

**Review of the  
safety of  
chlorproguanil–dapson  
in the treatment of  
uncomplicated  
falciparum malaria  
in Africa**

REPORT OF A  
TECHNICAL CONSULTATION  
CONVENED BY WHO

*Geneva, 1–2 July 2004*



**World Health  
Organization**

**Review of the  
safety of  
chlorproguanil–dapson  
in the treatment of  
uncomplicated  
falciparum malaria  
in Africa**

REPORT OF A  
TECHNICAL CONSULTATION  
CONVENED BY WHO

*Geneva, 1–2 July 2004*



**World Health  
Organization**

© World Health Organization 2005

All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

Designed by minimum graphics  
Printed in Switzerland

# Contents

Foreword	v
Executive summary	1
1. Introduction	3
2. Review process	5
3. Background information	6
3.1 Formulations	6
3.2 Indications for use	6
3.3 Pharmacological aspects of the individual drug components	6
3.3.1 Mechanism of action and development of resistance	6
3.3.2 Drug disposition	7
3.3.3 Adverse effects	9
4. Review	12
4.1 Statement of issues	12
4.2 Presentations and discussions	13
4.2.1 Review of preclinical toxicology of chlorproguanil–dapsone	13
4.2.2 Review of the toxicity of chlorproguanil–dapsone in clinical trials	13
4.2.3 Review of the clinical efficacy of chlorproguanil–dapsone	17
4.2.4 Risk–benefit analysis of chlorproguanil–dapsone	18
4.3 Review of ongoing and planned phase-IV studies of Lapdap	19
5. Conclusions and recommendations	20
Experts and authors of the report	25
References	27
APPENDIX I. Terms of reference for the review of the safety of chlorproguanil–dapsone (Lapdap), organized by the WHO Roll Back Malaria department in collaboration with the Essential Drugs and Medicines department	30
APPENDIX II. List of reports, publications and other materials reviewed	35



# Foreword

Resistance to antimalarial medicines has spread and intensified over the past 15 years, leading to a dramatic decline in the efficacy of the most affordable products available. In order to ensure high cure rates and delay the emergence of resistance to new treatments, WHO now recommends the use of combination therapies, preferably containing artemisinin derivatives, as first-line treatment of falciparum malaria. The rapid loss of many antimalarial medicines due to resistance has necessitated, more than ever before, the development of medicines that are effective against malaria and safe for use in populations at risk for this disease.

Chlorproguanil–dapson (Lapdap™) is a new antimalarial medicine developed and registered in the United Kingdom and Africa and currently available for use in African countries. The safety of medicines, particularly those that may be used on a large scale, as for malaria, is an important concern of WHO. Accordingly, WHO convened a Technical Consultation to review the safety of chlorproguanil–dapson for use in Africa.

The recommendations of the Technical Consultation have been made on the basis of data on safety and efficacy of chlorproguanil–dapson available for regulatory approval and information from other sources.\* The most important practical implication of the recommendations of this report is that, in areas where glucose-6-phosphate dehydrogenase (G6PD) deficiency is prevalent, use of an antimalarial medicine other than chlorproguanil–dapson should be considered. If no suitable alternative medicine is available and if the G6PD status of the patients is unknown, chlorproguanil–dapson should be used only under medical supervision to ensure patients' safety.

Further information on the safety of chlorproguanil–dapson is required and is being sought in post-registration surveillance and pharmacovigilance as well as studies being conducted or sponsored by several organizations, including WHO. The studies are designed to evaluate effectiveness and safety under operational conditions in populations in Africa, including vulnerable groups such as pregnant women, persons infected with HIV and patients with G6PD deficiency. A combination of this medicine with artesunate could be a potentially valuable addition to the available artemisinin-based combination therapies. A fixed-dose combination of chlorproguanil–dapson–artesunate is already in an advanced stage of development, and this programme will also generate additional information on the safety of chlorproguanil–dapson.

---

\* The full list of documents that were available to the review committee can be found in APPENDIX II.

Any action by health authorities regarding the use of chlorproguanil-dapsone should be based on up-to-date scientific evidence. WHO, together with the relevant responsible organizations, will review the safety of chlorproguanil-dapsone as additional data become available.

A handwritten signature in black ink, appearing to read 'Lepakhin', with a long horizontal stroke extending from the bottom of the name.

**Dr V.K. Lepakhin**  
Assistant Director-General  
Health Technology and  
Pharmaceuticals

A handwritten signature in black ink, appearing to read 'J. Chow', with a long horizontal stroke extending from the end of the name.

**Dr J. Chow**  
Assistant Director-General  
HIV/AIDS, TB and Malaria

# Executive summary

WHO convened a technical consultation to review the current status of safety and efficacy of chlorproguanil–dapsone (CD). The aim of the review was to provide national health authorities with interim recommendations on use of this medicine in the treatment of uncomplicated falciparum malaria in Africa, until more data become available.

The recommended doses of CD are effective in children aged 3 months to 12 years with uncomplicated falciparum malaria. CD appears to have therapeutic efficacy in areas where falciparum parasites resistant to sulfadoxine–pyrimethamine (SP) are encountered, but additional tests with 28-day follow-up and comparative trials with alternatives to SP are needed to provide a clear definition of the benefits of CD for the treatment of uncomplicated falciparum malaria. As the pharmacodynamics of CD is similar to that of SP, it is important to assess the impact of increasing levels of resistance to SP on the useful therapeutic life of CD in Africa.

Although the development of resistance to this medicine is relevant, its safety is of greater concern, because CD, like many other antimalarial drugs, is likely to be taken by large numbers of patients with febrile illnesses, many of whom might not have malaria but who are treated for this condition because of lack of laboratory confirmation. According to the marketing authorization of the medicine in the United Kingdom, it is contraindicated in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency. This raises questions about its role in areas with a high prevalence of G6PD deficiency but a limited capacity for patient screening.

The main difference between the safety profiles of CD and SP in the studies reviewed was the incidence of haematological adverse effects, notably anaemia and methaemoglobinaemia. Randomized clinical trials involving children showed significantly greater haemoglobin reductions in the group receiving CD than in that given SP on day 7, although there was no difference from baseline by day 14. Decreases in haemoglobin concentration by  $> 2$  g/dl were more likely to occur in patients receiving CD who were G6PD-deficient, owing to the known effects of dapsone in such patients.

Falciparum malaria is potentially life-threatening, particularly in children. If it is not treated rapidly with effective antimalarial medicines, it causes death and considerable morbidity in all age groups. The number of available antimalarial medicines that are still effective in Africa is limited. Therefore, the risk–benefit ratio of CD might be considered to be acceptable, provided that the following recommendations are implemented:

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 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.

These recommendations will be reconsidered when more data become available from pharmacovigilance and active post-marketing surveillance.

The pharmacology of the CD components indicates that certain subpopulations might be at higher risk for serious adverse effects than others. Greater experience and more information on the safety of this medicine are needed, in particular in relation to G6PD status, the presence of renal or hepatic diseases, pregnancy, HIV/AIDS, the elderly, malnutrition, haemoglobinopathy and specific cytochrome P450 polymorphisms and acetylator status. Studies addressing some of these issues are in progress.

# 1. Introduction

The antimalarial medicine chlorproguanil–dapson (CD), also known under the proprietary name ‘Lapdap’, was developed in a collaboration between GlaxoSmithKline (GSK) and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), with financial support from the United Kingdom Department for International Development. The idea of combining chlorproguanil with dapson originated from studies performed in East Africa in the 1980s. Chlorproguanil was developed initially for malaria prophylaxis and marketed as Lapudrine™. Dapson, more widely known for its use in leprosy, also has antimalarial activity and was used in prophylaxis in combination with pyrimethamine. Chlorproguanil and dapson act synergistically on enzymes in the folate pathway, i.e. dihydrofolate reductase and dihydropteroate synthase. Studies in vivo and in vitro suggested that CD could have advantages over sulfadoxine–pyrimethamine (SP) in the treatment of falciparum malaria.

The medicine was granted a marketing authorization by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) in July 2003 for the treatment of uncomplicated falciparum malaria in children of at least 5 kg body weight, adolescents and adults. It is proposed primarily for treatment of patients in malaria-endemic regions of Africa.

WHO currently recommends that countries endemic for falciparum malaria adopt and use artemisinin-based combination therapies, because: they result in rapid clinical and parasitological cure, there is as yet no documented parasite resistance, they reduce gametocyte carriage rate, and they are generally well tolerated (WHO, 2001). Because of its relatively short half-life and low production cost, CD is a potential candidate for use in combination with an artemisinin compound, and TDR is collaborating with several stakeholders in developing chlorproguanil–dapson–artesunate. Evaluation of the safety of CD before its potential widespread, uncontrolled use is essential for the development of chlorproguanil–dapson–artesunate for public health use.

In view of the short interval between the registration of this medicine in the country of origin (United Kingdom), its marketing in a number of malaria-endemic countries in Africa at a relatively low price, and its potential widespread use, WHO has undertaken this assessment of its safety and efficacy in order to provide recommendations on its safe use. The MHRA considered that CD was contraindicated in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency, a condition which is highly prevalent in sub-Saharan Africa. There was therefore an urgent need for WHO advice to malaria-endemic countries. This guidance is provisional and subject to revision when more

evidence becomes available from post-marketing surveillance and phase-IV studies.

