, only if other antimalarials are unsuitable.

Lactation:
The amounts of antimalarials in breast milk are small. Therefore, lactating women can receive artemisinin-based combination therapies (including artesunate amodiaquine fixed-dose combination) for malaria treatment.

11.4. Drug interactions

Interaction with drugs used for treatment of HIV and/or tuberculosis may occur, though little clinical data is available. Prescribers should be vigilant for adverse events potentially related to such interactions, including liver toxicity and neutropenia.

In the absence of clinical data, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is not recommended to be administered concomitantly with drugs known to inhibit the liver enzymes cytochrome 5CYP) 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) and/or CYP2C8 (e.g. trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast)

No pharmacokinetic interactions of artesunate with other antimalarial drugs of importance have been identified. However, concomitant administration of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION with other antimalarial treatments is not recommended, as no data on efficacy and safety are available.

A statistically significant decrease in dihydroartemisinin (DHA), the main active metabolite of artesunate, occurs with concomitant use of artesunate and amodiaquine (C\text{max} decreased 47%, AUC\text{0-inf} decreased 17%)

Agranulocytosis and hepatitis have been reported following the use of amodiaquine in long term prophylaxis treatments (see Section 15.4.8). Therefore, caution should be observed when prescribing amodiaquine-containing products, such as ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION, concurrently with other drugs with potential for liver and/or hematological toxicity.

Though no pharmacokinetic interactions have been documented, amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant
interactions with some β-blockers, antidepressants, antipsychotics drugs. Caution should be exercised when co-administration of these agents with ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is deemed necessary.

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

Effective malaria treatments are often not accessible to those who need it, because of their price, inappropriate distribution channels or lack of information. Sanofi aventis has developed a comprehensive program, called Impact Malaria that aims at mobilizing the expertise and resources of a major pharmaceutical manufacturer against malaria.

Develop pricing policies that give access to high quality drugs to all population segments is one segment of the Impact Malaria program. Without compromising quality, production costs have been optimized to offer the lowest possible "no profit-no loss" prices. Drugs are made available through both the public and the private distribution channels to reach all population segments. The same "no profit-no loss" approach is used for sales to the public sector, NGOs, etc.

Our involvement goes beyond the provision of drugs, by supporting projects that will demonstrate what is required for an effective and sustainable control of malaria in a variety of settings.

The pharmaceutical dosage form for paediatric patients is the same than the one for adults. The paediatric formulation is homothetic to the adult formulation and the manufacture is done on the same equipment. This leads to production and cost viability for these paediatric formulations.

Sanofi-Aventis has developed a program that makes drugs available through both the public and private distribution channels to reach all population segments:

- On the private market, the whole sailer price for the artesunate/amodiaquine fixed dose combination is 2.3 € (around 3 USD)
- On the public market, the only fixed dose combination which is comparable to artesunate/amodiaquine is artemether/lumefantrine. Based on the fluctuation of the public tender prices and on the latest tender prices observed, artesunate/amodiaquine fixed dose combination can be estimated to be cheaper than Coartem® at the present time.

As mentioned in the press release from MMV and Novartis for the launch of Coartem dispersible (22), “…the average cost of a full treatment is 0.80 USD. For the youngest patients, a full treatment course costs just 0.37 USD through public sector sources.”

With a “no profit-no loss” approach, for Artesunate/amodiaquine Winthrop, the average cost of a full treatment is about 0.54 USD. For the pediatric patients (from 6 months to 13 years of age) the average cost of a full treatment is 0.38 USD.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
To allow the manufacture of the fixed dose combination, the registration file was first submitted in Morocco on December 7, 2005 and the Marketing/Manufacturing Authorisation was granted on February 1, 2007. Following this initial registration, several endemic countries have then granted local Marketing Authorisation. These countries are: Benin, Burkina Faso, Burundi, Cameroon, Centrafrican Republic, Chad, Congo, Côte d’Ivoire, Democratic Republic of Congo, Gabon, Ghana, Guinea, Kenya, Madagascar, Mali, Mauritania, Morocco, Mozambique, Niger, Nigeria, Senegal, South Sudan, Tanzania, Togo, Uganda, Zambia and Zanzibar. Registration procedures are ongoing in a couple of other African countries: Malawi, Sierra Leone.

