

Expert Opinion

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Artemether/lumefantrine in the treatment of uncomplicated falciparum malaria

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At present, artemether/lumefantrine (AL) is the only fixed-dose artemisinin-based combination therapy recommended and pre-qualified by WHO for the treatment of uncomplicated malaria caused by *Plasmodium falciparum*. It has been shown to be effective both in sub-Saharan Africa and in areas with multi-drug resistant *P. falciparum* in southeast Asia. It is currently recommended as first-line treatment for uncomplicated malaria in several countries. However, AL has a complex treatment regimen and the issues of adherence to treatment with AL by adult patients and real-life effectiveness in resource-poor settings will be critical in determining its useful therapeutic life, especially in Africa, where the major burden of malaria is felt. There are also issues of safety of the artemisinin derivatives, including AL, which will need to be monitored as their use in resource-poor settings becomes more widespread. There are limited pharmacokinetic studies of AL in African patients, and the relationship between plasma drug concentration and efficacy in these patients is unknown. Moreover, the effects of factors such as concurrently administered drugs, malnutrition and co-infections with HIV and helminths in malaria patients are not well understood. These will need to be addressed, although a few studies on possible drug–drug interactions with commonly used drugs, such as quinine, mefloquine and ketoconazole, have been reported. This review focuses on the status of clinical pharmacology, efficacy and real-life effectiveness of AL under a variety of settings, and highlights some of the challenges that face policy makers during the deployment of AL, especially in Africa, with regards to ensuring that those who most need this therapy will not be denied access due to official inefficiency in procurement and distribution processes.

Keywords: artemether, artemether/lumefantrine, lumefantrine, uncomplicated falciparum malaria

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1. Introduction

The emergence and spread of resistance to chloroquine and sulfadoxine/pyrimethamine, two previously effective and affordable (< US\$1.0 per treatment course) treatments, threatens to reverse previous gains in controlling and managing cases of malaria, especially in sub-Saharan Africa. Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite administration and absorption of a drug that is given in doses equal to or higher than those usually recommended, but within the limits of tolerance. This definition has been modified to specify that the particular drug being referred to 'Must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action' [1].

Combination therapy (CT) is now widely accepted as the way forward to slow the rapid emergence and rapid spread of resistance to malaria, and to increase the useful therapeutic life (UTL) of antimalarial drugs. Ideally, CT for malaria should contain

an artemisinin derivative because i) they are effective against multi-drug resistant parasites, ii) they cause a rapid reduction in parasite biomass in addition to rapid reduction of fever, iii) they are gametocytocidal and could potentially reduce malaria transmission and iv) they are rapidly eliminated and, hence, have less potential to select for resistant parasites. Ideally, artemisinin-based combination therapies (ACTs) should be fixed-dose CTs to improve adherence and avoid the temptation by some patients to use single components of the CT, as would occur when they are co-packaged. To curb the emergence and rapid spread of resistance to currently available antimalarial drugs, the WHO now recommends the use of ACTs [2]. ACT in malaria involves the simultaneous use of two or more blood schizonticidal drugs (one of which is an artemisinin derivative) with independent modes of action and different biochemical targets in the parasite [2].

At present, artemether/lumefantrine (AL) is the only fixed-dose ACT recommended and pre-qualified by the WHO. A commitment has been made by the manufacturing pharmaceutical company to make the drug available at an average price of US\$1 per adult treatment course, and US\$0.45 per pediatric treatment course in young children. AL is registered in several countries, and has already been adopted as first-line treatment for uncomplicated malaria in numerous countries in sub-Saharan Africa, such as Kenya, Uganda, Tanzania, South Africa and Niger. The purpose of the review is to summarize what is known on AL in two broad parts: i) the clinical pharmacology (pharmacokinetics and toxicology) of AL, its potential to delay the emergence of resistant parasites, reported efficacy and effectiveness under 'real-life' conditions, accessibility by those who most need it, the ease with which patients are likely to adhere to the treatment regimen and suggestions of some critical areas where more research is still needed; ii) an expert opinion on selected issues based on a checklist of ideal properties of a combination antimalarial drug.

Not all of the available literature on AL could be cited in this review, and a deliberate emphasis has been placed on reports on efficacy studies and clinical pharmacology (pharmacokinetics and clinical toxicology) because, with the deployment of this drug in several resource-poor settings, these will be two main areas of concern. The discussion on the clinical pharmacokinetics of artemether is restricted to oral administration, as this is the relevant formulation when artemether is used as AL.

2. Clinical pharmacology

2.1 Clinical pharmacokinetics

The greatest burden of malaria is borne by children in sub-Saharan Africa. Understanding the clinical pharmacology of antimalarial drugs in African patients, including children, is crucial for the safe and effective use of these drugs in this population. Due to the complications of evaluating pediatric patients, only a few pharmacokinetic studies on AL have been

conducted in African children [3-5], although several detailed pharmacokinetic studies have been reported in children and adults elsewhere [6-11]. However, there are no known ethnic differences in the disposition of AL [8]. Following oral administration, artemether is rapidly absorbed and rapidly converted to dihydroartemisinin, with peak plasma concentrations of artemether and dihydroartemisinin achieved within 2 h. Both compounds are rapidly eliminated, with elimination half-lives of < 3 h [6,10]. Lumefantrine (formerly known as benflumetol), an aryl amino alcohol with chemical and structural similarities to quinine, mefloquine and halofantrine, is highly lipophilic. Its absorption rate is slow, with a 2-h absorption lag time, an absorption half-life of ~ 5 h and peak lumefantrine concentrations occurring ~ 10 h after drug administration. The terminal elimination half-life is ~ 4 – 5 days [6,10].

The dosing schedule for AL is summarized in Section 9.6. Food enhances the absorption of both artemether and lumefantrine, with a more pronounced effect produced on lumefantrine [10], and efficacy of the combination is enhanced when it is taken with a small amount of fat [6,12]. Partly because of differences in food intake by patients with uncomplicated malaria, absorption of lumefantrine is erratic, and may be lower in some patients. The AUC of lumefantrine increases with subsequent doses, and is associated with an increased chance of cure. Increased artemether and dihydroartemisinin AUCs are associated with decreased parasite clearance time [6]. The factors that may contribute to the observed increase in lumefantrine AUC with subsequent doses could be those affecting bioavailability (F), fraction unbound (f_u) or intrinsic clearance (CL_{int}), according to the following equation:

(1)

$$AUC_{oral} = (F \times Dose) / CL_{Total} = (F \times Dose) / (f_u CL_{int})$$

Lumefantrine has a long elimination half-life relative to its dosing interval, and accumulation occurs following multiple doses as the drug from previous doses is not completely eliminated when subsequent doses are administered. This natural accumulation and the increase in bioavailability is due to return to normal food intake following recovery from acute malaria [11]. This is a reasonable explanation for the reported increase in lumefantrine AUC with subsequent doses.

Lumefantrine is highly protein bound (> 99%), and binds mainly to high density lipoproteins [13]. The extent of protein binding is probably unaffected by malaria. It is most probably metabolized to a low extent *in vivo*, suggesting that it can be classified as capacity-limited (poorly extracted) binding-sensitive drug (i.e., a highly bound drug with a low hepatic extraction ratio) [11]. Following oral administration, changes in hepatic blood flow would not affect the pharmacokinetics of such a drug [14]. However, the AUC is inversely proportional

to intrinsic clearance. Therefore, the reported increase in lumefantrine AUC with repeated dosing is consistent with either an increase in F or a decrease in CL_{int} . Decreased CL_{int} is difficult to detect as absorption kinetics complicate the elimination profile during days 2 and 3 when absorption is still in progress (it would take 20 – 25 h for absorption to be complete from a given dose, based on an absorption half-life of ~ 5 h, and the fact that it takes five half-lives for absorption to be completed).

Increased parasite count at baseline has been associated with decreased lumefantrine absorption in Thai patients [11], and decreased intestinal perfusion could, theoretically, also decrease drug absorption. However, in a small study of African children (aged 6 months – 13 years; $n = 113$) with symptoms suggestive of severe disease (that may be associated with decreased intestinal perfusion) and treated with AL, it has been shown that malaria does not affect the oral absorption of lumefantrine (determined from the day-7 lumefantrine concentration) [3].