The target audiences of this report are national health authorities, particularly those responsible for malaria treatment policy, nongovernmental organizations and health professionals who treat patients with malaria in both the public and private sectors in the endemic countries of Africa, where this medicine is being marketed.

## 2. Review process

The Roll Back Malaria (RBM) and Essential Drugs and Medicines (now Medicines Policy and Standards) departments of WHO convened a technical consultation in Geneva on 1–2 July 2004 to assess the risks and benefits of using CD in malaria-endemic countries in Africa. The participants were nine independent experts (see list below) with complementary competencies to cover the terms of reference (TORs), which were prepared by the WHO secretariat before the meeting and approved by the consultation (*see* APPENDIX I).

Before the meeting, full reports of preclinical toxicological studies and formal clinical studies with chlorproguanil and dapsone alone or in combination were made available to the participants. These included published studies and reports that had already been accepted and evaluated by regulatory agencies. They comprised most of the data<sup>1</sup> available to WHO, the United Kingdom MHRA and the manufacturer, GSK, who generously permitted use of their proprietary information. The full list of documents that were available to the review committee is presented in APPENDIX II.

Specific topics were assigned to one or two members of the committee, who prepared a working paper or presentation for in-depth discussion in plenary, with the objective of reaching consensus among all reviewers. The presentations and discussions are summarized in section 4.2. Then, the meeting prepared recommendations in response to the questions formulated in the TORs.

The draft report of this meeting was reviewed by TDR, MHRA, GSK and the scientists who had taken part in the product development team. WHO then recruited an independent expert (Professor U. Hellgren) to review all the comments received and to make recommendations to WHO on the report. Finally, on 13–14 January 2005, a subgroup of four members of the technical consultation, selected by the Chairperson, was convened to finalize the report on the basis of all the comments and recommendations received. After approval of the document by the five remaining experts who had attended the technical consultation in July 2004, further input from TDR and assessment by the Office of the WHO Director-General, the report was considered final and the review process concluded. The process undertaken does not imply endorsement of the report by the groups and agencies that provided comments to WHO.

---

<sup>1</sup> All documents requested from GSK were provided, except for the report of a study on effects on postnatal development in rats, which was mentioned in the expert review of preclinical studies of Lapdap but was not available to the reviewers owing to the lateness of the request to GSK. Also not available were the replies of GSK to the MHRA to specific questions about drug resistance, post-marketing surveillance in Africa and G6PD labelling. The latter were kindly provided to the review committee by MHRA during the meeting itself. The MHRA's clinical assessment report was provided to the reviewers.

## 3. Background information

### 3.1 Formulations

Lapdap tablets contain chlorproguanil hydrochloride and dapsone in a fixed ratio of 2:2.5. They are available as low-dose tablets (15:18.75 mg, white) and as higher-dose tablets (80:100 mg, pink). The tablets are uncoated, with a break-line on one side.

### 3.2 Indications for use

CD is schizonticidal in action and is indicated for the treatment of uncomplicated *Plasmodium falciparum* infections in children weighing at least 5 kg, adolescents and adults. The target dose is based on administration of 2 mg/kg chlorproguanil and 2.5 mg/kg dapsone once daily for 3 consecutive days, up to a maximum daily dose of 160 mg chlorproguanil and 200 mg dapsone for patients weighing  $\geq$  60 kg.

### 3.3 Pharmacological aspects of the individual drug components

#### 3.3.1 Mechanism of action and development of resistance

Dapsone, or diaminodiphenylsulfone, acts against bacteria and protozoa in the same way as sulfonamides, by inhibiting the synthesis of dihydrofolic acid by competition with *para*-aminobenzoate for the active site of dihydropteroate synthase. It therefore acts synergistically with dihydrofolate reductase inhibitors like proguanil, chlorproguanil and pyrimethamine.

The resistance of *P. falciparum* to pyrimethamine is due to simple point mutations of the gene encoding for the enzyme dihydrofolate reductase (*dhfr*) (Basco et al., 1995; Plowe et al., 1996), and similar mutations in the genes encoding for the enzyme dihydropteroate synthase (*dhps*) govern resistance to sulfadoxine (Brooks et al., 1994). SP was originally an effective antimalarial agent; resistance to it first developed in Southeast Asia after a few years of wide-scale use. Today, high levels of SP resistance are found in large parts of the world, including countries in Eastern and Southern Africa (Bredenkamp et al., 2001; East African Network for Monitoring Antimalarial Treatment, 2003)

When the parasite has become virtually insensitive to pyrimethamine due to serial triple mutations (ser-108-asn, asn-51-ile and cys-59-arg) in the *dhfr* gene, chlorproguanil is still active. There is reason to believe that mutations in the *dhps* gene occur only after the *dhfr* mutations manifest. *P. falciparum* becomes insensitive to CD only when a fourth mutation, at position leu-164 of the *dhfr* gene, has occurred, resulting in the pattern ser-108-asn, asn-51-ile, cys-59-arg and ile-164-leu. This pattern of *dhfr* mutations is widely present in South America and Southeast Asia, with high failure rates with biguanide-

dapsone combinations documented in Thailand (Wilairatana et al., 1997). This pattern of mutations has been reported at low frequency in travellers from Africa (Färnert et al., 2002) and in malaria patients in the United Republic of Tanzania (Hastings et al., 2002) but not in other studies in Africa (Ochong et al., 2003; Wichmann et al., 2003). A study in which a yeast-expression system was used to detect rare parasites with quadruple mutants, which is more sensitive than the standard polymerase chain reaction, did not provide evidence of the leu-164 mutation in isolates from 25 patients who had persistent parasitaemia on day 14 after treatment with either SP or CD (Bates et al., 2004), suggesting that the alleles that confer high levels of resistance to antifolates were rare in 2000 in five African countries: Gabon, Malawi, Kenya, Nigeria and the United Republic of Tanzania.

### **3.3.2 Drug disposition**

The studies of pharmacokinetics showed no major interactions between chlorproguanil and dapsone at the ratio and doses used to treat uncomplicated falciparum malaria.

#### **3.3.2.1 Disposition of dapsone**

Dapsone is slowly absorbed after oral administration. It then undergoes entero-hepatic recycling and is metabolized mainly in the liver, up to 15% being excreted unchanged. The absolute oral bioavailability of dapsone is calculated to exceed 85% (Pieters et al., 1987). The medicine is widely distributed throughout the tissues; it crosses the placenta, and 14% of a maternal dose reaches the newborn through breast milk (Brabin et al., 2004).

Approximately 50–80% of dapsone in the circulation and nearly 100% of the monoacetylated metabolite are bound to plasma proteins. The elimination half-life of dapsone is about 31 h, but there is large interindividual variation. The main routes of metabolism are acetylation and *N*-hydroxylation. Monoacetyldapsone is the major circulating metabolite; it has a half-life similar to that of dapsone (Zuidema et al., 1986) and no antimalarial activity. In contrast to sulfonamides, monoacetyldapsone can again be deacetylated to dapsone. Acetylation and deacetylation take place continuously, and a constant equilibrium is reached within a few hours. Acetylation is mediated by the *N*-acetyltransferase-2 enzyme, and the acetylation ratio (ratio of concentrations of monoacetyldapsone and dapsone) shows large interindividual variation owing to differences in the activity of *N*-acetyltransferase, which is genetically determined. The prevalence of the slow metabolizer phenotype in white and African populations is 40–60%.

*N*-hydroxylation to a hydroxylamine metabolite is the second pathway of dapsone metabolism and is considered to be responsible for dapsone-associated methaemoglobinaemia and haemolysis. *N*-hydroxylation is a major metabolic

pathway, as up to 40–50% of excreted dapsone can consist of the N-hydroxy metabolite. Hydroxylation is mediated by the cytochrome P450 enzyme system, which also shows genetic polymorphism, with rapid and slow metabolizers. Genetic factors are therefore likely to contribute to the toxicity of dapsone.

### 3.3.2.2 Disposition of chlorproguanil

Like proguanil, chlorproguanil is metabolized to the active metabolite that is responsible for its antimalarial activity, chlorcycloguanil, which is more active than cycloguanil. In patients with uncomplicated falciparum malaria, about 63% of chlorproguanil and 28% of chlorcycloguanil are bound in plasma. Conversion of chlorproguanil to its active metabolite is mediated partly by the polymorphic cytochrome P450 isozyme 2C19 (S-mephenytoin hydroxylase). The elimination half-lives in healthy adults given chlorproguanil (160 mg) and dapsone (200 mg) were 32 h for chlorproguanil and 33 h for chlorcycloguanil.

The high interindividual variation in cycloguanil formation is determined by genetic polymorphism of the isozyme. Reduced efficacy of chlorproguanil and proguanil can be expected in poor metabolizers, but the evidence is not clear (Skjelbo et al., 1996). The prevalence of poor metabolizers differs between ethnic groups, with low proportions of  $\pm 5\%$  among whites and Africans.

Late pregnancy and use of oral contraceptives impair formation of the active metabolite cycloguanil from the parent proguanil, which might be mediated by inhibition of 2C19 activity by estrogen (McGready et al., 2003). This inhibition probably also affects chlorcycloguanil (Wright et al., 1995).

### 3.3.2.3 Pharmacokinetics of chlorproguanil–dapsone

The pharmacokinetics of CD in adults with malaria is comparable to that in healthy adult volunteers, but peak concentrations of chlorproguanil and dapsone were achieved after 8 h in children with malaria and within 4 h in healthy adults.