In parallel, on February 23, 2007, Sanofi-Aventis submitted the fixed dose combination dossier to the World Health Organisation, as part of the pre-qualification registration program concerning Artemisinin based antimalarial products. Sanofi-aventis fixed dose combination was approved by the WHO prequalification program on October 14, 2008.

14. Availability of pharmaceutical standards

Artesunate standards:
- Chinese and Vietnamese Pharmacopoeia.
- In house Standard according to the International and the European Pharmacopoeias.

Amodiaquine standards:
- USP 29, NF 24, S2 monograph,
- French Pharmacopoeia.
- In house Standard according to the French Pharmacopoeia

Fixed dose combination:
- In house standart

15. Proposed text for the WHO Model Formulary

15.1. NAME OF THE MEDICINAL PRODUCT

Artesunate Amodiaquine fixed dose combination 25mg/67.5mg
Tablet

Artesunate Amodiaquine fixed dose combination 50mg/135mg
Tablet

Artesunate Amodiaquine fixed dose combination 100mg/270mg
Tablet

15.2 CLINICAL PARTICULARS
15.2.1 THERAPEUTIC INDICATION

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains, which are susceptible to amodiaquine as well as to artesunate.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION. Official guidance will normally include WHO (http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf) and public health authorities’ guidelines (see also sections 15.2.4 and 15.3.1).

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should not be used in regions where amodiaquine resistance is widespread. (See also Sections 15.2.4 and 15.3.2 regarding pharmacokinetic interactions between artesunate and amodiaquine).

15.2.2 POSOLOGY and METHOD OF ADMINISTRATION

**Oral use**

The dosage of artesunate and amodiaquine is:

- 4 mg/kg (range 2 to 10 mg/kg) body weight of artesunate and
- 10 mg/kg (range 7.5 to 15 mg/kg) body weight of amodiaquine base once daily for 3 days.

<table>
<thead>
<tr>
<th>Weight range (approximate age range)</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; day of treatment</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; day of treatment</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; day of treatment</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4.5 kg to &lt; 9 kg (2 to 11 months)*</td>
<td>25 mg AS 67.5 mg AQ</td>
<td>25 mg AS 67.5 mg AQ</td>
<td>25 mg AS 67.5 mg AQ</td>
<td>1 tablet 25 mg/67.5 mg on three consecutive days</td>
</tr>
<tr>
<td>≥9 kg to &lt; 18 kg (1 to 5 years)*</td>
<td>50 mg AS 135 mg AQ</td>
<td>50 mg AS 135 mg AQ</td>
<td>50 mg AS 135 mg AQ</td>
<td>1 tablet 50 mg/135 mg on three consecutive days</td>
</tr>
<tr>
<td>≥18 kg to &lt; 36 kg (6 to 13 years)*</td>
<td>100 mg AS 270 mg AQ</td>
<td>100 mg AS 270 mg AQ</td>
<td>100 mg AS 270 mg AQ</td>
<td>1 tablet 100 mg/270 mg on three consecutive days</td>
</tr>
<tr>
<td>≥36 kg (14 years and above)*</td>
<td>200 mg AS 540 mg AQ</td>
<td>200 mg AS 540 mg AQ</td>
<td>200 mg AS 540 mg AQ</td>
<td>2 tablets 100 mg/270 mg (in one intake) on three consecutive days</td>
</tr>
</tbody>
</table>

* if a weight-age mismatch occurs, dosing should be weight-based

AS : artesunate
AQ : amodiaquine

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should not be taken with a high fat meal (see section 15.3.2).
The tablets should be swallowed with water.
For patients unable to swallow the tablets whole, e.g. very young children, the tablets can be dissolved in water before administration. The tablets can also be crushed and administered with water.

Should vomiting occur within half an hour after dosing, a repeated dose of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is to be taken. In case of further vomiting, treatment for severe malaria should be considered.

Renal/hepatic impairment:
No data are available on dosing in hepatically or renally impaired patients (see section 15.2.4).

