



EMLc

Codes ATC: P01BF03

Indication	Malaria due to Plasmodium falciparum	Code ICD11: 1F40
INN	Artesunate + amodiaquine	
Type de médicament	Biological agent	
Type de liste	Liste de base (EML) (EMLc)	
Additional notes	Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives	
Formulations	Oral > Solid: 25 mg + 67.5 mg tablet ; 50 mg + 135 mg tablet ; 100 mg + 270 mg tablet	
Historique des statuts LME	Ajouté pour la première fois en 2011 (TRS 965)	
Sexe	Tous	
Âge	Aussi recommandé pour les enfants	
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique	
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.	
Wikipédia	Artesunate + amodiaquine	
DrugBank	Artesunate Amodiaquine	

Résumé des preuves et recommandation du comité d'experts

Artesunate and amodiaquine (AS+AQ) have been recommended by WHO as one of the preferred artemisinin combination treatments for malaria since the WHO treatment guidelines published in 2006. Sanofi-Aventis has submitted an updated application to list the fixed-dose combination product containing AS+AQ in three different strengths: 25 mg+67.5 mg, 50 mg+135 mg, and 100 mg+270 mg. The application was first considered by the Subcommittee in 2007, and subsequently by the Expert Committee in October 2007. The application was rejected because of uncertainty about the dose of amodiaquine in the FDC compared to the usually recommended dose, the relatively premature nature of the presentation of one of the key clinical trials and the uncertainty about the availability of a quality-assured product. The current application, based on the regulatory dossier for the Sanofi-Aventis product, was submitted in June 2009, and updated again in October 2010, to reflect changes in the new WHO treatment guidelines (2010 edition) and updated information about licensing. The Sanofi-Aventis product was approved as prequalified by WHO at the end of 2008. It is licensed in several African countries and in India. Expert reviews were provided by Professor Jennifer Welbeck and Mr Andy Gray. As in 2007, there are two studies in the application that use the proposed FDC: the Burkina Faso study (1), which is a comparison of the FDC with a loose combination in a different dose, and the ATAQ EASY study (2), comparing the FDC with artemether + lumefantrine (AL). A complete overview of comparative effectiveness studies is provided in the Cochrane Review by Sinclair et al. (3) and the (unpublished) 2011 update of this review has been completed and provided to the Committee. It includes: - 2 trials of AS+AQ versus DHA-PPQ (day 28 data are available from 2 trials, day 42 from 1 trial); - 1 trial of AS+AQ versus AS+MQ (day 28 data only); - 12 trials of AS+AQ 6 doses of artemether + lumefantrine (polymerase chain reaction (PCR)-adjusted day 28 data are available from 11 trials, day 42 from 1 trial; - 3 further trials excluded due to baseline differences);

- 7 trials of AS+AQ versus AS+SP (day 28 data only); - 9 trials of AS+AQ versus AQ+SP (PCR-adjusted day 28 data available from 7 trials). When assessing AS+AQ compared to other artemisinin combination therapies, the updated results from the Cochrane Review for the comparisons of the outcome day 28 PCR treatment failure are: - AS+AQ versus DHA-PPQ: 2 studies, 329 subjects, pooled RR 2.36 (95% CI 0.74–7.54), favours DHA-PPQ; - AS+AQ versus AL: 11 studies, 2791 participants: RR 0.65 (95% CI 0.40–1.04), favours AS+AQ; and - AS+AQ versus AS+MQ: 1 study, 482 subjects, 0 events so comparative relative risk not estimable. In terms of comparative safety, the information in the application has been updated by a safety review, prepared by a member of the Advisory Committee on the Safety of Medicines, that identifies adverse drug reactions suggestive of extra-pyramidal reactions in adults consistent with previous similar reports noted with amodiaquine monotherapy. No other new information concerning safety has been identified. The Committee noted that the current WHO treatment guidelines recommend a target dose of 4 mg/kg per day of artesunate (therapeutic range 2–10 mg/kg per day) and 10 mg/kg per day (range 7.5–15 mg/kg per day). A proportion of potential 'weight bands' receive less than the target dose of 4 mg/kg per day artesunate but more than the minimum of 2 mg/kg per day. Doubling the dose usually results in excess amodiaquine with the resultant risk of increased toxicity. The trials provided show that the FDC appears to have similar efficacy compared with the loose combination at a slightly different dose. The Committee was assured by the relevant WHO Department that the doses delivered were considered appropriate to deliver at least 2 mg/kg per day of artesunate. The FDC composition had been included in WHO treatment guidelines and there were WHO prequalified products available for the FDCs proposed. The Committee decided to include the proposed FDCs on the EML and EMLc, but with a note specifying that appropriate doses may also be achievable using combinations of the monocomponent products, including as co-blistered presentations. The mono-component amodiaquine cannot be deleted as a separate listing in the EML, but the note needs to be consistent with existing guidelines for the treatment of *Plasmodium vivax*, *P. ovale* and *P. malariae* malaria. 1. Sirima SB et al. The efficacy and safety of a new fixed-dose combination of amodiaquine and artesunate in young African children with acute uncomplicated *Plasmodium falciparum*. *Malaria Journal*, 2009, 8:48. 2. Ndiaye JL et al. Randomized multicentre assessment of the efficacy and safety of ASAQ – a fixed-dose artesunate-amodiaquine combination therapy in the treatment of uncomplicated *Plasmodium falciparum* malaria. *Malaria Journal*, 2009, 8:125. 3. Sinclair D et al. Artemisinin-based combination therapy for treating uncomplicated malaria. *Cochrane Database of Systematic Reviews*, 2009, (3):CD007483.