Analyses of population pharmacokinetics in children and adults after oral administration of CD showed an apparent volume of distribution for dapsone ranging from 45 l in a 6-kg person to 109 l in a 98-kg person. The apparent volume of distribution for chlorproguanil is approximately 1900 l in both children and adults. Population pharmacokinetics showed increased clearance of both chlorproguanil and dapsone with increasing body weight (from 6 to 98 kg).

Elimination of chlorproguanil and dapsone occurs predominantly via metabolism. About 90% of a dose of dapsone is excreted (predominantly as metabolites) in urine, and 11% is excreted in faeces. About 45% of a dose of chlorproguanil is excreted in urine. There is considerable interindividual variation in the plasma concentrations of chlorproguanil, chlorcycloguanil, dapsone and monoacetyldapsone, which might be due partly to the effects of genetic polymorphism on the metabolism of chlorproguanil and dapsone. No studies of pharmacokinetics have been conducted in elderly persons or

in persons with renal or hepatic insufficiency, and the effect of food on the absorption of chlorproguanil or dapsone has not been evaluated.

### **3.3.3 Adverse effects**

#### **3.3.3.1 Adverse effects of dapsone**

Dapsone is an old drug. It has been used mainly in the treatment of leprosy (50–100 mg daily for years in adults, 1 mg/kg per day in children), dermatitis herpetiformis (100–200 mg/day for several months) and malaria in combination with pyrimethamine (100 mg once a week). Nevertheless, the effects of long-term administration of low doses (e.g. 1–2 mg/kg per day in leprosy treatment) might be different from those of the single higher doses recommended for malaria treatment. Although several millions of patients with leprosy have been treated with dapsone, experience in children under 5 years is limited. It is difficult to estimate the number of children under 5 who have been treated with dapsone for leprosy in Africa over the past few decades, but it probably does not exceed 10 000 (Dr D. Daumerie,<sup>1</sup> personal communication). The daily dose of dapsone in CD (2.3–4.7 mg/kg for children and 2.0–4.0 mg/kg for adults) is substantially higher than that used for most other approved indications (e.g. 1–2 mg/kg in the treatment of leprosy). Dapsone has been used in circumstances in which reporting systems were generally lacking. Consequently, there is little information about its safety in leprosy patients with G6PD deficiency.

The toxic dose of dapsone is close to its therapeutic dose. Severe poisoning has been observed after doses of 1 g in adults and 100 mg in children (International Programme on Chemical Safety, 1993). The most frequent adverse effects are haemolysis and methaemoglobinaemia. Haemolytic anaemia and agranulocytosis can occur with the relatively low doses used for leprosy treatment, whereas peripheral neuropathy and hepatitis have been observed only with the higher prolonged doses used in the treatment of dermatitis herpetiformis.

The life span of erythrocytes is reduced when the drug is taken, to a degree related to the dose and length of exposure. A fall of about 1 g/dl of haemoglobin occurred within 7 days of therapy in volunteers with normal erythrocyte concentrations who received dapsone at doses of 50–300 mg/day. Shortened erythrocyte survival is more marked in G6PD-deficient persons than in normal persons receiving the same daily dose of dapsone (Degowin et al., 1966). The commonest of the many variants of G6PD deficiency that have been identified over the past 40 years are clinically important, as they are associated with a risk for drug-induced haemolytic anaemia (Beutler, 1991). G6PD deficiency makes erythrocytes extremely sensitive to oxidative damage by reducing their capacity to regenerate glutathione. Administration of daily doses of 200 mg can cause severe haemolysis in individuals with fully expressed G6PD deficiency. In a study on 15 volunteers given doses of 25–300 mg of dapsone daily, G6PD-

---

<sup>1</sup> Dr D. Daumerie, WHO staff member responsible for leprosy elimination in WHO/HQ

deficient African-Americans were more susceptible to dapsone-induced haemolysis than whites without this deficiency; the haemolytic effect during short-term daily administration was dose-dependent (Degowin et al., 1966)

Methaemoglobin is formed in the reaction of *N*-hydroxylated metabolites of dapsone with oxyhaemoglobin, resulting in oxidation of iron from its ferrous to its ferric form and formation of dapsone-nitric oxide and reactive oxygen species. The dapsone-nitric oxide compound that is formed can be reduced back to *N*-hydroxylated metabolites of dapsone by glutathione, which is an important antioxidant and plays a major role in scavenging toxic hydroxylamine metabolites. The high incidence of toxicity due to sulfamethoxazole hydroxylamine metabolites in patients with AIDS has been explained by the low glutathione concentrations of these patients (Carr et al., 1993).

Persons with G6PD deficiency did not develop increased methaemoglobinaemia in a chemoprophylactic trial of dapsone (Willerson et al., 1972); however, these persons have a reduced capacity to detoxify the reactive oxygen species that are formed, leading to greater haemolytic activity (Jaeger et al., 1987). Haemolytic anaemia with the formation of Heinz bodies and reticulocytosis is common in cases of severe methaemoglobinaemia (Lambert et al., 1982). The role of methaemoglobin in the sequence of events leading to haemolysis is, however, subject to some controversy. Persons with certain types of haemoglobinopathy and methaemoglobin reductase deficiency are more susceptible to methaemoglobin formation and haemolysis than others (Ganer et al., 1981).

A variety of rare serious adverse reactions has been described, mostly in case reports of drug sensitization (Naisbitt et al., 1999). The reactions include peripheral neuropathy and several cutaneous reactions (exfoliative dermatitis, erythema multiforme, erythema nodosum and urticaria), which may be dose-dependent. Adverse reactions generally occur after several weeks of therapy with over 100 mg daily; however, a 'dapsone syndrome' was seen after only 4 weeks of dapsone-pyrimethamine (Grayson et al., 1988). Severe adverse reactions have been documented after treatment with dapsone (50 and 100 mg) in patients with inflammatory dermatoses who were slow acetylators and rapid hydroxylators (Bluhm et al., 1999). In this study, of 18 patients receiving dapsone for inflammatory dermatoses, two had adverse reactions within 48 h (i.e. after one dose of 50 mg and one dose of 100 mg): one had acute haemolytic anaemia and the other had acute confusional state. Both had to be withdrawn from the study. Four of the 18 participants had toxic reactions (neurotoxicity in two and haemolytic anaemia in two); all four were slow acetylators, and three were rapid hydroxylators, and the reactions were consistent with the toxic nature of dapsone hydroxylamine.

### 3.3.3.2 Adverse effects of chlorproguanil

There is less information about the safety of chlorproguanil than about that of dapsone. Chlorproguanil, and especially proguanil, has been used as an

antimalarial prophylactic for the past 35 years. Both agents have a good safety record, although most of the use of these drugs was before the era of good post-marketing surveillance. The most frequently mentioned adverse effects of proguanil are stomatitis and oral ulceration (Daniels, 1986).

The plasma concentrations of chlorproguanil do not increase significantly with doses higher than 2 mg/kg, but any marginal benefits of increasing dose are counterbalanced by unwanted effects such as nausea and vomiting.

## 4. Review

Although the development of resistance to CD is of major concern, its safety is of even greater importance, since, like many other antimalarial drugs, it is likely to be taken by large number of patients with febrile illnesses, many of whom may not have malaria.

### 4.1 Statement of issues

The main issues identified for the review are described below.

GSK markets CD only in Africa. The product has been registered in 21 African countries and submitted for registration in 12 other African countries (GSK, situation in October 2004). A very large number of people could thus potentially be exposed to the drug.

Falciparum malaria is rapidly becoming resistant to the antimalarial drugs, such as chloroquine, amodiaquine and SP, that have commonly been used to treat the disease. WHO currently recommends that countries endemic for falciparum malaria, in which these drugs are failing, review their treatment policies and adopt antimalarial drug combinations that include an artemisinin derivative (WHO, 2001). CD is not a constituent of these combinations; because of its relatively short half-life and low production cost, however, it is a candidate for use in combination with an artemisinin derivative.

At present, it is impossible to state the extent to which CD will find use in the treatment of malaria. As CD is pharmacodynamically similar to SP, it is important to understand the impact of the increasing levels of resistance to SP on the useful therapeutic life of CD. According to the United Kingdom marketing authorization, the drug is contraindicated for patients with known G6PD deficiency because it may induce haemolytic anaemia, which raises the question of the role of this drug in areas where there is a high prevalence of G6PD deficiency (WHO, 1989) and a limited capacity for patient screening. The drug regulatory authorities of several African countries have approved use of this medicine without this contraindication.

As for any newly registered medicine, with current regulatory standards, not many people (fewer than 3000 in this case) have received this drug in clinical trials; therefore, rare but serious adverse events might not have been detected. For instance, if the true frequency of a particular adverse event is 1/1000, then administering the drug to 3000 patients will result in a 95% chance of detecting at least one instance of that event, provided that appropriate methods for detection are used. Therefore, the data from the clinical trials available for this review are insufficient to detect a rare adverse event. For this reason, TDR is conducting and planning further research and pharmacovigilance to assess

the safety and effectiveness of the product in specific patient groups, including patients with G6PD deficiency, pregnant women and persons co-infected with HIV. This research is in its early phase, and generation of the necessary evidence will require at least 1–2 years.

The aim of the review is to evaluate critically the present status of the safety and antimalarial efficacy of CD, to serve as a basis for interim recommendations on its use in the treatment of uncomplicated falciparum in Africa, until more data become available.