15.2.3. CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients,
- History of liver injury during treatment with amodiaquine;
- Previous haematological event during treatment with amodiaquine.
- Retinopathy (in case of frequent treatment).

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION must not be used for malaria prophylaxis, since it may result in agranulocytosis and severe hepatotoxicity (see section 15.2.4)
15.2.4. SPECIAL WARNING AND PRECAUTIONS FOR USE

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should not be used in regions where amodiaquine resistance is widespread, as the treatment with the combination under such conditions may mean effectively a treatment with artesunate alone with an insufficient duration and decreased plasma concentrations as compared to artesunate alone (see section 15.2.5). As a result, the risk of development of resistance of *P. falciparum* to artesunate increases significantly.

Amodiaquine is effective against some chloroquine resistant strains of *P. falciparum*, although there is cross-resistance.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been evaluated in the treatment of malaria due to *Plasmodium vivax*, *Plasmodium malariae* or *Plasmodium ovale* and is therefore not recommended.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been evaluated for malaria prophylaxis. The use of amodiaquine for prophylaxis results in an unacceptably high risk of agranulocytosis and liver toxicity and is contraindicated. Therefore, the combination of amodiaquine and artesunate is also contraindicated for malaria prophylaxis (see section 15.2.3).

It is not known, whether the toxicity of amodiaquine, observed with prophylactic use (i.e. agranulocytosis, hepatotoxicity), may also develop after repeated cycles of curative treatment.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION has not been studied specifically in patients with thalassemia, sickle cell anaemia or G6PD deficiency.

In absence of specific clinical studies, caution should be exercised in patients with renal or hepatic impairment.

Symptoms suggestive of the following diseases should be carefully monitored:
- Hepatitis, pre-icteric phase and especially when jaundice has developed;
- Agranulocytosis (as suggested, for instance by a clinical condition including fever and/or tonsillitis and/or mouth ulcers).

When these symptoms develop or exacerbate during the course of the therapy with ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION, laboratory test for liver function and/or blood cell counts should be performed at once. Immediate discontinuation of treatment may be required.

In such cases, continuation of treatment with amodiaquine increases the risk of death.

Cardiovascular effects have been reported with other amino-4-quinoleine derivatives during high dose treatment. There is no evidence that an overdose of amodiaquine causes any of the life-threatening cardiovascular complications often seen after an overdose of chloroquine. However, by chemical class analogy, caution should be exercised, especially with patients...
who have recently taken other antimalarial drug with cardiovascular side effects (quine, quinidine, halofantrine, lumefantrine, mefloquine) or those who are under treatment with cardiovascular drugs or other drugs with the potential to prolong the QT interval (see section 15.2.9 overdosage).

The combination of artesunate and amodiaquine may induce neutropenia (see section 15.2.8) and increase the risk of infection.

Caution is advised when combining ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION tablets with drugs exhibiting inhibition, induction or competition for CYP2C8 (see section 15.2.5).

Co-administration of ARTESUNATE AMODIAQUIN FIXED DOSE COMBINATION and efavirenz should be avoided, since this combination has been noted to cause marked hepatotoxicity.

15.2.5. INTERACTION WITH OTHER MEDICINAL PRODUCT AND OTHER FORMS OF INTERACTION

Interaction with drugs used for treatment of HIV and/or tuberculosis may occur, though little clinical data is available. Prescribers should be vigilant for adverse events potentially related to such interactions, including liver toxicity and neutropenia.

In the absence of clinical data, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is not recommended to be administered concomitantly with drugs known to inhibit the liver enzymes cytochrome 5CYP 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) and/or CYP2C8 (e.g. trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast) (see section 15.3.2)

No pharmacokinetic interactions of artesunate with other antimalarial drugs of importance have been identified. However, concomitant administration of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION with other antimalarial treatments is not recommended, as no data on efficacy and safety are available.

A statistically significant decrease in dihydroartemisinin (DHA), the main active metabolite of artesunate, occurs with concomitant use of artesunate and amodiaquine (Cmax decreased 47%, AUC0-inf decreased 17%)

Agranulocytosis and hepatitis have been reported following the use of amodiaquine in long term prophylaxis treatments (see Section 15.4.8). Therefore, caution should be observed when prescribing amodiaquine-containing products, such as ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION, concurrently with other drugs with potential for liver and/or hematological toxicity.