Artemether is also highly bound (95 – 98%) to plasma proteins [13], and the substantial hepatic first-pass metabolism contributes to incomplete oral bioavailability [6]. Artemether is well absorbed orally, but a fraction will be metabolized by CYP2C19, 2B6 and 3A4 in the gut wall. The remainder is metabolized to the pharmacologically active metabolite, dihydroartemisinin, in the liver. For drugs eliminated via metabolism in the liver, systemic clearance is determined by three factors: i) the fraction unbound in blood (f_u), ii) the rate of blood flow to the liver (Q) and iii) the ability of the liver to irreversibly remove the drug from liver water (CL_{int}) [15]. Several models have been developed to describe hepatic drug elimination, one of which is the 'well-stirred' model that assumes instantaneous and complete mixing within the liver [15]. It can easily be used to summarize changes in drug clearance when the above factors are altered. If the well-stirred model of hepatic clearance applies to artemether, then:

(2)

$$F^* = 1 - (f_u CL_{int} / Q)$$

where F^* is the fraction of the absorbed dose that appears as intact artemether in the hepatic portal vein and then escapes first-pass metabolism in the liver, and Q is the liver blood flow. Therefore, F^* will be influenced by changes in hepatic blood flow, intrinsic clearance (enzyme activity) or plasma protein binding. Any of these factors, in addition to factors that affect gut wall metabolism, could explain the reported increase in bioavailability of artemether for the third dose in Thai patients [6].

The probability of encountering parasites with susceptibilities exceeding the *in vivo* effective drug concentrations increases with the size of parasite biomass, but this is only

relevant if there is a possibility of encountering a naturally resistant parasite to one or both components of an ACT [16]. A recent study showed that increased *pfmdr1* copy number in *P. falciparum* isolates from patients treated with AL was associated with increased cases of recrudescence following the four-dose AL regimen, but not the six-dose regimen [17]. It was concluded that the six-dose regimen (with a longer course of artemether) reduced the initial parasite biomass to levels low enough for the infection to be eliminated by the lumefantrine even in the presence of partially resistant parasites [17]. The six-dose, 3-day regimen of artemether and lumefantrine covers two asexual parasite life cycles and probably achieves an overall reduction in parasite biomass by a factor of 10^8 . Thus, the two drugs have complementary pharmacokinetics: artemether is rapidly absorbed and metabolized to dihydroartemisinin, which produces a rapid reduction in parasite biomass, giving symptomatic relief, and lumefantrine acts to clear residual parasites that may remain after both artemether and dihydroartemisinin have been cleared from the body. The exposure of parasites to both artemether and lumefantrine is thought to minimize the risk of resistance development [16,18]. Due to the long half-life, some parasites may be exposed to lumefantrine alone after 3 days of treatment, especially when AL is used in areas of high malaria transmission where chances of re-infection are high. In such areas, mismatched pharmacokinetics can play a role in facilitating the development of resistance to the unprotected (long half-life) component of a CT [19] (in addition, see Section 3).

Artemether is metabolized to dihydroartemisinin, and lumefantrine is metabolized to *N*-desbutyl lumefantrine by CYP3A4/5 [8,10]. *N*-desbutyl lumefantrine is more hydrophilic than lumefantrine, and is undetectable in most samples from patients receiving AL. Following the metabolism of artemether to dihydroartemisinin, the latter is subsequently glucuronidated to inactive products [20,21]. The pharmacokinetics of both drugs are not altered when they are administered as a combination compared with when they are administered separately, suggesting that there is no apparent pharmacokinetic interaction [22,23,201]. Drug–drug interactions due to competitive or non-competitive inhibition of specific isoenzymes can occur between AL and other antimalarial drugs. For example, quinine is also metabolized by CYP3A4 [24-26], mefloquine is thought to be either a substrate or an inhibitor of CYP3A4 [27,28] and lumefantrine produces significant inhibition of CYP2D6 *in vitro* at therapeutic concentrations [29]. Some patients receiving AL may also be administered quinine, and this may lead to potential drug–drug interaction. Quinine is known to be cardiotoxic, especially following intravenous infusion [30-33]. Given the reported QT interval prolongation in animals treated with artemether, it would be expected that clinically important pharmacokinetic or pharmacodynamic interactions involving AL, quinine and mefloquine or with substrates/inhibitors/inducers of CYP3A4 and CYP2D6 could occur when these drugs are co-administered or administered sequentially [34].

However, this is not supported by clinical studies that have been reported. For example, a study in healthy volunteers has shown no clinically important pharmacokinetic interaction between AL and quinine, although prior administration of AL seemed to enhance the inherent risk of QTc interval prolongation caused by intravenous quinine [35]. Another two studies reported that co-administration of AL and mefloquine resulted in no significant cardiac effects, but a significant decrease (30 – 40%) in lumefantrine bioavailability in healthy volunteers [36,37]. Although similar studies have not been conducted in patients (see also Section 9.9), as a precaution, if AL is administered to patients who have been previously exposed to mefloquine or quinine, close monitoring of food intake (mefloquine) or the ECG (quinine) is advised (see Section 2.2). A separate study showed that ketoconazole, a potent inhibitor of CYP3A4, causes a modest *in vivo* inhibition of the metabolism of artemether, dihydroartemisinin and lumefantrine in healthy subjects. The inhibition was not thought to be potent enough to warrant AL dose adjustment in patients [38]. Nevertheless, caution is recommended when combining AL with substrates, inhibitors or inducers of CYP3A4 (see Section 2.2). Other physiologic or pathophysiologic changes that might influence the activities of CYP3A4 also need to be taken into account when using AL. For example, a recent study in southeast Asia has reported that pregnant women in their second and third trimesters had lower concentrations of artemether, dihydroartemisinin and lumefantrine, and that the elimination of lumefantrine was more rapid in pregnant women than previously reported in non-pregnant adults [39]. The potential inhibition of CYP2D6 by lumefantrine is the reason why the drug is contraindicated in patients concurrently being administered drugs metabolized by the CYP2D6 isoenzyme (see Section 2.2).

2.2 Clinical toxicology

2.2.1 Pediatric population

There are no data on the use of AL in newborns and very young children. The current recommendation for use in infants and children weighing between 5 and 35 kg. Results from safety and efficacy trials in older African children have reported no remarkable safety issues [40,41].

2.2.2 Adolescents and adults

A pooled analysis of data from individual trials of the six-dose AL regimen in adolescents and adults with uncomplicated falciparum malaria has shown that this regimen is more effective than the four-dose regimen, without compromising safety [42].

2.2.3 Pregnant women

Over 50 million pregnancies occur in malaria-endemic regions every year [43]. Even though there are concerns about possible teratogenicity when artemisinin derivatives are used in the first trimester of pregnancy [44], this is based on reported embryotoxicity and teratogenicity when these compounds are administered in animals [45,46]. There are currently no human

data on what the actual risks may be. From the available, limited, clinical data, there is no early signal for potential reproductive toxicity of artemisinin derivatives [47,48]. A recent study in which four pregnant women were mistakenly treated with full courses of AL during their first trimesters reported normal deliveries by all the four women, with no abnormal outcomes among the babies during the subsequent 1 year of follow-up [5]. Nevertheless, similar to all ACTs, AL is contraindicated during the first trimester of pregnancy. The practicality of this recommendation in resource-poor settings, such as health facilities in most parts of sub-Saharan Africa, is discussed in Section 9 of this review. According to the manufacturer of AL, breastfeeding women should not consume AL. In cases in which AL is administered to a breastfeeding mother, it is recommended that breastfeeding should not resume until 28 days after the last dose, unless the potential benefits to the mother and child outweigh the risks of AL treatment (see Section 9). During the second and third trimesters of pregnancy, treatment should only be considered if the potential benefit to the mother outweighs the risk to the foetus. An ongoing study in Zambia is aimed at generating some of the data on the risks associated with administration of AL during pregnancy [49]. In brief, the study in Zambia is a prospective observational study that is recruiting pregnant women with symptomatic uncomplicated falciparum malaria who have been exposed to AL or sulfadoxine/pyrimethamine during the second or third trimesters of pregnancy. The primary objective is to measure the risk of perinatal mortality (stillbirths after 28 weeks gestation, and death within 7 days after birth). Results on the perinatal mortality will be available in the first quarter of 2008.

2.2.4 Elderly patients and those with renal and hepatic impairment

There are no studies in these subpopulations. Hence, no specific dose recommendations are available. However, in the literature insert that accompanies the product, the manufacturer recommends that care should be taken when using AL in these groups of patients.