## **4.2 Presentations and discussions**

### ***4.2.1 Review of preclinical toxicology of chlorproguanil–dapson***

The available preclinical studies were designed to investigate whether the toxicity of the combination differs from that of each of the two components. They are not designed to determine the dose at which no adverse effects are produced. In general, the studies in experimental animals confirmed general clinical experience with the two drug components. Studies in rodents showed that chlorproguanil potentiates the methaemoglobinaemia induced by dapson. There was no evidence of haemolysis, probably because the animals tested were not G6PD-deficient. No teratogenic effects were observed. Chlorcycloguanil has clastogenic activity *in vitro*, but, in view of the short duration of treatment (3 days), it is not likely to present a carcinogenic hazard. The margin of safety, as measured by the ratio of the concentrations of the drug in plasma that caused toxic effects in animals to those found at the therapeutic dose in humans, is low, in the range of 0.2–2.6. It was concluded that the combination of drugs in CD has the same pattern of toxicity as the individual drug components.

In view of the frequency of treatments that is to be expected in endemic areas, it was considered that more attention should have been given to the toxicity of repeated doses of CD. Most such studies were conducted in rabbits for 7 days and only in females. Although a 28-day study with repeated doses was performed in rats, this species cannot metabolize chlorproguanil to chlorcycloguanil. Furthermore, although the rats were treated with Lapdap or chlorcycloguanil separately, none were treated with the combination of dapson and chlorcycloguanil. No trend analysis was performed, and the power of the studies was low. The reviewers therefore considered that extrapolation of the results of the studies in animals for use as a guide to potential toxicity in patients with malaria is particularly questionable.

### ***4.2.2 Review of the toxicity of chlorproguanil–dapson in clinical trials***

A total of 2252 persons have been included in phase I–III clinical trials, but most of the data on safety are derived from the major phase-III study in children aged 1–10 years (Allouche et al., 2004). In this study, no difference was found in the numbers of children receiving CD and SP who had at least one adverse event (46%

vs 50%,  $n = 1480$  and  $370$ , randomization 4:1, respectively); however, adverse events considered probably or possibly related to treatment were significantly more common in the group receiving CD (11% vs 7%). The commonest drug-related adverse events in the children given CD were haematological disorders (5%) and gastrointestinal disorders (2%), while haematological disorders (2%) were commonest in the group given SP. The incidences of all other drug-related adverse effects were  $\leq 1\%$ .

Sixteen patients (1%) receiving CD and four (1%) receiving SP had at least one serious adverse event. The commonest were haematological disorders (including anaemia, haemolytic anaemia and haemolysis), affecting 10 and 1 patients in the respective treatment groups. These findings are common during treatment for acute falciparum malaria, but the difference between the groups receiving CD and SP merits consideration. The lack of prospective G6PD testing and of measurement of haemoglobin in all patients on day 3 limits assessment of the haematological safety of CD in the malaria patients enrolled in these studies. Although the proportion of patients lost to follow-up was low, further information on these patients was not available, which is a matter of concern.

#### **4.2.2.1 Review of the haematological toxicity of chlorproguanil–dapson**

Methaemoglobinaemia occurs regularly in patients treated with dapson, and its levels are dose-related (Carrazza et al., 2000). Methaemoglobin does not carry oxygen and therefore it worsens the consequences of anaemia. The concentration of methaemoglobin correlates well with symptoms in most cases (Hall et al., 1986).

The methaemoglobinaemia seen in the patients included in the trial conducted by Allouche et al. was considered mild according to the classification used by the authors (Carrazza et al., 2000); however, other classifications are available (Williams et al., 2005). Even a mild degree of methaemoglobinaemia can have clinical consequences in patients with severe anaemia.

In the double-blind multicentre clinical study in children (Allouche et al., 2004), methaemoglobin could be measured in only one of four centres. At this centre, in Kenya, 7% (22/320) of patients treated with CD and 0% (0/80) of those given SP had methaemoglobinaemia exceeding 10%, and 20% of CD-treated patients developed methaemoglobin values over 6%; the highest value seen was 19.7% in one child.

A greater concern is drug-induced haemolytic anaemia. In the Allouche et al. study, 12% of children given CD and 11% of those given SP had an appreciable drop in haemoglobin concentration between day 0 and day 7. In patients for whom there was clinical concern, the protocol allowed measurement of haemoglobin on day 3, and such concern was expressed for a total of 42 patients: 35 treated with CD (2.4%) and 7 with SP (1.9%). In this subsample, a difference in mean haemoglobin concentration of 1.3 g/dl was observed between the patients receiving CD (6.7 g/dl) and those given SP (8 g/dl). The

mean haemoglobin concentration on day 7 had decreased significantly more in the patients receiving CD (8.9 g/dl) than in those given SP (9.3 g/dl), from values on day 0 of 9.4 and 9.6 g/dl, respectively. The proportion of children who developed a reduction in haemoglobin concentration  $\geq 2$  g/dl on day 7 was 16% in both groups; the proportions who developed a reduction  $\geq 4$  g/dl were 3.4% in those given CD and 2.2% in those given SP (statistically nonsignificant). Severe anaemia emerging after treatment was observed in 13/1480 (0.9%) patients given CD and 0/370 given SP (statistically nonsignificant). The study was not powerful enough to evaluate differences in the occurrence of severe anaemia between the two treatment groups.

A large study of repeated treatment has been conducted in children aged 3 months to 6 years in Kenya and Malawi (Sulo et al., 2002). The target doses of chlorproguanil and dapsone were those recommended (2 mg/kg and 2.5 mg/kg), but a syrup was used instead of tablets. In part of the study conducted in Kilifi, Kenya, the extent of reduction in haemoglobin concentration between days 0 and 7 was greater with CD than with SP during the first four treatment episodes: episode 1: 0.65 g/dl vs 0.25 g/dl; episode 2: 0.69 g/dl vs 0.24 g/dl; episode 3: 0.64 g/dl vs 0.1 g/dl; episode 4: 0.83 g/dl vs 0.39 g/dl. The number of children at Kilifi who developed severe anaemia (haemoglobin < 5 g/dl) at any time during follow-up was greater in the group given CD (5.9%; 3/188) than in the group given SP (1.5%; 3/195) (statistically significant), but most cases of anaemia occurred before re-treatment (10 in the CD group and 1 in the SP group). Up to six new cases of infection per year were treated with CD, but this study was not designed to evaluate the safety of repeated sequential treatments with this combination.

Amukoye and colleagues (1997) compared haemoglobin concentrations on day 2 in 150 patients treated with CD and 150 treated with SP. CD was given as a suspension at 1.2 or 2.4 mg/kg per day. The haemoglobin concentration was 7.4 g/dl (95% confidence interval, 7.1–7.7) in the group given CD and 7.7 g/dl in the group given SP (95% confidence interval, 7.4–8.0)

The proposal to introduce dapsone, which is known to cause haemolysis, especially in G6PD-deficient patients, into this new combination targeted to Africa at a higher daily dose than that which is generally used must be preceded by specific studies to evaluate the risk of haematotoxicity. In the study by Allouche et al. (2004), the G6PD genotype was determined, when possible, for patients with a fall in haemoglobin concentration of 2 g/dl and evaluated by conditional logistic regression analysis. Patients with a fall in haemoglobin concentration > 2 g/dl or > 4 g/dl or with a haematological adverse event were identified and matched for age and sex with a control group with no fall in haemoglobin (nor a notable increase). Female patients who had a normal G6PD genotype were classified as 'normal', while those with deficient homozygotes and heterozygotes were classified as 'deficient'. Male patients were classified as 'normal' or 'deficient' hemizygotes. Table 1 shows that G6PD-deficient patients

are at greater risk for anaemia after CD treatment (odds ratio = 2.49;  $p < 0.001$ ) than after SP treatment (odds ratio = 0.89;  $p = 0.94$ ). The risk for having a  $> 4$  g/dl drop in haemoglobin concentration can be at least doubled in G6PD-deficient patients after CD treatment (odds ratio = 3.2;  $p = 0.02$ ).

**TABLE 1**  
**Glucose-6-phosphate dehydrogenase status of patients with a  $> 2$  or  $> 4$  g/dl fall in haemoglobin concentration or with an adverse haematological effect – study 001<sup>1</sup>**

Reduction in haemoglobin concentration (g/dl)	Chlorproguanil–dapson		Sulfadoxine–pyrimethamine	
	Deficient	Normal	Deficient	Normal
$> 2$	81 (35%)	149 (65%)	13 (23%)	43 (77%)
Control	40 (18%)	183 (82%)	16 (25%)	47 (75%)
$> 4$	22 (46%)	26 (54%)	3 (33%)	6 (67%)
Control	9 (21%)	34 (79%)	5 (36%)	9 (64%)

The data were analysed by conditional logistic regression, allowing for the effects of G6PD score, treatment group, country, baseline parasites and baseline temperature, forming a stratum for each matched set (study report 001). The analysis showed that G6PD patients taking CD were 10.4 times more likely to have a  $> 2$  g/dl fall in haemoglobin concentration than those with a normal G6PD score. G6PD-deficient patients who took SP were 2.9 times more likely to have such a drop (see TABLE 1). G6PD-deficient patients treated with CD were also more likely (3.6-fold) to have a  $> 2$  g/dl fall than those taking SP. Patients with a  $> 4$  g/dl fall in haemoglobin concentration were three times more likely to have a deficient G6PD score than the controls, but there was no significant treatment effect. Therefore, the risk for severe worsening of anaemia after CD treatment might be significantly increased in G6PD-deficient patients.

