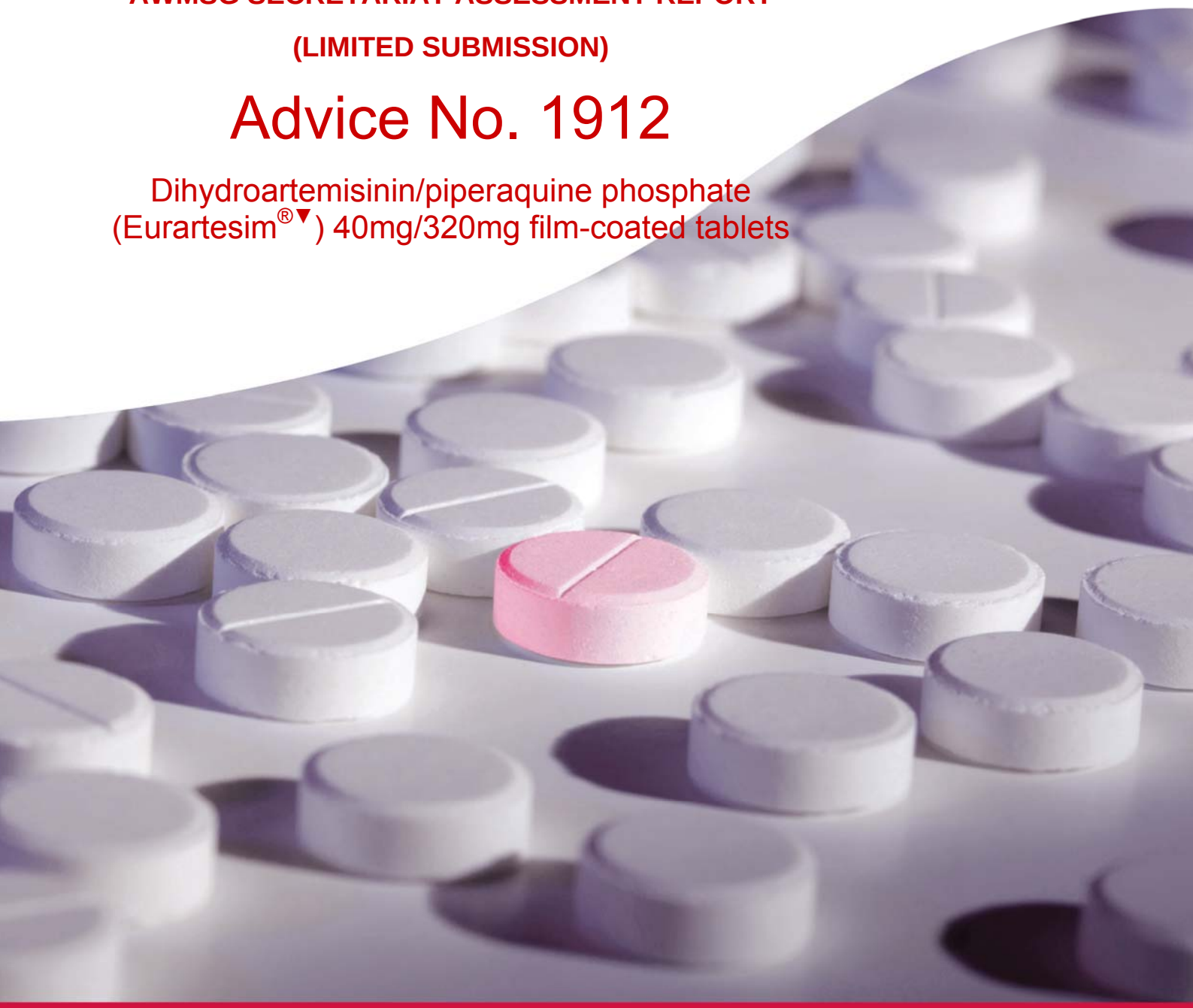
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 1912

Dihydroartemisinin/piperaquine phosphate (Eurartesim®▼) 40mg/320mg film-coated tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 1912
Dihydroartemisinin/piperaquine phosphate (Eurartesim®▼) 40 mg/320 mg film-coated tablets

