Reviewer No.1 check list for application for addition: artesunate (AS)/amodiaquine (AQ) fixed dose combination tablets (25 mg/67.5 mg, 50 mg/135 mg and 100 mg/270 mg AS/AQ)

(1) Have all important studies that you are aware of been included?

Yes ◎ No ✓

If "No", add missing references with brief summary of key findings.

As with the overall section review application lodged for the 15th EML meeting in March 2007, this application cited the most recent WHO treatment guidelines (WHO Guidelines for the Treatment of Malaria WHO/HTM/MAL/2006.1108 - see http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf). However, the major evidence presented was from the WHO/TDR and DNDi programmes. More recent studies (from 2006) and systematic reviews not cited in the application have supported the efficacy of AS+AQ combination therapy, and are summarised in the table below.

Study	Design	Setting	Outcome (efficacy)	Outcome (other)	Comment
Systematic reviews					
Obonyo CO et al. Trans R Soc Trop Med Hyg 2007.[1]	Systematic review of randomised trials comparing AQ + sulphadoxine - pyrimethamine (SP) and either AS+AQ, AS+SP or artemether-lumefantrine (AL); 7 trials involving 4472 children	All trials were conducted in Africa	Day 28 treatment failure with AQ + SP was lower than with AS+SP (RR 0.56, 95% CI 0.42-0.75), similar to that with AS+AQ (RR1.12, 95% CI 0.81-1.54), but higher than with AL (RR 2.80, 95% CI 2.32-3.39)	All treatment regimens were characterised as "safe and well tolerated"	AS dosage was 4mg/kg once daily for 3 days; AQ dosing was 10mg/kg once daily for 3 days in 3 trials and 10mg/kg once daily for 2 days then 5mg/kg on day 3 in 4 trials
Recent randomised trials (not included in Obonyo et al.)					
Bukirwa H et al. PLoS Clinical Trials 2006.[2]	Randomised, single-blind trial of AS+AQ (n=201) vs. AL (n=202), aged 1-10 years	High transmission area in Uganda	Unadjusted risk of recurrent symptomatic malaria was lower with AL (27%) than with AS+AQ (42%), risk difference	Serious adverse events were uncommon in both treatment arms.	Similar results for recurrent parasitaemia (risk difference 16%, 95% CI 6.2-25.2%) All dosing was directly

Study	Design	Setting	Outcome (efficacy)	Outcome (other)	Comment
			15%, 95% CI 5.9-24.2%		observed. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 2 days then 5mg/kg on day 3 Genotyping showed that almost all recurrent cases were new infections
Meremikwu M et al. Malaria J 2006.[3]	Randomised trial of AS+AQ (n=59) vs. AL (n=60), aged 6-59 months	Nigeria, in an area with known high chloroquine (CQ) and SP resistance	Adequate clinical and parasitological response at day 14 in both treatment arms (82.5% vs. 87.0%; odds ratio 0.7, 95% CI 0.22-2.22)	No serious adverse events noted	All dosing was directly observed. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 2 days then 5mg/kg on day 3 Short follow-up period is a limitation
Guthmann JP et al. Am J Trop Med Hyg 2006.[4]	Randomised trial of AS+AQ (n=64) vs. AL (n=61), aged 6-59 months	Central Angola	Day 28 recurrent parasitaemia was similar (6.2 vs. 3.2%), all were re-infections	Similar decreases in anaemia seen in both treatment arms	Cure rate was 100% in both treatment arms. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 3 days
Swarthout TD et al. Trop Med Int Health 2006.[5]	Open-label, randomised trial of AS+AQ (n=90) vs. AS+SP (n=90), aged 6-59	High transmission seasonal area in DR Congo	Day 28 parasite recurrence (after PCR-based adjustment for re-	No adverse events were reported by parents	All dosing was directly observed. The doses of AS and AQ are, however, not stated.