At the request of the local investigators in Gabon, testing for G6PD phenotype was introduced part way through the study because of concern about a drop in haemoglobin in some patients. At this study site, patients with known G6PD deficiency were thereafter excluded from the study. In the remaining study sites, no prospective G6PD testing was carried out, and the haematological data for the subsets of G6PD-deficient patients were not reviewed in detail (Allouche et al., 2004).

In the study by Allouche et al. (2004), the G6PD genotype was determined only where genotyping was available, for patients with a fall in haemoglobin concentration of 2 g/dl. The data should have been reported separately for

<sup>1</sup> Report 001 SB-433372/RSD-101LL2/1 A multicentre, double-blind, phase III study comparing the safety and efficacy of chlorproguanil/dapsone (daily for three days) versus sulfadoxine/pyrimethamine (single dose) in the treatment of uncomplicated falciparum malaria in children in Africa.

G6PD-deficient males (who are all hemizygous) and for homozygous and heterozygous G6PD-deficient females, as a significant proportion of the genetically heterozygous G6PD-deficient females are phenotypically normal, and grouping the data might have diluted the effect of G6PD deficiency. For the same reason, the sex ratios of patients and controls should have been presented, as they might have influenced the results. Genotyping by DNA analysis should have been complemented by erythrocyte phenotyping with a simple fluorescent spot test. The extent of the drop in haemoglobin concentration in G6PD-deficient hemizygous males and in homozygous-deficient and heterozygous-deficient females was not presented. In general, the analysis of answers to questions related to G6PD deficiency was considered inappropriate. Erythrocyte phenotyping to complement genotyping would have given a clearer picture of the haematological risks related to G6PD deficiency.

A fall in haemoglobin concentration > 4 g/dl could be life-threatening in an already anaemic child. In fact, the MHRA-approved Summary of Product Characteristics contraindicates use of CD in patients with severe anaemia. Haemoglobin concentrations that place a patient at risk of a drop to 5 g/dl should be considered contraindications for the use of CD. Thus, in patients with a haemoglobin concentration < 7 g/dl, CD should be administered with great caution.

#### **4.2.3 Review of the clinical efficacy of chlorproguanil–dapson**

The clinical trials were conducted almost entirely in children. The recommended doses of CD were effective in children aged 3 months to 12 years with uncomplicated falciparum malaria.

Review of the pivotal study (Allouche et al., 2004) showed that CD was more effective than standard therapy with SP in three of five countries, with cure rates on day 14 of 93–99% with CD and 79–94% with SP. In two countries in which the two drugs had similar therapeutic efficacy, the level of resistance to SP was low during the study period (2000). It was of concern that patients in the pivotal study were followed-up for only 14 days, as the longer the follow-up the greater the likelihood of detecting treatment failures. A follow-up of 28 days with polymerase chain reaction analysis for parasite genotyping to differentiate as far as possible between reinfections and recrudescences would have been preferable. A total of 46 (3%) patients treated with CD and 8 (2%) patients on SP were lost to follow-up. A cohort study of repeated treatment carried out in Kenya and Malawi between 1996 and 1999 with a syrup formulation, but with the same target doses, showed that CD was more effective than SP at both sites, with treatment failure rates of 4.3% vs 11.3% and 5.4% vs 20.5%. The incidence of malaria episodes during one year of follow-up was similar in the group given CD and that given SP, despite more rapid elimination of CD (Sulo et al., 2002).

Treatment failures with SP can be treated with CD. Although, in a recent study, the re-treatment failure rate was significantly lower than with SP, 7% of

patients treated with CD and 61% of those given SP were parasitaemic even on day 7 (Mutabingwa et al., 2001). In randomized trials, up to six new infections per year were treated with CD, but these studies were not designed to evaluate the safety of repeated sequential treatments with this combination (Sulo et al., 2002).

These results indicate that CD could be useful in areas where high levels of resistance to SP are prevalent; however, the high failure rates of biguanide–dapsone combinations reported in Thailand suggest that the usefulness of CD might diminish over time.

Additional studies, with an adequate, 28-day follow-up, are required to substantiate the safety and efficacy of CD for the treatment of uncomplicated falciparum malaria in endemic areas.

#### **4.2.4 Risk–benefit analysis of chlorproguanil–dapsone**

##### **4.2.4.1 Potential benefits accruing from the therapeutic efficacy of chlorproguanil–dapsone against sulfadoxine–pyrimethamine-resistant parasites**

All the evidence from the studies in the GSK regulatory dossier, the published studies in the literature and the recent Cochrane review show a consistent pattern of fewer treatment failures with CD than with SP. The differences were, however, small and uneven across different geographical areas. Lapdap maintains activity against strains of *P. falciparum* that have triple serial point mutations in *dhfr*, but the combination is no longer effective against parasites with the quadruple leu-164 mutation. SP exerts a strong selection pressure for resistance (Watkins et al., 1993), and there is concern that use of SP might reduce the useful therapeutic life of CD in Africa. It has been argued that CD could have an advantage over SP owing to its more rapid elimination, which would make CD less likely to select for drug-resistant parasites than SP. The lack of comparisons with other alternatives to SP makes it difficult to define the potential role of CD for treatment of uncomplicated falciparum malaria.

##### **4.2.4.2 Potential risks from adverse effects**

The evidence shows that haematological adverse events are more frequent with CD than with SP, and some of the events are potentially serious. Dapsone is associated with potentially dangerous adverse effects, and some haematological effects of dapsone, i.e. methaemoglobinemia and anaemia, are relatively common. Haemolysis can be severe in G6PD-deficient patients.

The pharmacology of CD components indicates that certain subpopulations might be at higher risk of severe adverse effects, in particular:

- patients with pre-existing anaemia,
- patients with G6PD deficiency and haemoglobinopathy,
- patients with HIV/AIDS,

- patients with malnutrition
- patients with renal and hepatic diseases
- potentially, some patients who are slow acetylators and rapid hydroxylators of dapsone

It should be noted that CD might be less effective in some patients who are poor metabolizers of chlorproguanil.

As for most newly developed medicines, no clinical data are available on the safety of CD in pregnant women or in infants weighing < 5 kg.

The available evidence indicates that the anticipated risks involved in exposing large populations to this drug without adequate appropriate screening or diagnosis exceed the potential benefits of Lapdap, although the overall effectiveness–risk relationship might be more favourable in areas where resistance to SP is high. More information on the safety and effectiveness of this medicine is required to fully assess its potential for widespread and probably unsupervised use in Africa.

Falciparum malaria is potentially life-threatening, particularly for children. If the disease is not treated rapidly with effective antimalarial medicines, it causes considerable morbidity and mortality in all age groups. Few antimalarial medicines with proven efficacy are still effective in Africa. Therefore, the available knowledge indicates that the risk–benefit relationship for CD can be considered acceptable, provided that the recommendations outlined below are implemented.

### **4.3 Review of ongoing and planned phase-IV studies of Lapdap**

The priorities identified for phase-IV studies were that they should be of adequate design and power to detect adverse drug reactions (expected frequency, < 1/500 in actual use), to add useful pre-marketing safety information and to provide evidence of drug effectiveness, including resistance. In addition, pharmacovigilance programmes must be established in countries where CD is to be used.

In order to evaluate the current standard CD regimen, further randomized controlled trials should be carried out, with follow-up to day 28, systematic recording of adverse events and use of an intention-to-treat analysis. Special attention must be given to patient populations who are at higher risk for adverse effects or low efficacy.

A group has been established under the auspices of TDR to plan and monitor the effectiveness and safety of CD in large post-licensure studies (phase IV). One phase-IV study has been completed, several are under way, and the remainder are about to start. The results of at least 30 000 CD treatments will be collated over the next 3 years, providing large-scale safety and effectiveness data.

# 5. Conclusions and recommendations

On the basis of the reviews and plenary discussions, the experts reached consensus on the recommendations below. The recommendations were finalized in a closed session of the meeting of the reviewers. For the sake of clarity, the recommendations are provided in the form of answers to specific questions.

The review was undertaken to guide potential use of CD on a wide scale for a common illness in Africa. Particular attention was paid to the G6PD-deficiency state, which is highly prevalent in Africa. According to the MHRA-approved labelling, the medicine is contraindicated for persons with this condition, if known.

The caution expressed below on the use of CD is necessitated by the lack of sufficient information to substantiate its safe and efficacious administration in the circumstances under which it is most likely to be used in Africa. The committee therefore emphasized that these recommendations should be reassessed when adequate information from pharmacovigilance and post-marketing studies becomes available.

The evidence base for the recommendations provided by the reviewers is outlined in various sections of the report: 3.3.2 for drug disposition, 3.3.3 for adverse events, 4.2.2 for toxicity in clinical trials and 4.2.2.1 for haematological toxicity.

## 1. With respect to the risk for anaemia:

### a. Do the safety concerns differ for children and for adults?

Children under 5 years of age are more likely than adults to be anaemic before getting infected with malaria. The malaria infection itself will often further reduce haemoglobin concentrations. If the treatment aggravates anaemia due to haemolysis, the severity of anaemia might be greater than in adults. Thus, use of a drug that can cause haemolysis could be more dangerous in young children than in adults with malaria.

### b. What is the clinical significance of the anaemia that might develop after treatment with CD?

The anaemia that might develop as a result of treatment with CD could be severe and life-threatening. If anaemia develops during treatment with CD, the medicine should be discontinued immediately and replaced with another effective antimalarial medicine.

