

QSM/MC/IEA.117

4 March 2008

## Information Exchange System

### Alert No. 117

#### **Antimalarial chlorproguanil-dapsone (LapDap™) withdrawn following demonstration of post-treatment haemolytic anaemia in G6PD deficient patients in a Phase III trial of chlorproguanil-dapsone-artesunate (Dacart™) versus artemether-lumefantrine (Coartem®) and confirmation of findings in a comparative trial of LapDap™ versus Dacart™**

GlaxoSmithKline (GSK) and Medicines for Malaria Venture (MMV) have decided to terminate the further development of Dacart™, a fixed-dose combination antimalarial product of chlorproguanil, dapsone and artesunate (CDA). GSK has also commenced a product recall process at pharmacy level in Kenya, for LapDap™, another anti-malarial product containing chlorproguanil and dapsone (CD). These decisions are based on data from two Phase III clinical trials assessing the efficacy and safety of CDA (Dacart™) and CD (LapDap™); significant reductions of haemoglobin levels in patients with G6PD deficiency have been observed with both CDA and CD.

### Background information

#### **Chlorproguanil-dapsone (LapDap™)**

This product was granted a marketing authorization in July 2003 by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of uncomplicated falciparum malaria. Chlorproguanil-dapsone (CD) was contraindicated in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency. In view of the potential widespread use of CD (LapDap™) in malaria endemic sub-Saharan Africa, the high prevalence of G6PD deficiency in the region (estimated to affect around 10-25% of the population in sub-Saharan Africa) and the limited availability of screening tests for this genetic condition in Africa, WHO had undertaken a safety assessment of the product in 2004, to provide recommendations on the safe use of CD (LapDap™) in Africa.

The WHO expert group cautioned against the use of the medicine in G6PD deficient patients and made the following recommendations:

1. This medicine should be used only if a diagnosis of malaria is confirmed.
2. CD should be used only after severe anaemia (haemoglobin concentration < 5 g/dl) and

منظمة الصحة العالمية • 世界卫生组织

Organisation mondiale de la Santé • Всемирная организация здравоохранения • Organización Mundial de la Salud

G6PD deficiency have been excluded by appropriate tests. In patients with a haemoglobin concentration of 7 g/dl, administration of CD should be considered with caution and should be undertaken only under clinical supervision, with monitoring of the haemoglobin concentration. The diagnosis of methaemoglobinaemia is less important.

3. In areas where G6PD deficiency is prevalent but appropriate tests are not available, an alternative antimalarial medicine should be used.
4. If there is no suitable alternative, CD should be used but in cognizance of the haematological risks associated with this medicine.

The group also advised that these recommendations should be reconsidered when more data become available from pharmacovigilance and active post-marketing surveillance.

The WHO safety assessment report also provided a series of recommendations for ongoing and planned clinical trials as well as phase IV studies to gather the necessary evidence on safety of CD (LapDap™), including in malaria patients with G6PD deficiency. However, several CD (LapDap™) phase IV studies which started in African countries did not continue beyond April 2006 due to low utilization of this medicine. Research on the safety aspects mainly continued as part of the Medicines for Malaria Venture (MMV)- sponsored studies on chlorproguanil-dapsone-artesunate (CDA).

### **Chlorproguanil-dapsone-artesunate (Dacart™)**

GSK's multi-center, double-blind Phase III clinical trial of chlorproguanil-dapsone-artesunate (CDA) versus the combination antimalarial lumefantrine-artemether (Coartem®) in Africa suggest a strong association between haemolytic anaemia and CDA treatment for uncomplicated falciparum malaria in G6PD deficient patients. The study included 1372 patients. Study results showed a significant reduction in haemoglobin due to haemolytic anaemia in patients with G6PD deficiency, with lowest levels of haemoglobin occurring seven days after treatment. At day 7, 35% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 2 g/dl compared to 8% of patients treated with Coartem®, and 10% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 4 g/dl compared to 0% of patients treated with Coartem®. 38% of the male patients with G6PD deficiency had severe anaemia after treatment with CDA, compared to 0% in the group treated with Coartem®. In total, 15 patients had severe post-treatment haemolysis requiring blood transfusion in the study: all 15 were in the CDA treated group, 13 of whom were G6PD deficient.

### **References:**

1. Press Release. GlaxoSmithKline and Medicines for Malaria Venture, 29 February 2008, London, UK; Geneva, Switzerland.
2. Review of the safety of chlorproguanil-dapsone in the treatment of uncomplicated falciparum malaria in Africa: Report of a Technical Consultation convened by the World Health Organization. WHO, 2005, Switzerland (<http://www.who.int/malaria/docs/LapDap.pdf>).