Artesunate + pyronaridine tetraphosphate

Statut de médicament essentiel

Section: 6. Anti-infective medicines > 6.5. Antiprotozoal medicines > 6.5.3. Antimalarial medicines > 6.5.3.1. Antimalarial medicines > For curative treatment

EMLc | Codes ATC: P01BF06

Indication	Malaria due to Plasmodium falciparum Code ICD11: 1F40
INN	Artesunate + pyronaridine
Type de médicament	Biological agent
Type de liste	Liste de base (EML) (EMLc)
Formulations	Oral > Solid: 60 mg + 180 mg tablet ; 20 mg + 60 mg granules (EMLc)
Historique des statuts LME	Ajouté pour la première fois en 2017 (TRS 1006)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Restriction de poids	> 5 kg
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 + pyronaridine tetraphosphate
DrugBank	Artesunate, Pyronaridine tetraphosphate (Pyronaridine)

Recommandation du comité d'experts

The Expert Committee recommended the addition of a fixed-dose combination formulation of artesunate and pyronaridine tetraphosphate to the core list of EML and EMLc as an artemisinin-combination treatment option for the first-line treatment of uncomplicated Plasmodium falciparum and for the blood stages of P. vivax malaria in adults, children and infants, on the basis of a favourable benefit–risk ratio. Availability of this FDC will provide an alternative treatment option to mefloquine- or amodiaquine-containing combinations. The Committee considered that that the availability of FDC formulations for treatment of malaria can offer the benefits of greater dosing accuracy, ease of administration and reduced pill burden and can contribute to better therapeutic adherence.

Contexte

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).

Pertinence pour la santé publique

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 declined to 214 million (range 149–303 million), and the number of deaths to 438 000 (range 236 000–635

000). The number of malaria deaths in children aged under 5 years had declined to 306 000 (range 219 000–421 000) in 2015. The global burden of mortality is dominated by countries in sub-Saharan Africa. Decreases in case incidence and mortality rates were slowest in countries that had the largest numbers of malaria cases and deaths in 2000 (1).

Bénéfices

The application presented the results of three phase 3 clinical trials of artesunate + pyronaridine (A+P) compared with AS+MQ (2), and A+L (3, 4) in a total of 2803 children and adults with acute, uncomplicated P. falciparum malaria in Africa, south-east Asia and India. The primary end-point was polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response (ACPR) on day 28 in the efficacy-evaluable (EE) population. Non-inferiority to the relative comparators was assumed if the lower limit of the two-sided 95% confidence interval (CI) for the difference in PCR-adjusted ACPR was greater than −5% (2, 3) or greater than −10% (4). For the comparison with AS+MQ, results at day 28 showed PCR-adjusted ACPR rates of 99.2% (95% CI 98.3–99.7%) and 97.8% (95% CI 95.8–99,1%). The treatment difference was 1.4% (95% CI 0.0–3.5%; P = 0.05), meeting the predefined criteria for non-inferiority. Non-inferiority was also met for the comparisons with A+L. The PCR-corrected ACPR rates at day 28 for A+P and A+L were: 99.5% and 99.2% (difference= 0.3%; 95% CI --0.7% to 1.8%;P = 0.578), and 97.1% and 98.8% (difference = −1.8%%; 95% CI −4.3% to 1.6%; P = 0.22). In addition, A+P was found to be non-inferior to the comparator treatments for the secondary end-point of PCR-adjusted ACPR at 42 days. New infection or recrudescence rates based on Kaplan–Meier estimates were statistically significantly lower with A+P compared with AS+MQ through day 42 (P = 0.049). For the comparison with A+L, no statistically significant difference was found between groups through day 28 or day 42 (2–4). In an integrated analysis of all A+P and comparator groups of phase 3 patients, the intention-to- treat (ITT) population was considered the primary analysis population, in contrast to the individual studies, given the variability of the EE population criteria across studies. No notable differences in PCR-adjusted ACPR were observed between the P+A group and the A+L or AS+MQ treatment groups at any time point in the ITT population (5).