Predisposing factors to severe anaemia after treatment with CD include:

- pre-existing anaemia,
- haemoglobinopathy,

- G6PD deficiency and
- malnutrition.

Drug-induced anaemia can be mistaken for malaria-induced anaemia. The two conditions can also occur concomitantly.

**c. How should patients with malaria and various levels of anaemia be treated with CD?**

Patients with a haemoglobin concentration  $< 5$  g/dl (i.e. severe anaemia) should not be treated with CD. Another effective antimalarial agent should be used.

In patients with a haemoglobin concentration  $< 7$  g/dl, administration of CD should be considered with great caution and it should be given only under close clinical supervision, with monitoring of the haemoglobin concentration. Treatment should be given in facilities where appropriate therapeutic action can be taken, including blood transfusion.

Dehydration can falsely elevate haemoglobin concentrations and should be taken into account in evaluating patients' blood picture.

**d. What is the clinical significance of the anaemia that might develop in patients with G6PD deficiency treated with CD for malaria, and what recommendations can be given for use of CD in these patients?**

As CD induces haemolysis in G6PD-deficient patients, the anaemia that might develop in such patients during treatment with CD for malaria could rapidly become severe, with serious clinical outcomes. CD should be given to G6PD-deficient patients only if the diagnosis of malaria is certain and if no other suitable alternative is available. Close clinical supervision is imperative.

**e. What is the clinical significance of the methaemoglobinaemia associated with CD treatment of malaria?**

Methaemoglobinaemia is of little clinical significance if the patient is not anaemic; however, it will worsen tissue hypoxia in all patients with anaemia.

**f. In countries endemic for malaria in Africa and other regions, where G6PD deficiency is prevalent, what are the recommendations for treatment of malaria with CD, in situations where it is not possible to provide a reliable clinical or laboratory diagnosis of anaemia, a test for G6PD deficiency or a diagnosis of methaemoglobinemia?**

This drug should be used only if a diagnosis of malaria is confirmed.

A diagnosis of methaemoglobinemia is less crucial than a reliable clinical or laboratory diagnosis of anaemia and testing for G6PD deficiency. CD should therefore be used only where there is reliable clinical or laboratory testing for anaemia and G6PD deficiency.

In areas where G6PD deficiency is prevalent and a reliable clinical or laboratory diagnosis of anaemia and a test for G6PD deficiency cannot be obtained, a suitable alternative to CD should be used. If there is no suitable alternative, CD should be used but taking into account all the associated risks .

The Summary of Product Characteristics approved by MHRA contraindicates the use of CD in patients with known G6PD deficiency but does not explicitly recommend G6PD testing prior to CD therapy. The Lapdap product monograph (GSK, 2003) states that “G6PD testing is not required before starting treatment with Lapdap”. The committee recommended that this statement be amended to read as follows: “In view of the haemolysis reported with CD, which can be severe in G6PD-deficient patients, testing for G6PD deficiency before giving Lapdap is recommended.” The recommendations for treatment with CD in areas without access to G6PD testing and haemoglobin determination are given below.

## **2. What is the expected dose-related toxicity of CD:**

### **a. in relation to the daily dose of dapsone?**

The dose of dapsone contained in CD is in the upper limit of the tolerated dose. Most previous experience with dapsone has been with lower doses but with longer treatment than the 3 days needed for treating malaria with CD. There is a direct relationship between dapsone dose and the extent of haematological adverse events. The recommendations for a simplified dosing regimen in relation to weight, as given in the GSK product monograph on CD for Africa, could lead to underdosing or overdosing.

### **b. with the repeated treatment courses to be expected in areas of intense transmission of malaria?**

In clinical trials, up to six new infections per year were treated with CD. Nevertheless, the available data are insufficient to form the basis for recommendations on the safety of repeated treatment with this medicine.

## **3. What is the expected risk to:**

### **a. the fetus of using CD during pregnancy?**

Fetuses are at known risk for haemolysis and methaemoglobinaemia when mothers are treated with dapsone. The risks would be greater if the fetus had G6PD deficiency. More information is needed on the use of CD in pregnancy.

### **b. the infant when CD is taken by the mother during the breastfeeding period?**

Whenever possible, an alternative effective antimalarial drug should be taken during breastfeeding. If no alternative is available and CD is administered, breastfed infants should be monitored closely for signs of anaemia or methaemoglobinaemia.

**4. With respect to drug history, what recommendations should be given for patients:**

a. with known hypersensitivity to sulfa drugs?

CD is contraindicated in patients with known hypersensitivity to sulfonamides and sulfones.

b. who have previously taken sulfadoxine–pyrimethamine, trimethoprim–sulfamethoxazole or primaquine?

If the previous treatment with sulfadoxine–pyrimethamine, trimethoprim–sulfamethoxazole or primaquine did not give rise to any problems, there is no special reason not to use CD.

**5. In view of the above, what are the recommendations for use of this drug for malaria treatment in endemic countries in Africa?**

CD should be used only when there is a confirmed diagnosis of malaria. The potential risks associated with CD use in areas where G6PD deficiency is prevalent outweigh the benefits if the drug is used for presumptive treatment.

In areas where G6PD deficiency is prevalent and a reliable clinical or laboratory diagnosis of anaemia and a test for G6PD deficiency cannot be obtained, a suitable alternative to CD should be used. If there is no suitable alternative, CD should be used but taking into account all the associated risks.

The pharmacology of the components of CD indicate that certain subpopulations might be at higher risk for serious adverse effects. Experience and information on the safety of this medicine are needed, in particular in relation to: G6PD status, presence of renal or hepatic disease, pregnancy, HIV/AIDS, the elderly, malnutrition, haemoglobinopathy and specific cytochrome P450 polymorphisms and acetylator status.

The information on the safety of CD is still too limited to warrant its widespread, unregulated use.

These recommendations will be reconsidered when more data become available from pharmacovigilance studies and post-marketing surveillance.

**6. What are the priorities for field research, and specifically for phase-IV and pharmacovigilance studies?**

Studies of safety and effectiveness are needed, which should include:

- appropriate protocols;
- good clinical practice (GCP) standards;
- use of an intention-to-treat analysis;
- appropriate patient monitoring;
- patient follow-up to day 28;
- rigorous recording of adverse events until resolved or outcome occurs;

- prospective study design, if possible, for patient populations at extra risk for adverse effects or insufficient efficacy (see question 5);
- subgroup analysis with adequate power in patient populations at extra risk for adverse effects or low efficacy (see question 5);
- subgroup analysis with a priori stratification.

Further studies of interactions between G6PD status and CD treatment should be performed, taking into account the recommendations under 1f. These studies should meet GCP standards and be conducted only in settings where close patient follow-up and safety monitoring can be ensured and where appropriate therapeutic action can be taken, including blood transfusion.

In prospective studies in areas with high prevalences of G6PD deficiency, G6PD status must be determined in all patients, and treatment with CD should be accompanied by serial haemoglobin measurements and adequate safety precautions.

## Experts and authors of the report

Professor Martin Danis, Service de Parasitologie-Mycologie, Paris, France

Professor I. Ralph Edwards, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

Professor Mohammed Hassar (Chairperson),\* Institut Pasteur du Maroc, Casablanca, Morocco

Professor Lucio Luzzatto, Istituto Nazionale per La Ricerca Sul Cancro, Genova, Italy

Dr Siddika Mithani,\* Therapeutic Products Directorate, Health Canada, Ottawa, Canada

Dr Veronique Mushiga, Ministry of Health, Kigali, Rwanda

Professor Olugbemiro Sodeinde,\* Department of Paediatrics, University of Ibadan, Ibadan, Nigeria

Professor Frank Sullivan, Brighton, England

Professor Chris J. van Boxtel (Rapporteur),\* University of Amsterdam, Nigtevecht, Netherlands

### **Consultant**

Associate Professor Urban Hellgren,\* Division of Infectious Diseases, Karolinska Hospital, Stockholm, Sweden

### **Secretariat**

Dr Fatoumata Nafo-Traore, Director, Roll Back Malaria Department (RBM), WHO, Geneva, Switzerland

Dr Andrea Bosman (Secretary), RBM, WHO, Geneva, Switzerland

Dr Kamini Mendis, RBM, WHO, Geneva, Switzerland

Dr Peter Olumese, RBM, WHO, Geneva, Switzerland

Dr Pascal Ringwald, RBM, WHO, Geneva, Switzerland

Dr Allan Schapira, Coordinator, RBM, WHO, Geneva, Switzerland

Dr Mary R. Couper (Co-secretary), Medicines Policy and Standards Department, WHO, Geneva, Switzerland

---

\* Also participated in the meeting to finalize the report on 13–14 January 2005.