Study	Design	Setting	Outcome (efficacy)	Outcome (other)	Comment
	months		infection) was lower for AS+AQ (6.7%, 95%CI 2.2-15.1) than for AS+SP (19.7% (95 CI 10.9-31.3)		There was a high prevalence of SP resistance in this group
van den Broek I et al. Malaria J 2006.[6]	Open-label, randomised trial of AS+AQ (n=101) vs. AS+SP (n=91) vs AL (n=106), aged 6-59 months	High transmission area in Republic of Congo	Day 28 parasite recurrence (after PCR-based adjustment for re-infection) was 98.5% (95% CI 92-100) for AS+AQ, 90.1% (80.7-95.9) for AS+SP and 100% (95.8-100) for AL	No serious adverse events reported	All dosing was directly observed. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 3 days.
Karema C et al. Trans R Soc Trop Med Hyg 2006.[7]	Open-label, randomised trial of AS+ AQ (n=252), vs. AQ + SP (n=258) vs. dihydroartemisinin-piperaquine (DP) (n=252), aged 12-59 months	3 sites in Rwanda (1 peri-urban two rural)	Day 28 cure rates (PCR-corrected) were 92.0% for AS+AQ, 84.7% for AQ + SP and 95.2% for DP	Parasite clearance was faster with the AS-containing regimens. Adverse events were less frequent in the DP arm (44/252) compared to the AQ-containing regimens (80/252 and 103/258)	All dosing was directly observed. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 3 days.
Bonnet M et al. Malaria J 2007[8]	Open-label, randomised trial of AS+ AQ (n=110) vs. AS+SP (n=110), aged 6-59 months	Central Guinea, where malaria is seasonal (June to October)	Day 28 failure rates (PCR-adjusted) were 1.0% (95% CI 0-5.3%)for AS+AQ and 1.0% (95% CI 0-5.5%) for AS + SP	Although both regimens were efficacious, a linked study detected molecular markers of SP resistance in a refugee	All dosing was directly observed. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 3 days.

Study	Design	Setting	Outcome (efficacy)	Outcome (other)	Comment
				setting in the south of Guinea	
Dorsey G et al. JAMA 2007[9]	Single-blind, randomised trial of AQ+SP (n=111), vs. AS+AQ (n=113) vs. AL (n=105), aged 1-10 years	Urban community in Kampala, Uganda	Day 28 failure rates (PCR-adjusted) were 14.1% (95% CI 10.3-19.2%) for AQ+SP, 4.6% (2.5-8.3) for AS+AQ and 1.0% (0.3-4.0) for AL	AL was the most efficacious regimen, but all regimens were characterised as "safe and generally well tolerated"; anorexia and weakness were more commonly seen in the first 14 days in those receiving AQ+SP	Only the first dose was observed. AS was dosed as 4mg/kg daily for 3 days, AQ as 10mg/kg once daily for 2 days then 5mg/kg on day 3
Other studies					
Grandesso F et al. Trop Med Int Health 2006.[10]	Single arm evaluation of AS+AQ (n=126), aged 6-59 months	Sierra Leone, where efficacy of AQ alone had been shown to be 70.2%	Day 28 efficacy (PCR-adjusted) was 84.5% (95% CI 76.4-90.7)	Notably, 54/110 (49.1%) who completed 28 days of follow-up developed a re-infection	

In addition to the studies conducted in Africa, two recent studies in other parts of the world have included an AS+AQ arm. One showed that AS+AQ was less effective and not as well tolerated as a dihydroartemisinin-piperaquine (DP) combination in treating malaria in southern Papua, Indonesia.[11] A feature of this study was the presence of mixed infections - of 334 participants, 185 were infected with *P. falciparum*, 80 with *P. vivax*, and 69 with both species. The overall parasitological failure rate at day 42 was higher in the AS+AQ group (45%; 95% CI 36%-53%) than in the DHP group (13%; 95% CI 7.2%-19%), as was the rate of recrudescence of *P. falciparum* infection and recurrence of *P. vivax* infection (HR 3.4; 95% CI 1.2-9.4 and 4.3, 95% CI 2.2-8.2, respectively). By the end of the study, AS+AQ recipients were 2.95-fold (95% CI, 1.2- to 4.9-fold) more likely to be anemic and 14.5-fold (95% CI, 3.4- to 61-fold) more likely to have carried *P. vivax* gametocytes. A small study in Colombia, which included some children (there were 43 and 42 in the two groups, with median ages of around 19 years), showed that both a combination of AS (4mg/kg daily for 3 days) and AQ (10mg/kg daily for 3 days) and the AQ alone were effective.[12] Adding AS did not affect the tolerability of the regimen.

The 3 TDR studies cited in the application have been combined in one report as a single RCT (Adjiuk et al., 2002). They have also been included in an individual patient data meta-analysis published in the Lancet.[13] There are, however, no peer-reviewed sources for the

phase III 3.1 ratio dose studies cited in the application, in which the co-blistered presentation was used (studies A to H). The Burkina-Faso study, in which the 2.7 ratio dose FDC was used, has also not been published, although extensive details are provided in the application, which has been placed in the public domain. A multi-centre non-inferiority study comparing the proposed 2.7 dose ratio FDC with the AL, in which a large proportion of the participants were children less than 5 years, has been completed but not yet reported.

(2) Is there adequate evidence of efficacy for the proposed use?

Yes ✓ No ◎

If "No", suggest what is needed.