Torts

The safety database for the phase 2/3 A+P clinical programme included 3017 subjects who received at least one dose of A+P across seven phase I, two phase II, and five phase III studies or, in the case of the mass balance study, pyronaridine alone. The adverse event profile of A+P in the individual studies and in the integrated analysis of all phase 2/3 studies was consistent with profiles reported for pyronaridine and artemisinins as monotherapy (7–10). The most common adverse events were headache (3.0%), eosinophilia (2.5%), neutropenia (1.9%), anaemia (1.6%), increased platelet count (1.4%), vomiting (2.2%) and abdominal pain (1.4%), bradycardia (1.1%), transaminase increases (1.6% alanine aminotransferase/1.8% aspartate aminotransferase) and hypoglycaemia (1.0%). Transient elevations in hepatic transaminase levels were a notable finding associated with A+P (5). However, early onset (day 3–7) and rapid resolution of the transaminase elevations appear consistent with a direct, low-level toxicity. The risk of progressive liver injury with a 3-day course of treatment is likely to be low. Artesunate + pyronaridine has been administered to patients who have had repeated episodes of malaria, and tolerability on repeat dosing (at intervals as short as 28 days) has been shown to be similar to that on first administration. Where transient elevations in alanine aminotransferase occurred, the adverse event profile was similar with repeat administration for both adults and children (11). Overall, changes in liver function tests due to drug-induced liver injury were mainly mild, with a small number of moderate cases (based on peak total bilirubin levels); the criteria were those of the Drug-Induced Liver Injury Network (12). No cases of liver failure or encephalopathy were observed. There was no evidence of coagulopathy or of a delayed effect.

Preuves supplémentaires

Data for A+P from six randomized controlled trials enrolling 3718 children and adults were included in a Cochrane systematic review (13). In two multicentre trials, enrolling mainly older children and adults from west and south-central Africa, there were fewer than 5% PCR-adjusted treatment failures at 42 days with both A+P and A+L, with no differences between groups (1472 participants, low-quality evidence). Fewer new infections at 28 days were observed in patients given A+P (risk ratio (RR) 0.60; 95% CI 0.40–0.90; 1720 participants; moderate-quality evidence), but no difference was detected at 42 days (1691 participants; moderate-quality evidence). In one multicentre trial, enrolling mainly older children and adults from south-east Asia, PCR-adjusted treatment failures were 6% by day 42 for A+P and 4% for AS+MQ (RR 1.64; 95% CI 0.89–3.00; 1116 participants; low-quality evidence). Fewer new infections at 28 days were observed in patients given A+P (RR 0.35; 95% CI 0.17–0.73; 1720 participants;

moderate-quality evidence), but no differences were detected at 42 days (1146 participants; low-quality evidence). This review found serious adverse events to be uncommon in the trials, with no difference detected between treatments. The analysis of liver function tests showed biochemical elevations were four times more frequent with A+P than with the other antimalarial treatment (RR 4.17; 95% CI 1.38–12.62; four trials; 3523 participants; moderate-quality evidence).

Rapport coût/efficacité

Costs excluding delivery, cargo insurance and tax from country of origin in public sectors: Tablet (A+P): 60 mg + 180 mg; US$ 0.60–2.40 per treatment, according to weight band Granule (A+P): 20 mg + 60 mg; US$ 0.44–1.33 per treatment, according to body weight Tablet (A+L): US$ 1.34–1.58 per treatment, according to body weight Tablet (AS+MQ): US$ 0.46–0.76 per treatment, according to body weight.

Directives de l'OMS

The 2015 WHO Guidelines for the treatment of malaria do not currently recommend A+P for general use (conditional recommendation) (14). The Guidelines Development Group considered that the data for A+P, based on the Cochrane systematic review (13) were promising, but that a recommendation for general use was not possible at the time. The Group noted that: - A+P may be as effective as A+L and AS+MQ in adults and older children. - Current evidence for young children (under 5 years) is insufficient to conclude that A+P is as effective as alternative treatments. - Elevations in liver function tests occurred four times more frequently with A+P as with alternative treatments. - The overall quality of evidence for the critical outcomes was moderate.

Disponibilité

A+P tablets and granules are included on WHO's list of prequalified medicines following a positive opinion under Article 58 by the European Medicines Agency. Both tablets and granules are undergoing national approvals in malaria-endemic countries, and some African and Asian countries have already approved the product.

Autres considérations

N/A

Considérations relatives à la mise en œuvre

N/A

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