Dr Thomas Y. Sukwa, Malaria Prevention and Control Programme, WHO  
African Region, Zimbabwe

***Observers***

Dr Mair Powell, Medicines Control Agency, London, England

Dr Thomas P. Kanyok, Special Programme for Research and Training in  
Tropical Diseases (TDR), WHO, Geneva, Switzerland

Dr Annette Kuesel, TDR, WHO, Geneva, Switzerland

Dr Graeme A. Clugston, Office of the Technical Ombudsman, WHO, Geneva,  
Switzerland

# References

- Allouche A et al. Comparison of chlorproguanil–dapson with sulfadoxine–pyrimethamine for the treatment of uncomplicated falciparum malaria in young African children: double-blind randomised controlled trial. *The Lancet*, 2004, 363:1843–1848.
- Amukoye E et al. Chlorproguanil–dapson: effective treatment for uncomplicated falciparum malaria. *Antimicrobial Agents and Chemotherapy*, 1997, 41:2261–2264.
- Basco LK et al. Point mutations in the dihydrofolate reductase–thymidylate synthase gene and pyrimethamine and cycloguanil resistance in *Plasmodium falciparum*. *Molecular and Biochemical Parasitology*, 1995, 69:135–138.
- Bates SJ et al. Rare, highly pyrimethamine-resistant alleles of *Plasmodium falciparum* dihydrofolate reductase from five African sites. *Journal of Infectious Diseases*, 2004, 190: 1783–1792.
- Beutler E. Glucose-6-phosphate dehydrogenase deficiency: current concepts. *New England Journal of Medicine*, 1991, 324:169–174.
- Bluhm RE et al. Development of dapson toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapson as risk factors. *Clinical Pharmacology and Therapeutics*, 1999, 65:598–605.
- Brabin BJ et al. Dapson therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Safety*, 2004, 27:633–648.
- Brendenkamp BL et al. Failure of sulfadoxine–pyrimethamine in treating *Plasmodium falciparum* in ZwaZulu-Natal. *South African Medical Journal*, 2001, 91:970–972.
- Brooks DR et al. Sequence variation of the hydroxymethyldihydropterin pyrophosphokinase:dihydropteroate synthase gene in lines of the human malaria parasite *Plasmodium falciparum*, with differing resistance to sulfadoxine. *European Journal of Biochemistry*, 1994, 224:397–405.
- Carr A et al. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients with *Pneumocystis carinii* and AIDS. *Journal of Infectious Diseases*, 1993, 167:180–185.
- Carrazza MZN, Carrazza FR, Oga S. Clinical and laboratory parameters in dapson acute intoxication. *Revidsa Saude Publica*, 2000, 34:396–401.
- Daniels AM. Mouth ulceration associated with proguanil. *The Lancet*, 1986, 1:269.
- Degowin RL et al. The haemolytic effects of diaphenylsulfone (DDS) in normal subjects and in those with glucose-6-phosphate-dehydrogenase deficiency. *Bulletin of the World Health Organization*, 1966, 35:165–179.
- East African Network for Monitoring Antimalarial Treatment. The efficacy of antimalarial monotherapies, sulfadoxine-pyrimethamine and amodiaquine in East Africa: implications for sub-regional policy. *Tropical Medicine in International Health*, 2003, 8:860–867.

- Färnert A et al. Polyclonal *Plasmodium falciparum* malaria in travellers and selection of antifolate mutations after proguanil prophylaxis. *American Journal of Tropical Medicine and Hygiene*, 2002, 66:487–491.
- Ganer A et al. Dapsone induced methaemoglobinaemia and haemolysis in the presence of familial haemoglobinopathy, Hasharon and familial methaemoglobin reductase deficiency. *Israeli Journal of Medical Sciences*, 1981, 17:703–704.
- Grayson ML, Yung AP, Doherty RR. Severe dapsone syndrome due to weekly Maloprim. *The Lancet*, 1988, 1:531.
- Hall AH, et al. Drug- and chemical-induced methaemoglobinaemia. Clinical features and management. *Medical Toxicology* 1986; 1:253–60
- Hastings MD et al. Highly pyrimethamine-resistant alleles of dihydrofolate reductase in isolates of *Plasmodium falciparum* from Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2002, 96:674–676.
- Jaeger A et al. Clinical features and management of poisoning due to antimalarial drugs. *Medicine and Toxicology of Adverse Drug Experience*, 1987; 2:242–273.
- International Programme on Chemical Safety. Dapsone (PIM 167)  
<http://www.inchem.org/documents/pims/pharm/dapsone.htm>.
- Lambert M et al. Delayed sulfhemoglobinemia after acute dapsone intoxication. *Journal of Toxicology and Clinical Toxicology*, 1982, 19:45–50.
- McGready R et al. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. *European Journal of Clinical Pharmacology*, 2003, 59: 553–557.
- Mutabingwa T et al. Chlorproguanil–dapsone for treatment of drug-resistant falciparum malaria in Tanzania. *The Lancet*, 2001, 358:1218–1223.
- Naisbitt DI et al. Cellular disposition of sulfamethoxazole and its metabolites: implications for hypersensitivity. *British Journal of Pharmacology*, 1999, 126:1393–1407.
- Ochong E et al. Molecular monitoring of the Leu-164 mutation of dihydrofolate reductase in a highly sulfadoxine/pyrimethamine-resistant area in Africa. *Malaria Journal*, 2003, 2:46.
- Pieters FA, Zuiderna J. The absolute oral bioavailability of dapsone in dogs and humans. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 1987, 25:396–400.
- Plowe CV et al. Community pyrimethamine use and prevalence of resistant *Plasmodium falciparum* genotypes in Mali: a model for deterring resistance. *American Journal of Tropical Medicine and Hygiene*, 1996, 55:467–471.
- Skjelbo E et al. Chloroguanide metabolism in relation to the efficacy in malaria prophylaxis and the S-mephenytoin oxidation in Tanzanians. *Clinical Pharmacology and Therapeutics*, 1996, 59:304–311.
- Sulo J et al. Chlorproguanil–dapsone versus sulfadoxine–pyrimethamine for sequential episodes of uncomplicated falciparum malaria in Kenya and Malawi: a randomised clinical trial. *The Lancet*, 2002, 360:1136–1143.

Watkins WM, Mosobo M. Treatment of *Plasmodium falciparum* malaria with pyrimethamine and sulfadoxine: a selective pressure for resistance in a function of long elimination half-life. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, 87: 75–79.

WHO. Glucose-6-phosphate dehydrogenase deficiency. WHO Working Group. *Bulletin of the World Health Organization*, 1989, 67: 601–611.

WHO. *Antimalarial drug combination therapy*. WHO unpublished document, WHO/CDS/RBM/2001.35, 2001.

Wichmann O et al. Molecular surveillance of the antifolate-resistant mutation 1164L in imported African isolates of *Plasmodium falciparum* in Europe: sentinel data from TropNetEurop. *Malaria Journal*, 2003, 2:17.

Wilairatana P et al. Poor efficacy of antimalarial biguanide–dapsones combinations in treatment of acute, uncomplicated, falciparum malaria in Thailand. *Annals of Tropical Medicine and Parasitology*, 1997, 91:125–132.

Willerson D et al. The chemoprophylactic use of diformyldiamino–diphenylsulfone (DFD) in falciparum malaria. *American Journal of Tropical Medicine and Hygiene*, 1972, 21:138–143.

Williams S et al. Methemoglobinaemia in children with acute lymphoblastic leukemia (ALL) receiving dapsones for *pneumocystis carinii* pneumonia (PCP) prophylaxis: a correlation with cytochrome b5 reductase (Cb5R) enzyme levels. *Pediatric Blood Cancer*, 2005, 44:55–62.

Wright JD, Helsby NA, Ward SA. The role of S-mephenytoin hydroxylase (CYP2C19) in the metabolism of the antimalarial biguanides. *British Journal of Clinical Pharmacology*, 1995, 39:441–444.

Zuidema J, Hilbers-Modderman ESM, Merkus FWHM. Clinical pharmacokinetics of dapsones. *Clinical Pharmacokinetics*, 1986, 11:299–315.

## **APPENDIX I**

### ***Terms of reference for the review of the safety of chlorproguanil– dapsone (Lapdap™), organized by the WHO Roll Back Malaria department in collaboration with the Essential Drugs and Medicines department***

#### **Summary**

The antimalarial drug chlorproguanil–dapsone (CD, submitted for registration as ‘Lapdap’) was developed in a collaboration between the WHO Special Programme for Research and Training in Tropical Diseases (TDR) and Glaxo Smith Kline (GSK), with funding from the United Kingdom Department for International Development. The drug has been approved by the Medicines and Health Products Regulatory Agency (MHRA) for registration in the United Kingdom.

The WHO Malaria Control Department will commission a safety review of CD based on inter alia the entire regulatory dossier submitted to the MHRA. This information was provided to WHO in confidence, strictly for the purpose of the aforesaid safety review.

The aim of the review is to assess the safety and efficacy of CD for the treatment of uncomplicated falciparum malaria in persons of all ages in malaria-endemic countries.

The materials to be provided to the reviewers should include the following:

- All preclinical and clinical studies performed with chlorproguanil and dapsone, used singly and in combination, including study protocols, data listings, individual case reports and any relevant special or expert reports, so that individual case records can be reviewed and audited independently.
- All published and unpublished materials that were used in support of the regulatory submission and of the claims made therein for efficacy, safety and risk–benefit analyses.
- Any available expert reports pertaining to efficacy, safety and risk–benefit that could have been included in the regulatory dossier or were considered by the company and TDR for the purpose of the regulatory submission.

The terms of reference of the WHO team responsible for the review will include:

- Consideration of all preclinical reports on chlorproguanil and dapsone, used alone and in combination, that are in the possession of GSK or TDR and of any expert reports, including all reports submitted to the MHRA for the purpose of approval of the registration of ‘Lapdap’.
- Review of all reports of clinical studies and expert reports submitted in support of claims made for ‘Lapdap’ for regulatory approval and of any other relevant case reports that might have bearing on the Committee’s judgement about the safety, efficacy and risk–benefit of the drug, regardless of whether

these studies have been published and whether they were submitted to MHRA.