2.2.5 Cardiotoxicity, drug–drug interactions and other contraindications

Due to its structural similarity to halofantrine, lumefantrine was expected to have similar cardiotoxic effects. With regard to artemisinin derivatives, Beagle dogs that were administered high doses of these compounds have been shown to have slight QT interval prolongation [50]. However, interpretation of electrocardiographic changes in malaria is confounded by associated changes due to malaria itself. For example, significant QTc (i.e., QT corrected for heart rate) interval prolongation that seemed to correlate both to baseline parasitemia and temperature, but not to the antimalarial treatment given (including AL), has been reported in African children with malaria [51]. The tachycardia of acute malaria is followed by a relative bradycardia at the time of defervescence, but the conventionally applied rate correction (Bazett's

formula; see below) does not adequately eliminate rate as a covariate affecting QT interval prolongation [52]. This leads to a systematic malaria-related apparent change in the QT interval that some investigators have incorrectly ascribed to antimalarial drugs (see also Section 9).

(3)

$$QTc(ms) = QT(ms) / \sqrt{RR(s)}$$

For adults with normal QRS duration, QTc is considered prolonged if > 450 ms for men and > 460 ms for women.

In vitro experiments using whole-cell patch-clamp techniques have shown that lumefantrine and its main metabolite desbutyl-lumefantrine are less likely to cause QTc interval prolongation, in contrast to halofantrine [53]. Moreover, there is no evidence of cardiotoxicity in patients [40,41,54] or healthy volunteers [35-38,55] who are administered AL. One study in particular has demonstrated that there is no relationship between plasma lumefantrine concentration and QTc interval [54]. However, as a precaution, the manufacturer states that AL is contraindicated in: i) patients with family histories of congenital prolongation of QTc interval, sudden death or any other clinical conditions known to prolong the QTc interval, such as patients with histories of symptomatic cardiac arrhythmias with clinical bradycardia or severe cardiac disease; ii) patients with known electrolyte disturbances, such as hypokalemia or hypomagnesemia; iii) patients taking drugs that are known to prolong the QTc interval, such as antiarrhythmics of classes IA and III, neuroleptics, antidepressants, certain antibiotics, such as macrolides and fluoroquinolones, imidazole and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride; iv) in patients taking drugs that are metabolised by CYP2D6; and v) in patients with severe malaria or with previous histories of hypersensitivity to either lumefantrine or artemisinin derivatives [22].

2.2.6 Patients with AIDS/severe malnutrition

Safety in these subgroups of patients is unknown. However, there is a potential for drug–drug interaction with some antiretroviral and anti-tuberculosis (TB) drugs, as well as some drugs used for opportunistic and HIV-related conditions (Table 1).

2.2.7 Neurotoxicity

Animal studies with high doses of parenteral lipid-soluble artemisinin derivatives indicated dose-dependent neurotoxicity [56,57], particularly affecting brainstem areas involved with hearing and balance [58]. Neurotoxicity has also been confirmed by *in vitro* cell model systems, raising concerns about possible neurotoxicity of artemisinin derivatives during clinical use [59-61]. From a pharmacokinetic consideration, it

has been suggested that neurotoxicity would be unlikely to occur in clinical practice following oral administration of artemisinin derivatives [62]. However, there are reports of prolonged times to recovery from coma (compared with patients treated with quinine) following artemether administration to patients with malaria [63,64], ataxia and blurred speech in a patient administered artesunate [65], a report of brainstem encephalopathy following artemisinin treatment [66] and one report of possible irreversible auditory impairment in a group of patients following treatment with AL [67], which have renewed concerns that clinical use of artemisinin derivatives may be associated with neurotoxicity. However, these concerns are not supported by results from more recent, better controlled studies with AL. For example, a large field trial [68], several case-controlled retrospective studies in patients [69-72] and a study in volunteers treated with AL following infection with experimental human malaria [73] have not found evidence of neurotoxicity (including auditory function impairment).

2.2.8 Common adverse drug reactions

Very common adverse drug reactions (> 10% prevalence) include CNS reactions (headache, dizziness) and gastrointestinal reactions (abdominal pain, anorexia).

Common side effects (> 1% prevalence) include CNS reactions (sleep disorders), gastrointestinal reactions (diarrhea, vomiting, nausea), CV events (palpitation), dermatologic (pruritis, rash), respiratory (cough) and myoskeletal reactions (arthralgia, myalgia), as well as general disorders (asthenia, fatigue) [22]. In addition, see Section 9.

3. Potential for delaying the emergence of resistance

The ideal antimalarial drug is one that is effective, safe, affordable and has a long UTL. The rationale for CT in malaria is that it would delay the emergence of resistance and thus increase the UTL of each of the components. Ideally, the drugs used for CT should have i) comparable (preferably short) elimination half-lives, ii) independent modes of action, and iii) gametocytocidal activity to decrease transmission.

3.1 Comparable elimination half-life

The elimination half-lives of the two drugs are different (see Section 2.1), and the mismatched pharmacokinetics (half-lives) is thought to be a factor that could lead to emergence of resistance, especially to the component with the longer elimination half-life [19]. This is especially relevant in areas of high transmission such as most parts of sub-Saharan Africa. For example, a recent study in Zanzibar provided evidence for the *in vivo* selection for resistance (selection for the 86N allele of *pfmdr1*) to lumefantrine following treatment with AL, suggesting that AL may not be robust enough to prevent selection of resistance-associated mutations under similar settings [74]. However, another study in Thailand showed no significant difference in the *in vitro* response and

Table 1. Some examples of drugs/food that may interact with artemether or lumefantrine.

Drug/food	Class	Possible mechanism for interaction	Consequences
Indinavir, nelfinavir	Antiretroviral	Inhibits CYP3A4	May increase concentrations of ART and LUM
Ritonavir	Antiretroviral	Inhibits CYP2D6 and CYP3A4	May increase concentrations of ART and LUM
Ketoconazole	Antifungal	Inhibits CYP3A4	Shown to cause modest increase in concentration of ART and LUM
Fluconazole	Antifungal	Inhibits CYP3A4	May cause increase in concentration of ART and LUM
Grapefruit juice	–	Contains compounds that inhibit CYP3A4	May increase bioavailability of ART
Rifampicin	Anti-tuberculosis	Induces CYP3A4	May decrease concentrations of ART and LUM
Nevirapine, efavirenz	Antiretrovirals	Induces CYP3A4	May decrease concentrations of ART and LUM
Phenytoin/phenobarbital /carbamazepine	Anticonvulsants	Induces CYP3A4	May decrease concentrations of ART and LUM

ART: Artemether; LUM: Lumefantrine.

polymorphisms at codon 86 [17]. The Thai study further showed that the molecular determinant of AL efficacy is an increase in *pfmdr1* copy number, and that although drug pressure can select for this polymorphism, the resultant resistance can be clinically overcome by re-treatment with the six-dose AL regimen [17]. Resistance can also develop to artemisinin derivatives, including artemether, especially in areas in which these drugs are being used inappropriately as monotherapies or as CT. For example, decreased *in vitro* susceptibility to artemether by *P. falciparum* field isolates from French Guiana and Senegal has been reported [75].

3.2 Independent modes of action

If the two components of the CT have de-linked modes of action, the chances of a parasite simultaneously selecting for resistance to both components are remote [76]. Both components of AL are blood schizonticides [9], and act synergistically *in vitro* against *P. falciparum* [76]. However, they have different modes of action, and act at different points in the *Plasmodium* life cycle [22,77-80].

Based on these earlier studies, artemisinin derivatives were thought to act through an iron-catalysed decomposition into free radicals. During its 48-h cycle of invasion, growth and release from an infected erythrocyte, the malaria parasite degrades up to 80% of the hemoglobin in the host cell. The degradation takes place in the lysosomal food vacuole and involves aspartic proteases (plasmepsins), the cysteine protease falcipain and many peptidases including a metallopeptidase. This results in the release of large amounts of Fe II heme, which is rapidly oxidized to Fe III hemozoin and sequestered as an inert pigment called hemozoin that comprises a structured lattice of aggregated heme dimers. Artemisinin derivatives are concentrated in the food vacuoles and are thought to act through interaction with heme. Thus, the artemisinins undergo oxidoreductive cleavage of their peroxide bond in the food vacuole, probably through interaction with Fe II heme, to form a heme adduct. This is

thought to generate carbon-centered free radicals that induce fatal damage to the parasite by inhibiting hemozoin. However, recent studies have shown that artemisinin derivatives have multiple mechanisms of action, including interference with parasite transport proteins, disruption of parasite mitochondrial function, modulation of host immune function and inhibition of angiogenesis, with the crucial mechanism being interference with plasmodial sarcoplasmic/endoplasmic calcium ATPase. These mechanisms are not discussed in detail here, but are covered in a recent review [81].