This assessment report is based on evidence from a limited submission by Sigma Tau Pharma Ltd UK on 17 February 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Dihydroartemisinin/piperaquine phosphate (Eurartesim®▼) is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults, children and infants 6 months and over and weighing 5 kg or more[2].
Dosing	Eurartesim®▼ should be administered once daily, with water and without food, i.e. no less than three hours after the last food intake. No food should be taken within 3 hours after each dose. It should be administered over three consecutive days for a total of three doses taken at the same time each day. Dosing should be based on body weight. Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing[2].
Marketing authorisation date	27 October 2011[3].
UK launch date	Dihydroartemisinin/piperaquine phosphate (Eurartesim®▼) is due to be launched in June 2012[1].

2.0 DECISION CONTEXT

2.1 Background

Malaria is an infectious disease caused by the *Plasmodium* parasite, which is transmitted to humans via the bites of female *Anopheline* mosquitoes[4]. There are four types of *Plasmodium* parasite species that commonly infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*[4,5]. The most serious form of malaria is caused by *P. falciparum*[3] and accounts for approximately three-quarters of reported cases in the UK[6]. Infection with *P. falciparum* can rapidly lead to severe or life-threatening multi-organ disease[6]. Malaria is a major cause of morbidity and death (especially in children < 5 years) in endemic areas such as Africa, South and Central America, Asia and the Middle East[3,4]. However, a number of travellers from non-endemic areas are also affected each year. In the UK, 1,500–2,000 cases are reported annually resulting in approximately 10–20 deaths[6]. In 2010, there were 1,761 cases of malaria in the UK of which 1,275 cases were caused by *P. falciparum*[1,7]. As there are no specific malaria case statistics for the Welsh population, the company has estimated that there are around 61 cases of *P. falciparum* malaria in Wales each year[1] (refer to Section 5 for further details).

The World Health Organization (WHO) recommends artemisinin combination treatment (ACT) in areas where *P. falciparum* malaria is predominant[8]. Dihydroartemisinin/piperaquine phosphate (DHA/PQP) is an ACT that alters the function of essential parasite proteins and causes the inhibition of haem detoxification by the parasite[3]. The only other ACT approved in the EU is Riamet®, a fixed combination of artemether and lumefantrine[3,9].

2.2 Comparators

The comparators requested by the Welsh Medicines Partnership* were:

- Artemether/lumefantrine (Riamet®)
- Atovaquone/proguanil (Malarone®)

2.3 Guidance and related advice

- WHO. Guidelines for the treatment of malaria (2011)[4].
- Health Protection Agency Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines (2007)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes data obtained from two pivotal phase III studies, DM040011[10] and DM040010[11]. Both studies have a randomised, open-label design, and compare the use of DHA/PQP with an active comparator in populations where malaria is endemic. Study DM040011 compared DHA/PQP with artemether/lumefantrine (A/L) in African children[10] whereas, study DM040010 compared DHA/PQP with artesunate-mefloquine (AS+MQ) in Asian patients[11]. It should be noted that AS+MQ is not licensed in the UK.

3.1 Clinical effectiveness evidence

3.1.1 Study DM040011[10]

This randomised, open-label phase III trial compared DHA/PQP with A/L in African children aged 6–59 months, weighing ≥ 5 kg, with uncomplicated *P. falciparum* malaria. DHA/PQP was given once daily, for three days, at a dose of 2.25 mg/kg and 18 mg/kg of DHA and PQP, respectively, rounded up to the nearest half tablet. A/L was administered twice daily, for three days, according to patient weight (5–14 kg: one tablet; 15–24 kg: two tablets; 25–34 kg: three tablets per dose). Patients in the intention to treat (ITT) population (n = 1,553) were randomised in a 2:1 ratio to receive either DHA/PQP (n = 1,039) or A/L (n = 514). Exclusion criteria included severe malaria, acute malnutrition, concomitant illness or underlying disease and contra-indication to receive the trial drugs or ongoing prophylaxis with drugs having anti-malarial activity[12].

