Dihydroartemisinin + piperaquine

Essential medicine status ✓

EMLc | ATC codes: P01BF05

Indication	Malaria due to Plasmodium vivax ICD11 code: 1F81
Medicine type	Chemical agent
List type	Core (EML) (EMLc)
Formulations	Oral > Solid: 40 mg + 320 mg tablet ; 20 mg + 160 mg tablet
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Weight restriction	> 5 kg
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Dihydroartemisinin + piperaquine
DrugBank	Artenimol, Piperaquine

Expert Committee recommendation

The Expert Committee recommended the inclusion of dihydroartemisinin + piperaquine phosphate in the core list of the EML and EMLc for use in malaria. The Committee noted both the favourable benefit–risk profile of the combination and its inclusion in the latest WHO guidelines for malaria. The product is safe and efficacious in pregnancy. Availability of this fixed-dose combination will provide an alternative treatment option to mefloquine- or amodiaquine-containing combinations. The Committee considered that that the availability of fixed-dose combination formulations for treatment of malaria can offer the benefits of greater dosing accuracy, ease of administration and reduced pill burden and contribute to better therapeutic adherence.

Background

Currently, the fixed-dose combination (FDC) artemisinin-combination treatments (ACTs) included in the EML are: artemether + lumefantrine (A+L), artesunate + amodiaquine (AS+AQ) and artesunate + mefloquine (AS+MQ).

Public health relevance

It is estimated that a cumulative 1.2 billion fewer malaria cases and 6.2 million fewer malaria deaths occurred globally between 2001 and 2015 than would have occurred if had incidence and mortality rates remained unchanged since 2000. Of the estimated 6.2 million fewer deaths, about 5.9 million (95%) were in children aged under 5 years. By 2015, it was estimated that the number of malaria cases had fallen to 214 million (range 149–303 million), and the number of deaths to 438 000 (range 236 000–635 000). The global burden of mortality is dominated by countries in sub-Saharan Africa. Decreases in case incidence and mortality rates were slowest in countries with the largest numbers of malaria cases and deaths in 2000 (1).

Benefits

The application presented the results two phase III clinical trials in adults and children with acute, uncomplicated P. falciparum malaria in Africa and south-east Asia. The Asian trial (2) was a randomized, active-controlled, non-inferiority trial to demonstrate the non-inferiority of DHA+PQP, in terms of efficacy, versus AS+MQ (the standard reference therapy in south-east Asia) in 1150 adult and paediatric patients aged between 6 months and 62 years. The primary efficacy end-point was the polymerase chain reaction (PCR)- corrected cure rate at day 63. At day 63, PCR-corrected cure rates for DHA+PQP versus AS+MQ were 87.9% and 86.6% (intention-to-treat (ITT) population; $P = 0.544$); 97.0% and 95.3% (modified-ITT population (m-ITT); $P = 0.161$); and 98.7% and 97.0% (per-protocol (PP) population; $P = 0.074$), demonstrating similar efficacy for both treatments. For all populations studied, the lower limit of the one-sided 97.5% confidence interval (CI) of the difference was above the prespecified non-inferiority margin of −5%, showing DHA+PQP to be non-inferior to AS+MQ. In addition, analysis of the 63 days of follow-up showed that DHA+PQP significantly reduced the risk of new infections; Kaplan-Meier estimates of the proportions of patients with new infections were 22.7% for DHA+PQP and 30.3% for AS+MQ, ($P = 0.0042$; ITT population). The African trial (3) had the same design as the Asian trial and investigated the efficacy and safety of DHA+PQP against A+L (the standard reference therapy in Africa) in 1553 paediatric patients aged 6 months to 5 years and weighing at least 5 kg. The primary efficacy endpoint was PCR-corrected cure rate at day 28. At day 28, PCR-corrected cure rates for DHA+PQP versus A+L were 90.4% and 90.0% (ITT population; $P = 0.820$); 92.7% and 94.8% (m-ITT population; $P = 0.128$); and 95.7% for both groups in the PP population ($P = 0.988$). The study demonstrated that the two ACTs were of similar efficacy in curing uncomplicated P. falciparum malaria. The lower limit of the one-sided 97.5% CI of the difference was above the non-inferiority margin of −5%, supporting non-inferiority for all populations. In addition, analysis at 42 days of follow-up showed that DHA+PQP significantly reduced the risk of new infections; Kaplan-Meier estimates of the proportions of patients with new infections were 13.6% (95% CI 11.35–15.76%) for DHA+PQP and 24.0% (95% CI 20.11–27.88%) for A+L ($P < 0.0001$; ITT population). Similar results have been obtained with DHA+PQP in two pharmacokinetics trials and in other clinical studies reported in literature and summarized in the application (4–10).