Lumefantrine also targets heme, preventing its detoxification. The toxic heme and free radicals are jointly responsible for the death of the parasite [22].

3.3 Gametocytocidal activities

Gametocytes are the stages in the life cycle of the malarial parasite that link the vector and host infectious cycles. Killing all gametocytes would, theoretically, eliminate malaria. Artemisinin derivatives, such as artemether, are gametocytocidal and, therefore, may reduce gametocyte carriage, thereby reducing malarial transmission [76]. Several studies have shown excellent gametocyte clearance by AL under clinical settings [40,41,82,83]. The clinical measure for rate of gametocyte clearance is the 'gametocyte clearance time' (Table 3, Section 6).

4. Patient adherence

A drug is of no benefit if it is not consumed by patients, or if it is used inappropriately (in inadequate doses). In this section, factors that may influence adherence to therapy are reviewed. The term 'adherence' will be used instead of 'compliance' (which implies that '*Patients are expected to do as they are told*' [84]). Adherence can be defined as the extent to which a patient fulfils the intention of the prescriber in taking medication [84]. In general, adherence to drug therapy has been shown to be associated with positive health outcomes [85]. The

Table 2. Factors that may influence adherence to treatment.

Factor(s)	Components
Demographic	Age, gender, educational achievement, socioeconomic status, employment, ethnicity
Drug- and treatment-related	Number of doses per day, number of drugs to be taken, size and taste of tablets, side effects, packaging, treatment duration, cost of medicines, compatibility of the dose regimen with daily activities
Disease-related	Type and duration of the disease, patient understanding of the disease, threat posed by the disease, presence or absence of symptoms, influence of the disease on the ability to cooperate (mental disorders)
Patient-related	Understanding of the disease and its consequences, perception of the threat posed by the disease, acceptance of the disease, comprehension of the cost benefit of the treatment, motivation of patient and family, possible support from family and neighbourhood
Patient–healthcare professional relationship	Circumstances surrounding the patient’s visit, ease of access to physician or healthcare, quality and effectiveness of the interaction, time spent by the healthcare providers with the patient, attitude of the physician towards the patient’s illness and treatment, involvement of the patient in decisions, quality of the communication and adequacy of the information provided

main factors that may influence patient adherence have been described elsewhere [86], and are summarized in Table 2.

Poor adherence to antimalarial treatment increases the chances of therapeutic failure [87], but few studies have investigated adherence with dosage regimen under real-life situations, and especially the effect of some of the factors described in Table 2 on adherence. One study reported a 60% adherence among southern Sudanese children aged ≤ 5 years who were administered AL ‘unsupervised’ by caregivers at home [88], and two other studies have reported $\sim 90\%$ adherence among Ugandan patients of different age groups (from < 5 to > 15 years of age) who were administered AL unsupervised [5,89]. In the latter study, lack of formal education (a demographic factor) was the only factor found to be associated with non-adherence. In the Sudanese study, some of the reasons for non-adherence were socioeconomic (*‘no food or milk to give with tablets’*) or linked to patient–healthcare professional relationship (*‘misunderstanding of the instructions’* or *‘forgotten doses’*), as well as the fact that the study was conducted in a war zone. It has been reported that adherence to oral antimalarials may be poor compared with injectable antimalarials among Sudanese [90]. In contrast, in the Ugandan study, age was not found to be a factor in adherence, and it was suggested that this demonstrated that tablets were well accepted by young children [89]. Although low adherence could not be linked to treatment failures in the Sudanese study [88], the numbers involved were too few, and the follow-up period was too short for any conclusions to be made from that study.

Patient-related factors have been addressed in one recent study in Ghana, which showed that properly trained community-based caregivers can ensure adequate adherence to prescribed AL treatment for children at home/within the community [91]. Other factors that might affect adherence are drug-related (dosage regimen, side effects and duration of treatment), but these have not been evaluated in previous studies. Although most efficacy/safety studies have reported that AL is safe, effective and well tolerated in children, adolescents and adults, side effects and tolerability may be

factors influencing adherence [22,40,41]. This has not been exhaustively investigated in previous studies on adherence, although five cases of patients vomiting the doses administered at home were reported in the Sudanese study [88].

5. Product availability

There are two issues with availability: i) production capacity and, ii) local availability (local registration and affordability). These two issues, together with factors such as reliable health and supply systems, determine accessibility to AL by those who need it most, especially at peripheral health facilities.

5.1 Production capacity

At present, AL that is produced according to Good Manufacturing Practices and pre-qualified by the WHO is single sourced. Lead time (from getting the raw materials to complete tablet production) is ~ 14 months. Due to the artemether component, the shelf-life of the tablets (similar to all other artemisinin derivatives-containing tablets) is only 24 months when stored at a temperature $< 30^\circ\text{C}$. However, the manufacturer has provided an assurance that they will be able to meet the increased demand for this agent as more countries switch to AL as first-line treatment for uncomplicated malaria. The manufacturer announced that they are on track to produce 100 million treatment courses in 2006 (an increase from 30 million in 2005). Several other pharmaceutical manufacturers are also making generic AL, and provided these meet the WHO pre-qualification criteria, there should be no supply short-fall.

5.2 Local availability

AL is recommended as first-line treatment for uncomplicated malaria in several African countries. In some countries, such as Kenya, it is being made freely available in the public sector. Hence, the only factors that might affect accessibility will be those related to the efficiency of the local supply chain.

Table 3. Some terms used in efficacy studies (in high-transmission areas).

Terminology	Explanation
Early treatment failure	Refers to any of the following: development of danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitemia, axillary temperature of > 37.5 °C on day 2, with parasitemia > day 0 count, axillary temperature > 37.5 °C on day 3 in the presence of parasitemia, or parasitemia on day 3 > 25% of count on day 0 [92].
Late clinical failure	Development of danger signs or severe malaria after day 3 in the presence of parasitemia without previously meeting any of the criteria of early treatment failure, or the presence of parasitemia and axillary temperature of > 37.5 °C on any day from days 4 – 28 without previously meeting any of the criteria of early treatment failure [92].
Late parasitologic failure	The presence of parasitemia on day 28 and axillary temperature < 37.5 °C, without previously meeting any of the criteria of early treatment failure or late clinical failure [92].
Adequate clinical and parasitologic response	Absence of parasitemia on day 28, irrespective of axillary temperature, without previously meeting any of the criteria of early treatment failure, late clinical failure or late parasitologic failure.
Intent-to-treat analysis	A method of analysis in randomized trials in which all patients randomly assigned to one treatment are analysed, regardless of whether or not they completed that treatment.
Per-protocol analysis	Analysis based only on those patients who adhered to the treatment study/protocol.
Evaluable patients	Those patients whose response to treatment can be measured because enough information has been collected.
Safety population	All patients that received at least one dose of a study drug and had at least one post-baseline safety assessment.
Recrudescence	The existence of positive blood smears after initial clearance of parasites from peripheral blood. PCR analysis is used to distinguish recrudescence from reinfection.
Day 28 cure rate	The proportion of patients with clearance of asexual parasitemia within 7 days of initiation of the trial medication, without subsequent recrudescence within 28 days after start of treatment with trial medication. This is the most important measure of cure rate, as it was used in most of the studies referred to, even though a 42-day follow-up period has been recommended for the assessment of AL efficacy [93].
Parasite clearance time	The time needed to clear asexual parasites from the blood (i.e., when parasite numbers fall below the limit of detection in a thick blood smear, and remain undetectable for at least 48 h).
Fever clearance time	The time taken from the first dose to the time when body temperature falls to normal and remains so for at least 48 h.
Gametocyte clearance time	The time from the start of treatment in patients who are gametocyte-positive in blood smears at the beginning of the trial, until the next blood films are negative, and remain so for at least 48 h.

AL: Artemether/lumefantrine; PCR: Polymerase chain reaction.