The primary efficacy endpoint was the polymerase-chain reaction (PCR)-corrected cure rate of DHA/PQP versus A/L at day 28. The study was designed to test non-inferiority of the two treatments; in terms of the primary endpoint non-inferiority was predefined as a margin of within −5% for the lower limit of the one-sided 97.5% confidence interval (CI). Secondary endpoints included the non-inferiority of PCR-uncorrected rates at days 28 and 42, and early and late treatment failures (ETF and LTF, refer to Glossary for full definitions)[10,12].

At day 28, the PCR-corrected cure rates for DHA/PQP were found to be non-inferior to A/L (90.4% for DHA/PQP versus 90.0% A/L at day 28, 97.5% CI -2.80%). Statistically significant non-inferiority was demonstrated for the PCR-uncorrected rates (87.7% for DHA/PQP versus 76.7% for A/L at day 28 and 74.1% versus 64.7% at day 42, $p < 0.001$). Results for ETF were comparable; however, differences were observed for LTF within the DHA/PQP group (5.9% for DHA/PQP versus 16.7% for A/L)[3,10].

* In April 2012 the Welsh Medicines Partnership became a part of the All Wales Therapeutics and Toxicology Centre (AWTTC).

3.1.2 Study DM040010[11]

This randomised, open-label phase III trial compared DHA/PQP with AS+MQ in Asian patients aged 3 months to 65 years with *P. falciparum* mono-infection or mixed infection. DHA/PQP was given once daily, for three days, at a dose of 2.25 mg/kg and 18 mg/kg of DHA and PQP, respectively, rounded up to the nearest half tablet. AS+MQ were administered as separate tablets: AS at a dose of 4 mg/kg and MQ at a dose of 15 mg/kg on day 1 and 10 mg/kg on day 2, but was not administered on day 0. Patients in the ITT population (n = 1,150) were randomised in a 2:1 ratio to receive either DHA/PQP (n = 769) or AS+MQ (n = 381). Exclusion criteria included severe malaria, treatment with mefloquine in the 60 days prior to screening, treatment with DHA/PQP within 3 months prior to screening, > 4% parasitized red blood cells and pregnant or lactating women[13].

The primary efficacy endpoint was the PCR-corrected cure rate of DHA/PQP at day 63, with the intention of demonstrating non-inferiority (defined as in study DM040011; see Section 3.1.1). Secondary endpoints included the non-inferiority of PCR-uncorrected rates at day 63 and ETF and LTF[11,13].

At day 63, the PCR-corrected cure rate for DHA/PQP was found to be non-inferior to AS+MQ (87.9% for DHA/PQP versus 86.6% for AS+MQ, 97.5% CI -2.87%). This is supported by results for the secondary endpoints.

3.1.3 Evidence of comparative safety

For both clinical trials discussed above, the type and frequency of adverse effects (AEs) were similar for DHA/PQP and the comparators[10,11]. In study DM040011, AEs were seen in 71.0% of patients (versus 72.2% for A/L), whereas in DM040010, 69.4% of patients receiving DHA/PQP experienced at least one AE (versus 72.4% for AS+MQ). AEs were mild to moderate and consistent with the symptoms attributed to malaria: headache, cough, nausea, vomiting and dizziness were commonly observed[3,10,11]. An elongation of the QTc interval was associated with the use of DHA/PQP in both studies, although this was statistically significant only in study DM040010 ($p < 0.001$), and in both studies it was observed that this effect was short-lived and not apparent after day 7 of treatment[3]. In both studies, a greater number of serious AEs was observed in the DHA/PQP group compared to the respective comparators[3]. Two deaths occurred in study DM040011 within each treatment group; neither death was considered to be related to the study medicines[3].

3.2 AWTTC critique

- The Welsh Medicines Partnership (WMP) requested atovaquone/proguanil as a comparator; however, evidence relating to this treatment has not been provided by the company in their submission. The only study discussed by the company comparing DHA/PQP to a relevant active comparator (A/L), was conducted in children. However, a literature search conducted by AWTTC revealed that comparative studies have also been carried out within children and adult populations: in a sub-Saharan study, Yavo and colleagues showed that there were no statistically significant differences between the recovery rates at day 28 when either DHA/PQP or A/L was used to treat uncomplicated malaria caused by *P. falciparum* in patients aged at least two years[14].
- Although marketing authorisation has been granted for two different DHA/PQP tablet doses (40 mg/320 mg and 20 mg/160 mg), only the 40 mg/320 mg tablet will be marketed in the UK. Correct dosing of children aged 5 to < 13 years requires the 20 mg/160 mg tablet.
- Patients from the UK were not included in either of the pivotal studies, as both trials were conducted in areas where malaria is endemic[10,11]. This is