Though no pharmacokinetic interactions have been documented, amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant interactions with some β-blockers, antidepressants, antipsychotics drugs. Caution should be exercised when co-administration of these agents with ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is deemed necessary.
15.2.6. PREGNANCY AND LACTATION

**Pregnancy:**
Malaria is known to be particularly hazardous during pregnancy. The benefits and risks of therapy with ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION to mother and foetus must be assessed by the prescriber.
The safety of amodiaquine in pregnant women has not been conclusively established, although many years of experience with the drug have not indicated any teratogenicity.
Data on limited number of exposed pregnant women do not indicate any adverse effect of artemisinins on pregnancy or on the health of foetus/newborn child. Animal data indicate a limited embryotoxic effect at doses of 6 mg/kg/day or more (see section 15.3.3)
During 1st trimester of pregnancy, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should not be used unless clearly necessary e.g. if treatment is life-saving for the mother, and if another antimalarial is not suitable or not tolerated.
During 2nd or 3rd trimesters of pregnancy, ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION may be used with caution, only if other antimalarials are unsuitable.

**Lactation:**
The amounts of antimalarial in breast milk are small. Therefore, lactating women can receive artemisinin-based combination therapies (including ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION) for malaria treatment.

15.2.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients receiving ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION should be warned that somnolence, dizziness or asthenia may occur, in which case they should not drive or use machines.

15.2.8. UNDESIRABLE EFFECTS

The tolerability to the fixed combination ARTESUNATE AMODIAQUINE has been evaluated through two studies involving 1003 patients treated with the fixed dose combination: one conducted in Burkina-Faso, and another one conducted in Senegal, Cameroon, Mali and Madagascar.
The tolerability was evaluated as comparable to reference treatments.

About 30% of treated patients experienced adverse reactions. Most of the reported adverse reactions were similar to symptoms usually seen during a malaria attack.

The most frequent adverse reactions observed were:
Anorexia, abdominal pain, nausea, asthenia, somnolence, insomnia and cough (see hereafter).

The most serious adverse reactions observed were:
Asthenia, anaemia and vertigo.
The adverse events considered at least possibly related to the treatment are listed hereafter by body system, organ class and absolute frequency.

The adverse events are ranked under body-system and frequency using the following convention: very common: ≥1/10; common: ≥ 1/100 to <1/10; uncommon: ≥ 1/1000 to < 1/100; rare: ≥1/10,000 to < 1/1000; very rare : < 1/10,000; not known: cannot be estimated from the available data.

The type and frequencies of all adverse reactions observed from the two pivotal studies are summarised hereafter:

<table>
<thead>
<tr>
<th>Class-organ</th>
<th>Frequency</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>Bronchitis acute, gastroenteritis, oral candidiasis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Anorexia, insomnia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hallucination</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Ocular icterus</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Arrhythmia, bradycardia</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Common</td>
<td>Cough</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Common</td>
<td>Nausea, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Diarrhoea, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Pruritus, rash, face oedema, skin disorders</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Oedema peripheral, pyrexia</td>
</tr>
</tbody>
</table>

The following adverse reactions have been reported with amodiaquine, especially at higher doses and/or during prolonged treatment:
- Blood and lymphatic system disorders: cases of leukopenia and neutropenia (agranulocytosis),
- Nervous system disorders: rare neuromyopathy,
- Eye disorders, varying in type and severity: transient accommodation disorders, corneal opacifications regressive once treatment is stopped, very rarely, irreversible retinopathy justifying specialist ophthalmic attention,
- Hepato-biliary disorders: severe cases of sometimes fatal hepatitis,
- Skin and subcutaneous disorders: slate-gray pigmentation, notably affecting the fingers and mucous membrane.