6. Therapeutic efficacy

During a WHO consultative meeting in Harare in 2003, experts on antimalarial treatment policy reached a consensus that persistent parasitemia is associated with increased risk of clinical episode, anemia and increased gametocyte carriage. Therefore, it was agreed that parasitologic response should be an additional indicator for interpretation of the therapeutic efficacy tests [92]. For this review, the definitions in Table 3 are useful, as they are used in some of the papers cited below on efficacy, and also in papers cited elsewhere in this review.

AL was previously registered in some countries as a four-dose regimen for treatment of partially immune adults. However, the dosing regimen has now been harmonized to a 3-day, six-dose regimen for all infants and children weighing 5 – 35 kg, and adults weighing > 35 kg, regardless of status of immunity. One study referred to below involved comparison of the four- and the six-dose regimens, and the rest involved the six-dose regimen. One study in Burundi [94] in which AL was administered to children who were then followed up for

14 days (instead of 28, as was the case in the rest of the studies cited below) is not included in the summary below. A list of a few efficacy/effectiveness studies on the six-dose regimen in Africa and southeast Asia, in which some of the terms described in Table 3 are used, is shown in Table 4.

A 100% polymerase chain reaction-corrected 28-day cure rate has been reported in Angolan children [96], but the number of children was small (n = 61). Another study that involved an extended 42-day follow-up period in children reported an age- and weight-adjusted cure rate of 94% [97].

6.1 Gametocyte clearance, reduction in malaria transmission

Several studies have confirmed the excellent gametocyte clearance properties of AL in infants, children and adults [10,40,41,82,83,98-100]. Clearance of gametocytes breaks the cycle of transmission between the mosquito vector and the human host. One study, using membrane-feeding *Anopheles* mosquitoes, has demonstrated a reduction in malaria transmission following the six-dose regimen of AL [101].

Table 4. Some examples of AL efficacy/effectiveness studies.

Study type	Study area	Type and number of subjects completing study	Primary end point	Cure rates
Randomized trial to assess effectiveness of AL [5]	Mbarara, Uganda	303 Children with uncomplicated <i>P. falciparum</i> malaria	28-day, PCR-adjusted parasitologic cure rate among S and US groups	97.7 and 98 in S and US groups, respectively
Analysis of pooled data from eight clinical trials comparing AL6 and AL4 in children [40]	Data from The Gambia, Tanzania, Kenya, Nigeria, and Thailand	544 Children with uncomplicated <i>P. falciparum</i> malaria	28-day PCR-corrected cure rate based on ITT and EP	93% (ITT, AL6), 96% (EP, AL6), 61% (ITT, AL4) 76% (EP, AL4)
Open-label, non-comparative, multi-center study [95]	Germany, Switzerland	57 Non-immune adult Caucasian travellers returning from endemic countries with uncomplicated <i>P. falciparum</i> malaria	28-day uncorrected cure rate, PP analysis	94.7%
Open-label, non-comparative, multi-center efficacy trial of AL6 [41]	Kenya, Tanzania, Nigeria	310 Children with uncomplicated malaria	28-day PCR-corrected cure rate, based on ITT population and PP	86% ITT population (268/310); 88.7 PP population (258/291)

AL: Artemether/lumefantrine; AL4: Four-dose AL regimen; AL6: Six-dose AL regimen; EP: Evaluable populations; ITT: Intention-to-treat; PCR: Polymerase chain reaction; PP: Per protocol; S: Supervised; US: Unsupervised.

6.2 Fever clearance

Rapid fever clearance by AL is due to the artemether component, with reported median fever clearance time of ~ 8 h in infants and children [40,41].

The lumefantrine plasma concentration profile is the main determinant of AL efficacy. In an earlier study in adult Thai patients, it was shown that a day-7 lumefantrine concentration of > 280 ng/ml was associated with cure in 75% of patients [6]. This relationship between day-7 plasma lumefantrine concentration of 280 ng/ml and cure has not been demonstrated in studies conducted in two sites in Africa [3,5]. In a Kenyan study for example, out of the 113 children with symptoms suggestive of severe malaria (described in that study as 'moderately severe malaria') and who were treated with AL, 57% had mean day-7 lumefantrine concentrations of < 280 ng/ml even though the day-28 efficacy was not compromised [3]. However, a recent report on pooled data from several studies in Thailand showed that a cut-off day-7 plasma lumefantrine concentration of 175 ng/ml predicted recrudescence with 75% sensitivity and 84% specificity in patients treated with AL [17]. When this latter value (175 ng/ml) is used for the children in the Kenyan study, there is a marked reduction in the number of treatment failures when lumefantrine concentrations are > 175 ng/ml.

7. Real-life effectiveness

Efficacy studies are undertaken under controlled conditions, in which administered drugs are of known (assured) quality, and total adherence is guaranteed. Effectiveness trials are aimed at measuring how a drug would perform under real-life

situations (i.e., how effective a drug is when taken unsupervised). The following general equation has previously been used to describe factors that may affect real-life effectiveness of antimalarial drugs [102]:

$$E = eA \sum_{i=1}^{i=n} Q_i U_i \quad (4)$$

where, E is effectiveness, e is efficacy, A is adherence, Q is quality, U is the Community Use Index (i.e., number of encounters with a product as a proportion of total in the class), n is the number of products and i is the given product.

Here is an example from work done by AA Amin (Malaria Public Health and Epidemiology Group, KEMRI/Wellcome Trust Research Programme, Nairobi, Kenya), and reported in part elsewhere [102], to illustrate the use of this equation:

- The difference between efficacy and effectiveness of sulphadoxine/pyrimethane (SP), the first-line treatment for uncomplicated malaria in Kenya at the time of the study, and amodiaquine (AQ), the second-line treatment at that time, were compared.
- Quality of SP and AQ products available in the Kenyan market was determined by pharmacopeal tests (content [C] and dissolution [D] scores) on randomly collected samples. A quality index (ranging from 0 to 1) was derived by multiplying results of content and dissolution tests for each

batch. Suspensions were given the highest possible dissolution score of 1, and each product (i) was assigned a quality index (Q) = $D_i C_i$.

- The proportionate use (U) of SP and AQ was determined through a community survey of childhood fever treatment practices. The term $\sum Q_i U_i$ defines the use-weighted quality index.
- Adherence (A) was estimated through a separate survey on reported over-the-counter drug use using a structured questionnaire.
- Estimates on clinical efficacy were derived from national surveillance data of SP and AQ from four sentinel districts between January 2000 and February 2003.
- Finally, real-life effectiveness for SP and AQ were estimated using the equation shown above.
- Using the WHO definition (Table 3), day 28 Adequate Parasitological Cure Rate of SP was 72% and AQ was 77%.
- However, estimated effectiveness was 51% for SP and 45% for AQ, the difference partly reflecting differences in adherence.

For the case in which there is only a single product that is recommended for first-line treatment, and where this product is of assured quality and is readily available at public health facilities, the above equation may need to be simplified in order to describe real-life effectiveness. Using this equation, and an analysis described by AA Amin (Malaria Public Health and Epidemiology Group, KEMRI/Wellcome Trust Research Programme, Nairobi, Kenya), the projected real-life effectiveness for AL is 85%.

For purposes of this discussion, it can be assumed that when the real-life effectiveness of AL is less than the estimated efficacy, there is a problem with either adherence, incomplete dosing or bioavailability of lumefantrine. In this review, incomplete dosing is distinguished from non-adherence as defined in Section 4, to refer to cases such as vomiting within 1 h of taking a dose without a replacement dose being given. The significance of incomplete dosing is discussed in Section 9.9.

7.1 Effectiveness in African children with uncomplicated malaria

Three studies [4,5,103] have reported real-life effectiveness for the six-dose AL regimen, which was essentially similar to reported efficacy for the respective study areas. In one study, high day-28 cure rates were achieved even among unsupervised patients with low (< 280 ng/ml) day-7 lumefantrine concentrations, suggesting good real-life effectiveness of this regimen [4].

7.2 Effectiveness in adult patients with uncomplicated malaria

So far, there are no studies on the real-life effectiveness of AL in adult patients. The implications of this are discussed in the Expert opinion section.

8. Conclusion

Based on the available data, AL is a highly effective fixed-dose ACT that should help slow the spread of drug-resistant *P. falciparum* in malaria endemic regions. It seems to be relatively safe and well tolerated, although the treatment regimen is rather complex and could pose problems of adherence. More pharmacokinetic studies and safety data are needed in subpopulations of patients such as malnourished patients, the elderly and patients with AIDS, in order to optimize its use in these populations. Some easily available foods that can be used to increase the bioavailability of lumefantrine need to be identified. Availability of four unit doses of AL may improve adherence, but may also add additional complexity of procurement. Studies on which of these two factors has the major negative effect of delivery of AL should be encouraged. Some of these issues are discussed in Section 9 below.