reasonable considering the nature of the indication and the low incidence of malaria in the UK[7]. However, it has been argued that the efficacy observed in patients who reside in endemic areas may not necessarily apply to returning EU travellers, as those who reside in endemic areas may have some residual immunity to malaria, whereas the majority of returning EU travellers do not[3].

- The Ad-Hoc Expert Committee of the European Medicines Agency (EMA) have advised that the QTc prolongation associated with DHA/PQP could pose a problem and serve as an unpredictable risk for a small proportion of people, as QTc prolongation can lead to serious cardiac arrhythmias. Therefore, the Committee for Medicinal Products for Human Use (CHMP) has deemed it necessary for the marketing authorisation holder to provide results of an epidemiological study addressing cardiac safety. The results of this study are due by 31 December 2014[2,3].
- EMA state that long-term follow-up information of patients in phase III trials would be beneficial in order to allow for the detection and assessment of long-term adverse reactions[3].
- The effect of concomitant administration of DHA/PQP and known CYP3A4 inhibitors has not yet been studied[3].
- Dosing DHA/PQP with food greatly enhances piperaquine plasma levels, an effect which is associated with QTc prolongation[3]. In order to minimise this, DHA/PQP should be dosed without food as stated in the SPC[2]. However, in the phase III studies included in the submission, the timing of the three daily doses in relation to food intake could not be discerned with confidence[3].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

Evidence of cost effectiveness is not required from the submitting company for a limited submission. Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of DHA/PQP (Eurartesim®▼) in this indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission[1] presents a simple estimation of budget impact associated with the use of DHA/PQP for the treatment of uncomplicated *P. falciparum* malaria in Wales. Due to a reported lack of statistics on malaria cases treated in Wales, the company used UK Health Protection Agency data from 2010[7] to estimate the number of patients eligible for treatment with DHA/PQP in Wales. According to this source, there were 1761 cases of malaria in 2010 in the UK, of which 72% were caused by *P. falciparum.* Using Welsh population statistics, the company estimates there may be 61 individuals with malaria eligible for treatment with DHA/PQP each year in Wales. The company has presented a scenario in which 50% of these individuals will be treated with DHA/PQP and 50% by A/L.

5.1.2 Results of company budget impact analysis

The company estimates the cost of acute treatment of one malaria episode with DHA/PQP will be £40 per patient, compared to £22.50 with an A/L regimen (assuming whole packs are issued, irrespective of patient age/weight). Assuming 94.8% efficacy and 50% market share for both A/L and DHA/PQP, the company estimates the use of

DHA/PQP to cost an additional £563 per year (£2,815 over the 5 years) for the treatment of uncomplicated *P. falciparum* cases in Wales. The company also suggests that there may be benefits in terms of re-infection rates and where there are multi-drug resistant strains of *P. falciparum*[1].

5.1.3 AWTTC critique of the budget impact analysis

- The analysis of budget implications presented by the company is based on the assumption of therapeutic equivalence of DHA/PQP and A/L. Clinical trials conducted in areas with endemic malaria have demonstrated the non-inferiority of DHA/PQP against this comparator in terms of PCR-corrected cure rates, and superior uncorrected cure rates and rates of new infection at all time points after Day 28[3]. However, CHMP noted that it is not possible to be sure that the efficacy observed in trial subjects resident in endemic areas would necessarily apply to returning EU travellers, the majority of whom will have no acquired immunity to malaria[3]. It should also be noted that DHA/PQP was non-inferior to comparators for rates of recrudescent infection[3], and any potential improvements in rates of new infection are irrelevant to patients who have returned to and are receiving treatment in Wales. Although the company asserts potential benefits in cases of multi-drug resistant strains of *P. falciparum*, no supporting evidence of improvements over existing comparators has been presented. Adverse event profiles are reported to be similar for DHA/PQP and comparators, with the exception of a greater risk of QTc interval prolongation with DHA/PQP
- The company has adopted a pragmatic approach to estimation of patient numbers, and notes this may overestimate the number of patients eligible for treatment with DHA/PQP, as UK rates of malaria from which Welsh figures are derived may be distorted by higher rates among travellers returning to London and the South East of England.
- The company has not provided compelling arguments or evidence to support the use of DHA/PQP in preference to the less costly A/L or any other alternative treatments (see Table 1 below), and it is unclear how many malaria cases are treated with A/L in practice in Wales; however, the budget impact from the use of DHA/PQP seems likely to be small.