There is sufficient evidence for the efficacy of AS+AQ as combination therapy, usually dosed as 4+10mg/kg daily for 3 days (referred to in the application as the 2.5 ratio dose). Results for the 2.7 ratio dose would not appear to be materially different. The justification for the FDC ratio and the 25/67.5 and 100/270 strengths has been extensively documented (Taylor et al., 2006).

(3) Is there evidence of efficacy in diverse settings and/or populations?

Yes ✓ No ◎

Also see response to question (6) below.

If "No", suggest what is needed.

(4) Are there adverse effects of concern?

Yes ◎ No ✓

If "Yes", (list / describe)

This issue has been covered adequately in the application.

(5) Are there special requirements or training needed for safe/effective use?

Yes ◎ No ✓

If "Yes", describe.

The suitability of the proposed FDCs has been justified, even though only 2 of the 3 strengths were initially mentioned (Taylor et al., 2006).

(6) Is this product needed to meet the majority health needs of the population?

Yes ✓ No ◎

If "No", is there a special reason why this should be on the Model List?

Although it could be argued that AL is sufficient as an ACT for all patients of 5kg r more, the latest WHO Guidelines indicate which of the artemesinin combinations should be used in each geographical area. This is necessary given the important geographic differences in resistance patterns. There is thus a need for a range of ACTs, to allow for regional specificity.

(7) Is the proposed dosage form registered by a stringent regulatory authority?

Yes ◎ No ✓

If "No", give details.

The application has proposed that the 3 different fixed-dose combinations be listed. Although there is a strong WHO stance in favour of the sale of ACTs, rather than stand-alone artemesinin-containing formulations, the review for the 15th EML noted that the evidence for the superiority of "unit-dose" packaging (whether FDC or co-blistered) is limited. A 2005 Cochrane Review found insufficient evidence (as at November 2004) to determine the effect of such packaging on treatment outcomes.[14] Another review noted some evidence that providing component medicines together was better than not doing so (though it was noted that the only study to measure the latter situation required patients to visit two facilities to collect the components), and high adherence to a co-formulated presentation.[15] Data from 14 therapeutic efficacy surveillance studies in Cambodia failed to show a difference in outcomes when AS and mefloquine (MQ) were provided as co-blistered presentations (in 2001 and 2002) and as separate medicines (in 2004).[16] In an open-label, randomised trial Thailand (n=500, adults and children), the day 63 PCR-adjusted cure rates were similar for the FDC of AS+MQ (91.9%, 95% CI 88.2-95.6) and the separate tablets (89.2%, 95% CI 85.0-93.4).[17]

An application for registration of the FDC formulations has been made in South Africa (which is a PIC/S member) and the dossier is also under consideration by the WHO PQ programme.

(8) What action do you propose for the Committee to take?

The current EML contains only the 50mg AS formulation and either a 153 or 200mg AQ tablet. Achieving the 2.5 or 2.7 ratio doses in younger children with these formulations would not be easy. The committee could consider listing the proposed FDCs, but noting that only pre-qualified products or products registered by stringent regulatory authorities should be procured. Even though the AL FDC can also be used in children of 5kg and more, it is felt that more than one ACT is needed.

(9) Additional comment, if any.

The entire malaria section, including sub-section 6.5.3.1 antimalarial medicines – curative treatments, was reviewed by the 15th EML committee in March 2007. The resulting changes to the WHO Model EML are reflected in the current listing:

6.5.3 Antimalarial medicines	
6.5.3.1 For curative treatment	
Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. The Committee recognizes that not all of these FDCs exist and encourages their development and rigorous testing. The Committee also encourages development and testing of rectal dosage formulations.	
amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride). * To be used (a) in combination with artesunate 50 mg OR (b) may be used alone for the treatment of *P.vivax, P.ovale and P.malariae* infections.
artemether	**Oily injection:** 80 mg/ml in 1-ml ampoule. For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
chloroquine	**Tablet:** 100 mg; 150 mg (as phosphate or sulfate). **Oral liquid:** 50 mg (as phosphate or sulfate)/5 ml.
doxycycline*	**Capsule:** 100 mg (as hydrochloride). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate) * Only for use to achieve radical cure of *P.vivax* and *P.ovale* infections, given for 14 days.
quinine*	**Injection:** 300 mg quinine hydrochloride/ml in 2-ml ampoule. **Tablet:** 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine *	**Tablet:** 500 mg + 25 mg. * Only in combination with artesunate 50 mg.

These changes were not acknowledged in the application, which relied on the 14th EML from March 2005 as its starting point. In addition to changes in the products listed, the use of artemesinin-lumefantrine in children weighing 5kg and more was mentioned (as opposed to the 10kg limit referred to in the application).

References

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