In published literature data, generated mostly during post-approval use of amodiaquine and/or artemesunate, additional types of events have been reported. Since frequency estimates are
highly variable across the studies, no frequencies are given for these events. For some of these events, it is unclear whether they are related to amodiaquine/artesunate or occur as a result of the underlying disease process: headache, dizziness, cold, flu, rhinitis, shivering, sore throat, splenomegaly, convulsion, jaundice and allergic reaction.

If any of the side effects is serious or unexpected, you should inform the supplier and/or health authority, as per local regulation.

15.2.9. OVERDOSE

In cases of suspected overdose, the patient should be urgently transferred to a specialized unit where appropriate monitoring and symptomatic and supportive therapy should be applied.

Amodiaquine

- Dangerous dose of amodiaquine cannot be stated precisely because of the low number of known cases; by analogy with chloroquine, it can be estimated at around 2 grams as a single administration in adults.
- Symptoms: headache, dizziness, visual disorders, cardiovascular collapse and convulsions, followed by early respiratory and cardiac arrest.

Artesunate

No overdose cases have been reported to date.

15.3. PHARMACOLOGICAL PROPERTIES

15.3.1. PHARMACODYNAMIC PROPERTIES

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION (ATC code P01BF03)
ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is an artemisinin-based combination therapy which consists of two blood schizonticides, with independent modes of action and different intraparasitic biochemical targets.

ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is indicated in areas where parasite resistance rate to amodiaquine remains below the threshold defined by WHO.

Efficacy and safety of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION in uncomplicated *P. falciparum* malaria have been demonstrated in clinical trials in West and Central Africa and in Madagascar. Inconsistent results have been seen in some areas where combinations of artesunate and amodiaquine have been studied, probably due to a higher prevalence of amodiaquine resistance.

ARTESUNATE: Antimalarial (ATC code: P01BE03).
Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (*Artemisia annua*).
The chemical mechanism of action of artesunate has been widely studied and appears well established. The artesunate endoperoxide bridge is split by haeme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

In-vitro experiments in *P. falciparum* have shown that artemisinin derivatives are active against a broad spectrum of the life cycle of the parasite, from the relatively inactive ring stage to late schizonts. The schizonticidal and gametocytocidal activities of artesunate, administered orally have been demonstrated in vivo on chloroquine-sensitive strains of Plasmodium (*P. berghei* in mice and *P. knowlesi* in monkeys) and on chloroquine-resistant strains (*P. berghei* in mice).

In-vitro Artesunate appears to be inactive against extra-erythrocyte forms, sporozoites, liver schizontes or merozoites.

When administered orally, artesunate consistently acts more quickly than orally administered chloroquine and intravenous quinine in all animal models studied, regardless of the strain or dose tested. In macaques (the animal model most similar to humans) infected with a chloroquine-resistant strain of *P. knowlesi*, cure was obtained with the same dose of artesunate and quinine.

**AMODIAQUINE:** Antimalarial (ATC code: P01BA06).

Amodiaquine is a synthetic 4-aminoquinoline antimalarial. Its activity is characterized by a schizonticidal action on *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae* by destroying intraerythrocytic forms.

The mechanism of action of 4-aminoquinoline derivatives against plasmodium is not yet completely known. It is nonetheless accepted that these derivatives, one of which is amodiaquine, penetrate the infected red blood cells and prevent the parasite from polymerizing haeme into an insoluble product called haemozoin, leading to parasite death.

Strains of *Plasmodium falciparum* resistant to 4-aminoquinolines (chloroquine, amodiaquine) are present in many areas, and their geographical distribution is constantly changing. However, amodiaquine remains active against many chloroquine-resistant *P. falciparum* strains.
15.3.2. PHARMACOKINETIC PROPERTIES

**Artesunate**

- **Absorption**
  After oral administration, absorption is rapid. Most of the artesunate is promptly biotransformed, mainly through plasma esterases, into the active metabolite dihydroartemisinin (DHA).

  After administration of two ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 100 mg/270 mg tablets (i.e total dose of 540 mg amodiaquine and 200 mg artemesunate) in healthy volunteers (n=32), the mean (CV) artemesunate Cmax value was 162.9 ng/ml (± 75%), and the corresponding value for AUC was 89.9 ng.h/ml (± 51%). The median (range) DHA tmax value was 0.25 hours (0.25-1.33 h).
  