5.2 Table of comparative unit costs

Table 1 provides acquisition costs of examples of drugs listed in the British National Formulary[15] for the treatment of *P. falciparum* malaria in adults and children. Since therapeutic doses of these drugs may be dependent on factors such as patient weight, the example acquisition costs are indicative only. The cost of treatment with DHA/PQP is based on the price provided by the company.

Table 1. Examples of drug acquisition costs for the treatment of uncomplicated *P. falciparum* malaria in adults, children and infants.

Example drug regimens	Example dosing	Maximum cost per acute treatment episode*
Dihydroartemisinin/piperaquine phosphate (Eurartesim®▼) 20/160 mg, 40/320 mg tablets	Between ½ and 4 tablets to be taken once daily for 3 days, depending on body weight	£40.00†
Artemether/lumefantrine (Riamet®) 20/120 mg tablets	1-4 tabs at time of diagnosis and then at 8, 24, 36, 48 and 60 hrs	£22.50
Atovaquone/proguanil (Malarone®) 250/100 mg tablets (11 kg and above) Atovaquone/proguanil (Malarone® paediatric) 62·5/25 mg tablets (5–11 kg)	1-4 tablets as a single dose for 3 consecutive days 2-4 tablets daily for 3 consecutive days	£25.21 £6.26
Quinine sulphate (non-proprietary) 200 mg and 300 mg tablets + doxycycline (non-proprietary)100 mg capsules	Quinine (salt) 600 mg (adults) or 10 mg/kg (maximum 600 mg, child) every 8 hours for 7 days, followed by Doxycycline 200 mg daily for 7 days (adults and children over 12 years)	£4.13

**Assumes branded products are supplied as one whole pack, with wastage as relevant.*
†Cost based on price provided by the company. Other costs are based on MIMS[16] and NHS eDrug Tariff[17] list prices as of March 2012.
See the relevant SPC[2] and guidance in the British National Formulary[15] for full dosing details.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that dihydroartemisinin/piperaquine phosphate (Eurartesim®▼) for the above indication may be appropriate for use within NHS Wales prescribed under specialist recommendation.

6.2 AWMSG review

This assessment report will be considered for review three years from ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.3 Evidence search

Date of evidence search: 2 March 2012
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

PCR-corrected cure rate
The proportion of patients with adequate clinical and parasitological response (ACPR) by the end of the follow up period[18]. ACPR is defined an absence of parasitaemia through to the end follow up date irrespective of temperature and not meeting any of the criteria for treatment failures[3].

Early treatment failure (ETF)[3]
One or more of the following:

1. Development of danger signs or severe malaria on days 0, 1, 2 or 3, in the presence of parasitaemia
2. Parasite density on day 2 > day 0 count, irrespective of temperature
3. Presence of parasitaemia on day 3 with fever (temperature ≥ 37.5°)
4. Parasitaemia on day 3 ≥ 25% of count on day 0

Late treatment failure (LTF)[3]
LTF could be due to late clinical failure (LCF) or late parasitological failure (LPF).

LCF is defined as any/all of the following:

1. Development of danger signs or severe malaria after day 3 in the presence of parasitaemia
2. Presence of parasitaemia and fever on any day from day 4 to study follow up date, without previously meeting the criteria for ETF or LTF

LPF was defined in the European Public Assessment Report (EPAR) as the reappearance of parasitaemia after initial clearance between day 7 and the study follow up date (identified as recrudescent infection by PCR analysis) in the absence of fever (temperature < 37.5°C) without previously meeting the criteria of ETF or LTF.

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