9. Expert opinion

The ideal properties of an antimalarial CT can be summarized as follows:

- Rapid (within 2 – 4 h) achievement of 99% effective concentration (EC_{99}), with minimum effective concentrations (MEC) maintained for three or four life cycles
- Complementary pharmacokinetics
- Independent modes of action
- Maximum oral bioavailability for both (all) components
- Duration of treatment of ≤ 3 days (for adherence)
- Simple dosing regimen and packaging (for adherence)
- Co-formulated (for adherence)
- Availability of a pediatric formulation
- Both components are to be stable (for reasonable shelf-life)
- Safe for use in all age groups
- No (undesirable) drug–drug or drug–food interactions, and no undesirable modification of disposition in disease and pregnancy
- Affordable and cost effective
- Effective against multi-drug resistant parasites; gametocytocidal

This section is based upon the discussion of the ideal properties of an antimalarial CT listed above.

9.1 Rapid achievement of EC_{99}

The artemether component of AL is rapidly absorbed and rapidly metabolized to dihydroartemisinin. Both artemether and dihydroartemisinin have potent antimalarial activity (dihydroartemisinin being the more potent) and, together, they reduce parasite biomass by a factor of $\sim 10^4$ per asexual life cycle (2 days). Thus, exposure to the 3-day regimen would reduce the parasite biomass by $\sim 10^8$. The important pharmacokinetic parameters that determine the duration of activity of a drug in the body are the C_{max} , the MEC and the $t_{1/2}$.

Taking MEC to correspond to concentrations producing 90% inhibition of a given parasite population and combining both dihydroartemisinin and artemether into 'artemisinin equivalents' (with duration of action = time taken for C_{max} to decay to MEC, during which, reduction in parasite biomass occurs, being represented by t_d , and with a composite $t_{1/2}$), the following equation holds true during a dosing interval, if we assume rapid attainment of C_{max} (and minimal reduction in parasite biomass before achievement of C_{max}):

(5)

$$MEC = C_{max} e^{-kt_d}$$

(6)

$$t_d = [\ln(C_{max}/MEC)] \times (t_{1/2}/0.693)$$

During multiple dosing, any artemether and dihydroartemisinin left from the previous dose will contribute to the new C_{max} . The above equations assume rapid absorption of artemether (which is not always the case), and that peak concentrations for artemether and dihydroartemisinin are achieved at approximately the same time, or at times that are reasonably close. Hence, for a given patient in whom $t_{1/2}$ and MEC are constant, the duration of action of 'artemisinin equivalents' is proportional to the peak concentrations. Now, for a given dose, peak concentrations will be higher the more rapid the absorption of artemether. A higher C_{max} can also be achieved by administering higher doses, but this may not be necessary or practical.

Returning to the equation, it is now clear why rapid absorption of the more potent artemether component of AL is important. The values of t_d in relation to the dosing interval and $t_{1/2}$ are also important in ensuring that concentrations are kept above MEC for a reasonable period of time. Due to the relatively short half-lives of artemether and dihydroartemisinin [6], both compounds should be completely cleared from the body within 5 h following administration of AL. However, terminal elimination of artemether (and dihydroartemisinin) is rate limited by absorption of artemether (the slower process), which would be complete in 8 – 10 h (based on an average reported absorption half-life of ~ 2 h). This is consistent with a report that both compounds are detectable in plasma 8 h after the first dose [6]. Therefore, the half-life in the above equation refers to absorption half-life of artemether. The manufacturer recommends that the first and second dose of AL be administered 8 h apart. The importance of this may not be apparent to some malaria treatment policy committees who may wish to recommend 12-hourly administration for

3 days in an attempt to simplify dosing regimen. The current WHO guidelines also recommend flexibility regarding the 8 h dose [2]. However, administration of the second dose of AL 12 h (instead of 8 h) after the first dose on day-1 would probably result in a day 1 dosing interval being much longer than t_d , thereby leading to therapeutic failure. At present, there are few reports on detailed pharmacokinetic studies on AL in patients from some malaria-endemic regions such as sub-Saharan Africa. More of these studies are needed in order to understand the relationship between the blood, drug concentration and cure.

9.2 Matching or complementary pharmacokinetics/pharmacodynamics

The pharmacokinetics of artemether and lumefantrine are not matched, but the pharmacodynamics are 'complementary'; the rapid absorption and metabolism of artemether to dihydroartemisinin within 48 h results in rapid reduction in parasite biomass to levels that can be adequately cleared by the slower acting, more slowly absorbed lumefantrine. It is probably not surprising that cure is related to AUC (not C_{max}) for lumefantrine. However, AL will be used in some populations with a high prevalence of AIDS, and also in malnourished individuals. The effects of these conditions on the pharmacokinetics of lumefantrine and artemether will need to be investigated. It has also been shown in a limited pharmacokinetic study in children that some who are administered AL 'unsupervised' (i.e., by caregivers at home) achieve low day-7 concentrations of lumefantrine [4]. This is consistent with findings in children of signs and symptoms suggestive of severe disease who were treated with AL in Kilifi, Kenya [3], and although in both studies day-28 cure rate was not compromised, such low concentrations of lumefantrine plus the long elimination half-life may encourage the emergence of resistant parasites. However, interpretation of these earlier studies now needs to be modified in light of a recent report indicating that cut-off day-7 lumefantrine concentrations of 175 ng/ml is a better predictor of recrudescence [17].

9.3 Independent modes of action

The ideal CT should be one in which each component targets a different (non-genetically linked) process, rather than have different molecular targets for the same essential process. AL fulfils this requirement (see Section 3.2).

9.4 Maximum oral bioavailability for both (all) components

There is considerable variability in the oral bioavailability of artemether and lumefantrine (see Section 2.1). For artemether, this is probably due to pathophysiologic factors (malaria and its effect on enzyme activity in the liver and changes in hepatic blood flow). For lumefantrine, variability could, in addition, be due to problems with aqueous solubility and the variable effect of food on solubility and gastric emptying time. As the effects of food and fluid volume on

drug absorption are complex, attempts to monitor adherence to AL treatment regimen by determining drug concentrations during the first few days (1–3) of treatment are probably not going to be successful. For example, any factor that increases gastric emptying rate will increase rate (but not necessarily extent) of absorption, and factors that delay gastric emptying rate (such as fatty meals) will delay rate, but may increase extent of bioavailability of lipophilic drugs such as lumefantrine. On the other hand, large fluid volumes may increase gastric emptying rate; hence, ingesting AL with milk would be expected to increase both the rate (increased gastric emptying due to distension) and extent (increased dissolution rate in presence of fat) of bioavailability of lumefantrine. However, it is known that the nutritive density (kcal/ml) of meals may also determine the rate of gastric emptying, and that this may supersede the effects of volume [104]. Finally, from a practical viewpoint, the recommendation that AL be administered with food will be problematic, especially for adult patients, because i) having meals in the morning is not usual in most settings in sub-Saharan Africa, hence the first doses on days 2 and 3 will be difficult to take with meals, and ii) fatty meals are probably a luxury that few can afford in such settings. Rather, a strong case can be made for promoting the administration of AL with milk or another commonly available fatty substitute.

9.5 Duration of treatment \leq 3 days

The duration of treatment with AL is 3 days. Anything longer than 3 days would pose serious problems of adherence. This is more so in rural parts of Africa in which cure is defined as resolution of the original symptoms, and given the rapid fever clearance property of artemether, may pose a problem especially with adult patients. However, duration of treatment shorter than 3 days would probably not be compatible, with the need to maintain adequate parasite exposure to the artemisinin component for at least two *P. falciparum* asexual parasite cycles (each cycle lasting 2 days). The 28-day cure rate achieved with the four-dose regimen has clearly been shown to be inferior to that produced by the six-dose regimen [54]. Therefore, as AL is being introduced in more countries in sub-Saharan Africa, public education efforts will need to be put in place to emphasize the need for completion of the prescribed 3-day treatment course, given that most patients will start feeling well as a result of fever reduction by artemether within < 3 days.