  The mean (CV) DHA Cmax value was 460.4 ng/ml (± 38 %), and the corresponding value for AUC was 712.2 ng.h/ml (±36 %). The median (range) DHA tmax value was 0.75 hours (0.5-1.33 h).

- **Distribution**
  DHA has been shown to substantially accumulate in *P. falciparum*-infected erythrocytes. Artesunate is not significantly protein-bound.

- **Metabolism**
  Artesunate is extensively hydrolysed by plasma esterases and perhaps also by CYP2A6. Its main metabolite, DHA is presumed to account for most of the in vivo antimalarial activity. DHA is further metabolised through glucuronidation prior to excretion.

- **Elimination**
  Artesunate has a plasma half-life of 3-29 minutes. The active metabolite DHA has a plasma half-life of 40 to 95 minutes. The modes of excretion of DHA have not been fully elucidated.

**Amodiaquine**

- **Absorption**
  After oral administration in healthy subjects, amodiaquine is quickly absorbed and transformed in its main active form, desethylamodiaquine. The absolute bioavailability of amodiaquine is not known.

  After administration of two ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 100mg/270mg tablets (i.e total dose of 540 mg amodiaquine and 200 mg artemesunate) in healthy volunteers (n=32), the mean (CV) amodiaquine Cmax value was 9.2 ng/ml (± 33 %), and the corresponding value for AUC was 65.7 ng.h/ml (± 45 %). The median (range) amodiaquine tmax value was 0.79 hours (0.48-8 h).

  The mean (CV) desethylamodiaquine Cmax value was 147.9 ng/ml (± 41%), and the corresponding value for AUC was 9947.8 ng.h/ml (± 43 %). The median (range) desethylamodiaquine tmax value was 2 hours (1.33- 8 h).

- **Distribution**
  The volume of distribution of amodiaquine is estimated at 20 to 40 l/kg.
Desethylamodiaquine, the main metabolite of amodiaquine, is assumed to be the main active form after oral administration. It is mainly found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4-6 times higher than in plasma.

- **Metabolism**
The hepatic first-pass metabolism of amodiaquine is high, with formation of the active metabolite, desethylamodiaquine, presumably via the CYP 2C8 isoenzyme. Further metabolism includes oxidation and glucuronocojugation.

- **Elimination**
Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Desethylamodiaquine is slowly eliminated with a terminal half-life of 9-18 days.

**Artesunate Amodiaquine fixed dose combination**

**Artesunate and amodiaquine interaction**
Single dose data have shown that the co-administration of artesunate and amodiaquine leads to a 47% decrease in the Cmax of dihydroartemisinin, and a 17% decrease of its AUC\(_{0-\infty}\), relative to what is seen when artesunate is administered alone. If ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION is used in the presence of amodiaquine resistance, this might further compromise the antimalarial activity of ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION (see also sections 15.2.1, 15.2.4 and 15.3.1).

**Special population**
For the combined use of artesunate and amodiaquine, no pharmacokinetic data are available for patients with impaired renal or hepatic function.

**Food effect**
When ARTESUNATE AMODIAQUINE WINTHROP was taken with a high fat meal in healthy volunteers, the Cmax and AUC\(_{0-t}\) of amodiaquine increased 23% and 58% respectively, compared to fasting. The Cmax and AUC\(_{0-t}\) of the active metabolite desethylamodiaquine (DeAQ) increased 18% and 12% respectively with a high-fat meal, compared to fasting.
Conversely, when ARTESUNATE AMODIAQUINE WINTHROP was taken with a high fat meal in healthy volunteers, the Cmax and AUC\(_{0-t}\) of artesunate decreased 66% and 13% respectively, compared to fasting. The Cmax and AUC\(_{0-t}\) of the active metabolite dihydroartemisinin (DHA) decreased 48% and 5% respectively with a high-fat meal, compared to fasting.

**15.3.3. PRECLINICAL SAFETY DATA**

**- General toxicity :**
Artesunate presents low acute toxicity but is potentially toxic to the haematopoietic organs, the immune system and response, the liver and kidneys after repeated administration of 50 mg/kg/day in rats and 82.5mg/kg/day in dogs, i.e.12.5 and 20.6 times the proposed therapeutic dose in man.