Harms

In the Asian study (2), the proportion of patients experiencing at least one treatment emergent adverse event (TEAE) was slightly lower in the DHA+PQP group (69.4%) than in the AS+MQ group (72.4%); the difference was not statistically significant. The most frequently reported TEAEs (related and unrelated) in the DHA+PQP and AS+MQ groups, respectively, were headache (18.0% vs 20.2%; $P = 0.364$), malaria (14.5% vs 22.6%; $P = 0.001$), P. falciparum malaria (13.4% vs 15.2%; $P = 0.409$) and pyrexia (10.6% vs 11.3%; $P = 0.769$). There were 12 serious TEAEs (1.6%) in the DHA+PQP group and three (0.8%) in the AS+MQ group, including one case of encephalitis that was probably related to MQ. Mild QTc interval prolongation was reported as a TEAE in 5.6% of the DHA+PQP group vs 3.2% of the AS+MQ group. The change in QTc from baseline to day 2 between treatments was statistically significant; by day 7, the QT prolongation was completely resolved. In the African study (3), the proportion of patients experiencing at least one TEAE was similar in the two treatment groups – 79.3% (DHA+PQP) vs 80.6% (A+L); $P = 0.550$. Serious TEAEs were similar in the two groups – 1.7% (DHA+PQP) vs 1.0% (A+L) ($P = 0.249$), respectively, as were the related STEAEs – 1.5% (DHA+PQP) vs 0.8% (A+L) ($P = 0.332$). Mild QTc prolongation was reported as a TEAE in 2.5% of DHA+PQP-treated and 2.6% of A+L treated patients. No arrhythmias were reported during the study. A study designed to investigate further the QTc interval effects of DHA+PQP observed in the phase III studies showed that the QTc prolongation observed at the end of the treatment with DHA+PQP administered with a high- or low-calorie diet is significantly reduced when the drug is given with water in fasting conditions (11). The Summary of Product Characteristics were consequently modified to state that DHA+PQP should be administered with water and without food. The safety and efficacy of DHA+PQP in children aged less than 6 months or weighing less than 5 kg have not yet been evaluated.

Additional evidence

A randomized trial compared the efficacy and safety of four artemisinin-based treatments for malaria in 3428 women in the second or third trimester of pregnancy (7). DHA+PQP demonstrated the best efficacy, with an overall PCR-adjusted cure rate at day 63 of 99.2% (95% CI 98.2–99.6) vs 94.8%, 98.5% and 96.8% for A+L, AS+AQ and AS+MQ, respectively. The safety profile of DHA+PQP was acceptable, and fewer adverse events were reported in the DHA+PQP group than in the AS+AQ and AS+MQ groups.

Cost / cost effectiveness

Ex-factory prices for DHA+PQP (40 mg + 320 mg, pack of 12 tablets) range from €28.56 to €41.59 in countries of the European Union (EU). Average ex-factory prices of DHA+PQP (40 mg + 320 mg, pack of 9 tablets) commercialized in 12 African countries range from €2.74 to €3.42. Median supplier price for A+L (20 mg + 120 mg) is reported as US$ 0.1703 per tablet/capsule (treatment course of 24 tablets/capsules for adults). The application claims that the greater effect of DHA+PQP in protecting against reinfection compared to artemether+lumefantrine will yield significant cost effectiveness benefits.

WHO guidelines

The 2015 WHO Guidelines for the treatment of malaria (12) recommend DHA+PQP as an ACT option for the first-line treatment of uncomplicated P. falciparum malaria worldwide (strong recommendation, high-quality evidence). The guidelines also recommend use of ACTs to treat uncomplicated P. falciparum in pregnant women in the second and third trimesters. Due to limited data on the safety of artemisinin derivatives in early pregnancy, quinine + clindamycin is recommended in the first trimester.

Availability

On 9 October 2015, DHA+PQP, manufactured by Sigma-Tau, Italy, achieved WHO prequalification status. DHA+PQP is marketed in some African, Asian and EU countries. In addition, the product has been sold through governmental agencies and non-profit organizations.

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