9.6 Simple dosing regimen, packaging

Once-daily administration of the drug would be ideal, but the pharmacokinetic properties of oral artemether do not make this possible as concentrations would fall below the MEC within 24 h with once-daily dosing. The dosing regimen for AL is not simple. A six-dose, 3-day regimen is currently recommended, with children and adults receiving approximately the same weight-adjusted dose (mg/kg) at 0 and 8 h on day 1, then every 12 h on days 2 and 3, as summarized in Table 5.

Although AL only needs to be administered twice daily, the requirement for an 8-h interval between the first and second

dose on day 1 may be problematic for some patients. In addition, although excellent efficacy and real-life effectiveness data have been reported in children, this probably reflects the maternal/caregiver dedication and availability of simple-to-use unit doses of AL. If part of the strategy is to eventually use AL for home-based management of malaria in children, then adequately trained caregivers would be invaluable in maintaining this high level of adherence to treatment as has been shown by a recent study in Ghana [91]. The training should include redosing (providing a redosing pack is available) of children who vomit within 1 h of taking AL (see also Section 7). However, introduction of a redosing pack, in addition to the available four different unit doses, may not only add to the complexity of dispensing AL at resource-poor settings, but might also affect adherence. For adult patients, an additional challenge is going to be the willingness to take (on average) four tablets per dose for 3 days, given that most will feel better before finishing the treatment course. The Ghanaian study re-emphasizes the importance of community/family involvement in efforts to improve adherence to complicated treatment regimens for malaria [91]. Similar efforts focusing on public education will need to be made to improve adherence by adult patients.

9.7 Formulation, stability and availability of a pediatric formulation

Tablets containing a 1:6 fixed combination of artemether (20 mg) and lumefantrine (120 mg) are available. The ratio was chosen based on extensive early toxicologic and efficacy studies in China. The tablets have a shelf-life of 2 years when stored at < 30 °C. AL is the only fixed dose ACT approved and pre-qualified by the WHO for treatment of uncomplicated malaria. Co-formulation makes taking medication easier and avoids the temptation by patients to take one component and not the other, as would occur in co-packaged products. However, co-formulation involving compounds with the endoperoxide bridge, such as artemisinin compounds, is technically challenging due to the inherent reactivity of endoperoxides.

The relatively short shelf-life of AL tablets is due to the artemether component, and is shared with other artemisinin derivative-containing tablet formulations. A dispersible pediatric tablet formulation is undergoing a Phase III trial in several countries. Nevertheless, some authorities have questioned the lack of a pre-constituted liquid formulation for pediatric use. This is probably based on a lack of clear understanding of the stability problems that preclude development of liquid formulations of artemisinin-based antimalarials.

Apart from the increased cost of transportation and storage, preconstituted liquid formulations of artemisinin-based antimalarials (including AL) would have serious stability problems. Assuming that the production of a liquid formulation was possible, and that the product would have a shelf-life of 2 years if stored in the fridge, a practical question is: what would be the maximum shelf-life for such a product at room

temperature (25 °C), given that most health facilities in sub-Saharan Africa do not have fridges to store medicines? The answer is that the shelf-life would be reduced (from 2 years if stored in the fridge) to ~ 6 months if stored at room temperature [105]. To calculate this, we use a factor called Q10 value, which is defined as the factor by which the rate constant of the decomposition reaction increases for each 10-°C rise in temperature. It allows for the determination of rough estimates of shelf-lives of liquid products. The relevant equation is [105]:

$$T_{T2} = T_{T1} \times Q^{10((T1 - T2)/10)} \quad (7)$$

where TT2 and TT1 are the shelf-lives in the fridge (T2, nominal temperature = 5 °C) and room temperature (T1, nominal temperature = 25 °C), respectively. The values for Q10 are derived from the activation energy and are likely to be between 2 and 4 [105].

Calculation using a value of 2 for the activation energy shows that 24 months in the fridge are equivalent to 6 months at room temperature. The decision by Novartis to go for a dispersible pediatric tablet formulation of AL rather than a preconstituted liquid formulation is clearly understandable as, in reality, even the most stable preconstituted liquid formulation would probably have a very short shelf-life when stored in the fridge, or just a few weeks at room temperature.

Therefore, considering the stability of the components, a preconstituted liquid formulation of an artemisinin derivatives-containing antimalarial is probably impractical with the current method of generation of artemisinin derivatives. Dry-powder formulations, for reconstitution into liquid formulations before administration, are another alternative that can be considered. From an operational point of view, the short shelf-life (2 years) for the tablet formulation will also pose some problems with regard to procurement, especially for those Ministries of Health that have inefficient procurement procedures. The short shelf-life and the long lead time (14 months from raw material production to the final tablet) means that even the manufacturer will not be able to stock large quantities of the tablets. Therefore, careful coordination between importing countries and the manufacturer will be needed to avoid health facilities running out of stock of AL.

9.8 Safe for use in all age groups

Based on the available data [3-5,9,40-42], AL is reported to be well tolerated, with few common side effects. However, long-term safety is unknown, especially following multiple exposures, and in special populations such as the very young and in pregnancy. One of the long-term safety issues with AL is the potential for neurotoxicity, which is probably related to

its antimalarial activity. Safety in pregnancy, especially in the first trimester, and in very young children (i.e., those weighing < 5 kg) is also unknown. As a precaution, AL, like other artemisinin derivative-containing products in use, is contraindicated during the first trimester of pregnancy (see also Section 2.2). However, the reality is that with large-scale deployment, some women visiting some resource-poor facilities, especially in sub-Saharan Africa, will consume AL (or other artemisinin-based antimalarials) without knowing that they are pregnant. It is also not known whether multiple and frequent exposures to artemisinin derivative-containing drugs have a greater impact on the safety of these drugs in early pregnancy and in young children, compared with single or less frequent exposures. Moreover, although it is discouraged by the WHO (see Section 9.9 below), several artemisinin-based monotherapies are also readily available in several countries in sub-Saharan Africa. Therefore, the possibility that repeated exposure to artemisinin derivatives-containing compounds will occur and the potential effect on the safety of these compounds will need to be taken into account.

There are no clear guidelines on the use of AL in lactating mothers. Lumefantrine is very lipophilic, and it is possible that the fraction bound to proteins may be decreased in pregnancy (see Section 9.9) and immediately following birth. Thus, substantial amounts may pass into breast milk and, given its long elimination half-life, it may be prudent for lactating mothers to follow the advice of the manufacturer and avoid taking AL. Unfortunately, the recommendations in the current WHO guidelines for treatment of malaria contradict this, by stating that lactating women should receive standard antimalarial treatment (including ACTs), except for tetracycline and dapsone, as the amounts of antimalarials that enter breast milk are relatively small [2]. This statement is clearly unhelpful because it completely ignores the physicochemical differences between lumefantrine and, for example, chloroquine, dapsone and mefloquine (three antimalarials for which there are some reports on extent of excretion in breast milk [106-108] and upon which the broad WHO recommendation is based). We are of the opinion that, in the absence of studies on the extent of excretion of lumefantrine in breast milk, the recommendation of the manufacturer should be followed by lactating mothers.

Finally, from a practical point of view, monitoring of cardiac changes in patients on AL, as mentioned in Section 2 of this review, is going to be impossible in most resource-poor settings in sub-Saharan Africa.

As a way forward, we have a number of suggestions. In Section 2.2.3, it was stated that '*There are currently no human data on what the risks of using artemisinin derivatives in pregnant women are*'. The wide deployment of AL provides an opportunity to evaluate its safety in a large number of patients under different settings. Therefore, one of the main priorities of Ministries of Health in sub-Saharan African countries should be to facilitate the collection of data on the long-term safety of AL (and other artemisinin derivative-containing antimalarials) in all populations who may be repeatedly

Table 5. Dosing regimen for artemether-lumefantrine.

Weight	Day 1	Day 2	Day 3
From 5 to < 15 kg	1 tablet stat 1 tablet after 8 h	1 tablet b.i.d.	1 tablet b.i.d.
From 15 to < 25 kg	2 tablets stat 2 tablets after 8 h	2 tablets b.i.d.	2 tablets b.i.d.
From 25 to < 35 kg	3 tablets stat 3 tablets after 8 h	3 tablets b.i.d.	3 tablets b.i.d.
For adults > 35 kg	4 tablets stat 4 tablets after 8 h	4 tablets b.i.d.	4 tablets b.i.d.

stat: Immediately.

exposed to these compounds. To this end, more studies, such as the one currently taking place in Zambia with AL and other artemisinin derivative-containing antimalarials [49] should be encouraged. Safety of AL should also be evaluated in those patients with HIV/AIDS and in malnourished patients as there is insufficient information on how these conditions can affect the disposition of AL.