For amodiaquine, pigmentary changes and histological changes were seen in the heart at 30 mg/kg/day in rats. The effects seen in vitro on ion channels in the heart appeared to be due to a non-specific multi-ion channel blockade, however significant effects were not observed in vivo up to doses of 30 mg/kg in the safety pharmacology studies.
The toxicity after acute and chronic administration of the combination artesunate/amodiaquine was similar to that of both, artesunate and amodiaquine, when administered alone. In repeat dose toxicity, the incidence and the severity of lesions were generally related to the dose levels. Amodiaquine given alone at 30 mg/kg/day induced very similar effects than the 12/30 mg/kg/day artesunate amodiaquine combination and therefore was responsible for the main toxic effects on the combination. No new toxicities was induced through the administration of the two substances in combination.

- **Genotoxicity:**
  Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames mouse nucleus). Although amodiaquine, like chloroquine, has shown both mutagenic and clastogenic potential, studies with the artesunate amodiaquine combination in the Ames test and micronucleus in rat did not demonstrated any evidence of genotoxicity.

- **Carcinogenesis:** No studies of the carcinogenic potential artesunate amodiaquine combination or the individual agents have been conducted.

- **Toxicity to Reproduction:**
  Artesunate appears to be safe on the main physiological functions. Slight sedative effect, a decrease in body temperature, a slight natriuretic effect and a decrease in endogenous creatinine clearance were observed but at very high dose levels (≥200 mg/kg intravenously or ≥180 mg/kg orally). Atrioventricular blocks and depressant effects on smooth muscles were also reported but the relationship to the treatment administration remains to be confirmed. Neither neurotoxicity nor prolongation og QT and corrected QT interval were shown. Amodiaquine is likely to induce cardiovascular adverse effects, particularly transient prolongation of QT interval duration at 30 mg/kg administered orally. This dose level corresponds to approximately 2 fold the maximum recommended dose [15 mg/kg for a child weighing between 9 (<5 years old) and 18 kg (>6 years old)]. At the dose level of 100 mg/kg administered orally (about 6.7 fold the maximum intended therapeutic dose), also slight respiratory depressant and natriuretic effects were noted. Oral administration of both products, amodiaquine followed by artesunate, was safe for the CNS, the cardiovascular and respiratory systems at dose levels of artesunate amodiaquine corresponding to approximately 1.67/1.81 fold the maximum intended therapeutic dose levels (15/5.5 mg/kg amodiaquine/arteasunate). The natriuretic effect on the kidney was very slight and transient. Since the duration of treatment is limited to 3 consecutive days, this is not considered a risk for patients. The combination artesunate and amodiaquine did not show any adverse effect on the main physiological functions up to the dose levels of artesunate amodiaquine corresponding to approximately 1.67/1.81 fold the maximum intended therapeutic dose levels.

### 15.4. PHARMACEUTICAL PARTICULARS

#### 15.4.1. SHELF LIFE

The shelf life of the product as packaged for sale is 36 months.

#### 15.4.2. SPECIAL PRECAUTIONS FOR STORAGE

The product should be stored below 30°C in the original package.
15.4.3. NATURE AND CONTENTS OF CONTAINER

**ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 25mg/67.5mg**
3 tablets packaged in an aluminium/aluminum blister pack

**ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 50mg/135mg**
3 tablets packaged in an aluminium/aluminum blister pack

**ARTESUNATE AMODIAQUINE FIXED DOSE COMBINATION 100mg/270mg**
3 tablets packaged in an aluminium/aluminum blister pack, for children between 6 and 13 years of age.
6 tablets packaged in an aluminium/aluminum blister pack, for patients aged 14 years and older.
16. References


8. WHOPAR MA056, MA057 and MA058 Artesunate/Amodiaquine 25mg/67.5mg, 50mg/135mg and 100mg/270mg tablets http://healthtech.who.int/pq/


10. Prequalification file stability studies dated December 2006


22. MMV and Novartis launch Coartem Dispersible http://www.mmv.org/article.php3?id_article=580