9.9 No (undesirable) drug–drug or drug–food interactions, and no undesirable modification of disposition in disease and pregnancy

There have been no clinically significant drug–drug interactions between AL and other concomitantly administered drugs, including other antimalarial drugs. However, this conclusion is based largely on studies done in healthy volunteers (see Section 2.1). However, the potential for drug–drug interaction exists, and there is a need for this to be investigated in patients with malaria co-infected with HIV and TB, and who may be receiving other CYP3A4 substrates or inducers (Table 1). Quinine and AL may be used sequentially in some settings, for example, when some children with severe malaria will first be treated with quinine, and then switched to oral AL when they are well enough to take oral medication. There have been no studies on the pharmacokinetics of AL and quinine in patients receiving both drugs concurrently, despite a study in healthy volunteers reporting no significant interaction between the two drugs [35]. Such studies are necessary because, in general, predicting the magnitude of such drug–drug interactions, especially in patients, based on theoretical considerations, would be difficult due to the wide variability in enzyme activity and the complexity of the mechanisms involved. For example, CYP3A *in vivo* activity can vary 400-fold [109], but as genetic variability does not seem to exceed 5-fold in healthy subjects [110,111], the remainder is associated with disease or drug–drug interactions involving induction or inhibition [109]. CYP3A4 (which metabolizes both artemether and lumefantrine) is found in the gut wall and in the liver. Thus, following oral administration of an inhibitor of CYP3A4, compared with those in the liver, the enzymes in the gut wall would be exposed to higher concentrations of the inhibitor. Hence, co-administration of the inhibitor of CYP3A4 with artemether, for example, would

result in more gut wall and less hepatic first-pass metabolism, leading to decreased C_{max} , but probably causing little change in the elimination half-life of artemether. However, other isoenzymes such as CYP2C19 and 2B6 are also involved in metabolism of artemether, hence the significance of alteration of CYP3A4 activity may be difficult to pinpoint.

Malaria alters the pharmacokinetics of AL (see Section 2.1). Malaria may also be associated with vomiting, which is possibly associated with incomplete dosing (as defined in Section 7). Bioavailability of lumefantrine is increased by food, but food may decrease gastric emptying rate. Thus, any subsequent vomiting that occurs will result in a larger fraction of the administered dose not being absorbed. Although details of food intake were not provided, one study has reported that, after controlling for age and baseline parasitemia, the only clinical parameter associated with subsequent AL treatment failure in Thai patients was a history of vomiting [17].

Pregnancy is another source of variability in AL pharmacokinetics that needs to be considered, especially as far as absorption and elimination of AL are concerned. Several factors associated with pregnancy are important: i) there is a 40% reduction in gastric acid secretion, reduced peptic activity and a significant increase in mucus secretion, all of which may result in increased gastric-acid pH and buffer capacity; ii) there is a 30–50% reduction in gastric emptying time; iii) there is a general decline in protein binding during pregnancy [112]; and iv) CYP3A4 activity may be induced in pregnancy [113]. It is probably not surprising that altered pharmacokinetics of AL has been reported in pregnant women [39]. Due to the expected variability in CYP3A4 activity in disease and pregnancy, more pharmacokinetic/pharmacodynamic studies on AL need to be carried out in patients with malaria. Little is known about the effects of co-infections (e.g., HIV and TB) on the disposition of AL. Therefore, there is also a need for pharmacokinetic/pharmacodynamic studies in patients with malaria and co-existing morbidities such as HIV infection, as it is known that increased parasite burdens and reduced host immunity due to HIV infection are associated with increased antimalarial treatment failure rates [2]. Other less serious, but equally common, childhood co-infections (such as helminths) may also affect the disposition of orally administered drugs, and should be investigated.

9.10 Affordable and cost-effective

The cost of antimalarial drugs is, in general, a major barrier to their accessibility. One study has shown that families that live in areas in which resistance to monotherapies is high are willing to pay for more expensive, effective alternative ACTs (including AL). However, the increased price that they are willing to pay is still far below the real costs of delivering such drugs. Thus, only with subsidies will ACTs have some real impact [114]. The WHO and Roll Back Malaria (RBM) targets are for antimalarial treatment to cost < US\$1 per treatment course in the public sector. On this account, AL, with a WHO-negotiated price per treatment course ranging from US\$0.45 for the smallest child to US\$1 for an adult (press release, January 2006), fulfils this criterion. Therefore, with donor support, most African countries will be able to procure AL and make it available free of charge in the public sector. However, not all the people who require AL will be able to get it through the public sector in most sub-Saharan African countries. Some people may have to buy it from the private retail sector, in which the price is relatively higher. For example, one study in Kenya has shown that an adult treatment course may cost up to US\$7 [115]. This price differential will need to be addressed to avoid leakage of free AL from public sector facilities into the private sector, thus creating artificial shortages in the public sector.

Cost-effectiveness of antimalarial treatment is a measure of cost per clinical outcome (clinical cure and/or radical cure). A few studies have addressed the question of cost-effectiveness of ACTs in general and AL in particular. One study that looked at ACTs in general suggested that countries in sub-Saharan Africa should shift resources to ACTs due to the potential gains in terms of averted deaths from malaria [116]. The study estimated that the use of ACTs as first-line treatment for uncomplicated malaria would result in ~ 63% reduction in case fatality. Another study that looked at ACTs in general concluded that ACTs are > 95% likely to be cost-effective under most conditions, other than where there are very low levels of initial resistance to sulphadoxine-pyrimethamine [117]. With regards to AL-specific studies, one study concluded that, although AL was considerably more expensive than sulphadoxine/pyrimethamine, its improved cure rate and reduced malaria transmission resulted in an estimated US\$201,065 cost savings in 1 year in the one particular area studied [118]. Another study in Tanzania comparing AL, amodiaquine (AQ) plus sulphadoxine-pyrimethamine (AQ + SP) and AQ plus artesunate (AQ + AS) with AQ alone, reported that AL, despite being more expensive, was the most cost-effective on day 14 following treatment [119].

Finally, it should be stressed that new fixed-dose ACTs will become available within the next 2 – 3 years, providing opportunities for comparative analysis of cost-effectiveness as a basis of rational selection of the most suitable antimalarial CT for a particular region/country. Although decisions by Ministries of Health on which ACT to change to, and how to implement the change to maximize benefits, are difficult to

make, it is now generally accepted that delaying decisions to switch to ACTs can only result in increased morbidity and mortality [120].

9.11 Effective against multi-drug resistant parasites; gametocytocidal

There are no known cases of resistance to artemisinin derivatives under clinical conditions, and several studies in south-east Asia (Thailand), an area with multi-drug resistant *P. falciparum*, have demonstrated high efficacy for AL. However, as discussed in Section 3.1, it has been shown that *in vivo* selection for resistance to lumefantrine is possible, even in areas in which multi-drug resistance has not been reported. Thus, despite the fact that lumefantrine has never been used as a monotherapy, AL may not be as robust as it might have been thought, based on the concept of CT, in delaying the emergence of resistance. Moreover, the continued availability of artemisinin-based monotherapies, especially in the private sector, will compromise the effectiveness of ACTs, including AL. To this end, the WHO has urged specific drug companies to stop manufacturing and marketing such monotherapies as one way of ensuring long UTL for ACTs such as AL. Other factors that may compromise the effectiveness of AL include i) inappropriate use due to wrong diagnosis, ii) availability of substandard (generic) products and/or counterfeit products, iii) poor storage conditions (leading to degradation of AL) and iv) use of expired drugs (some health workers will take a while to get used to the 2-year expiry period for AL tablets). Therefore, more studies on real-life effectiveness of AL will be needed.

Similar to other artemisinin derivatives, artemether is gametocytocidal. This may help reduce transmission, as has been demonstrated in a study on Gambian children treated with AL [101]. However, in areas of high endemicity, immune asymptomatic adults carrying gametocytes represent a large reservoir of infections, which may threaten non-immune individuals such as infants, pregnant women and travelers [22]. As immune adults do not present with symptoms of sickness, they will not be treated with AL, and this is a fact that will negate the gametocytocidal effects of AL in such areas. Thus, effective vector-control measures are needed to complement the use of ACTs such as AL in malaria-endemic areas.

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