- Recommendations on how to answer the questions listed below for the purpose of constituting WHO's advice to countries on the safety of this drug.

### ***Modus operandi***

The WHO review committee established for this purpose will comprise at least eight persons with expert knowledge that collectively covers the fields of toxicology, drug safety, drug regulatory practice, malaria chemotherapy, post-marketing surveillance and clinical and experimental haematology. All the work of the committee will be conducted within the usual WHO requirements for confidentiality and declarations of interest. WHO (RBM, EDM, TDR) will provide secretariat for the review but will not take part in the review process, which will be carried out independently by the Committee. A representative of MHRA will be invited to the meeting as an observer.

### **Terms of reference of the WHO review of the safety of 'Lapdap'**

The aim of the review is to assess the safety of CD ('Lapdap') for the treatment of uncomplicated falciparum malaria in persons of all ages and to identify strategies for the optimal safe use of this drug in malaria-endemic countries, including pharmacovigilance.

### ***Components of the technical review***

1. Review of all reports (published and unpublished) on the safety and efficacy of CD, regardless of whether they were submitted by GSK to MHRA, including all preclinical reports, the final reports of all clinical studies and any relevant special or expert reports, as well as the correspondence between MHRA and GSK on approval of the dossier on CD.
2. Review of additional information on the safety of the two drug components (as single compounds and as a fixed-dose association), from published and unpublished systematic reviews and additional databases, such as the WHO Global Database on Drug Safety.
3. A risk-benefit assessment of CD ('Lapdap') for the treatment of uncomplicated malaria.
4. Review of on-going and planned post-registration phase-IV studies and post-marketing surveillance of CD.

### ***Expected outcomes***

The expert review is expected to result in recommendations for answers to the following questions, which will constitute the Organization's advice to ministries of health of WHO Member States, policy-makers and health professionals on safe use of this drug.

1. With respect to the risk of anaemia,
  - a. Do the safety concerns differ for children and for adults?
  - b. What is the clinical significance of the anaemia that might develop after treatment with CD?
  - c. How should patients with malaria and various levels of anaemia be treated with CD?
  - d. What is the clinical significance of the anaemia that might develop in patients with G6PD deficiency treated with CD for malaria, and what recommendations can be given for use of CD in these patients?
  - e. What is the clinical significance of the methaemoglobinaemia associated with CD treatment of malaria?
  - f. In countries endemic for malaria in Africa and other regions, where G6PD deficiency is prevalent, what are the recommendations for treatment of malaria with CD, in situations where it is not possible to provide a reliable clinical or laboratory diagnosis of anaemia, a test for G6PD deficiency or a diagnosis of methaemoglobinaemia?
2. What is the expected dose-related toxicity of CD:
  - a. in relation to the daily dose of dapsone?
  - b. with the repeated treatment courses to be expected in areas of intense transmission of malaria?
3. What is the expected risk to:
  - a. the fetus of using CD during pregnancy?
  - b. the infant when CD is taken by the mother during the breastfeeding period?
4. With respect to drug history, what recommendations should be given for patients:
  - a. with known hypersensitivity to sulfa drugs?
  - b. who have previously taken sulfadoxine-pyrimethamine, trimetoprim-sulfametoxazole or primaquine?
5. In view of the above, what are the recommendations for use of this drug for malaria treatment in endemic countries in Africa?
6. What are the priorities for field research, and specifically for phase-IV and pharmacovigilance studies?

***Profile requirements of the review committee***

In order to maximize the inputs from the experts, the committee should comprise a minimum of four professionals, with the following areas of expertise:

- drug toxicology, with in-depth experience in evaluating studies of preclinical toxicology for drug regulatory approval;
- drug toxicology, with expertise in evaluating studies of haematological

- toxicology, with specific knowledge of prenatal and paediatric toxicology;
- malaria chemotherapy, with knowledge of the effects of drugs on the pathophysiology of malaria-induced anaemia, haemoglobinopathy and haematological reactions induced by antimalarial drugs;
- malaria chemotherapy, with expertise in risk–benefit evaluation of drugs for treatment of malaria in areas of intense transmission where there is high prevalence of malaria-related anaemia;
- antimalarial drug use and registration in Africa and post-marketing surveillance in developing countries; and
- malaria control, with expertise in malaria chemotherapy.

### ***Documentation to be submitted to the reviewers***

- a) All documents on CD, regardless of whether they have been submitted by GSK to MHRA, including all preclinical reports, the final reports of all clinical studies and any special or expert reports, as well as all correspondence between MHRA and GSK on approval of the CD dossier.
- b) All known published and unpublished data on the use and safety of the two drug components (as single compounds and as a fixed-dose association), including the reviews of adverse events reported to the WHO Global Database on Drug Safety.

In particular, RBM will request to GSK to provide, under confidential cover, the registration dossier, which will include the following:

- reports of all preclinical and clinical studies performed with chlorproguanil and dapson, alone or in combination (all studies, observational and randomized controlled trials). The reports should include all the usual appendices (e.g. study protocols, data listings, statistical analyses plans);
- published literature and unpublished data that were used to support claims of the safety and efficacy of ‘Lapdap’;
- the expert reports; and
- the final labelling (or data sheet).

In addition, RBM will request MHRA to provide, under confidential cover, the following documents:

- MHRA comments on the registration dossier submitted for approval, and
- the outcome of the MHRA review.

Finally, RBM will request GSK to provide other relevant documentation and information, as described above.

### ***Confidentiality***

The data that will be reviewed will be made available to WHO under confidential cover. The confidential dossiers will be handled and stored according to the

procedures for confidential documents that have been established by the WHO Office of Internal Audit and Oversight. The review should therefore take place with due respect for this confidentiality, and all experts will have to sign an undertaking of confidentiality as well as a declaration of interest.

***Publication of the report***

The final report of the review may be published by WHO and it may be made widely available to inform ministries of health, policy-makers and health professionals.

## **APPENDIX II**

### ***List of reports, publications and other materials reviewed***

#### **1. Documents provided by GSK (available on CD-ROM - D2004-0414-WHO-LAPDAP-MAA-Feb04 (SB433372))**

- Expert report on the pharmaco-toxicological documentation 05/09/2002
- Clinical expert report 06/09/2002

#### ***Responses to MHRA***

- Medicines Control Agency (MCA) response on mixed infections
- Response to MCA questions on study 001
- Response to MCA questions on studies 005, 004 and 002
- Response to MCA questions on dose recommendations
- Response to MCA question on metabolism
- Response to MCA question on slide reading

#### ***Preclinical study reports***

- 1552/25-D6144 *Chlorproguanil and dapsona: maximum tolerated dose study in the rabbit using rising single oral dose levels.*
- 1552/26-D6144 *Chlorproguanil and dapsona: single dose toxicity in the rabbit for each test article individually and in combination.*
- 1552/27-D6144 *Chlorproguanil and dapsona: 7 day repeated dose toxicity study in the rabbit for each test article individually and in combination.*
- 1552/81-D6154 *Chlorproguanil and dapsona: 7 day repeated dose toxicity study in the rabbit for each test article individually and in combination (reduced dose levels).*
- 1552/036 *Chlorproguanil/dapsona and chlorcycloguanil: 28 day oral (gavage administration) toxicity study in the rat.*
- 1552/37 *Chlorproguanil/dapsona and chlorcycloguanil: oral (gavage) range-finding study of fertility and early embryonic development in the rat.*
- 1552/38 *Chlorproguanil/dapsona and chlorcycloguanil: oral (gavage) study of fertility and embryo-foetal development in the rat.*
- 1552/66 *Chlorproguanil/dapsona: 9 week oral (gavage administration) study of effects on sperm in the male rat with a 4 week recovery period.*
- 1552/40 *Chlorproguanil/dapsona: oral (gavage) study of embryo-foetal development in the rabbit.*
- 1552/20-D5140 *Chlorproguanil: reverse mutation in four histidine-requiring strains of Salmonella typhimurium and two tryptophan-requiring strains of Escherichia coli.*
- 1552/19-D5140 *Chlorproguanil: mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y (MLA) using the microtitre® technique.*
- 1552/32 *Chlorproguanil: induction of micronuclei in the bone marrow of treated mice.*

- 1552/22-D5140 *Dapsone: reverse mutation in four histidine-requiring strains of Salmonella typhimurium and two tryptophan-requiring strains of Escherichia coli.*
- 1552/21-D5140 *Dapsone: mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y (MLA) using the microtitre® technique.*
- 1552/31 *Dapsone: induction of micronuclei in bone marrow of treated mice.*
- 1554/24-D5140 *Chlorcycloguanil: reverse mutation in four histidine-requiring strains of Salmonella typhimurium and two tryptophan-requiring strains of Escherichia coli.*
- 1552/23-D5140 *Chlorcycloguanil: mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y (MLA) using the microtitre® technique.*
- 1552/48-D6183 *Chlorcycloguanil: mutation at the hprt locus of L5178Y mouse lymphoma cells using the microtitre® technique.*
- 1552/33 *Chlorcycloguanil: induction of micronuclei in the bone marrow of treated mice.*
- 1552/036 *Supplementary chlorproguanil/dapsone and chlorcycloguanil: 28 day oral (gavage administration) toxicity study in the rat.*
- 1552/39 *Chlorcycloguanil: two day oral (gavage administration) pharmacokinetic study in the mouse.*
- 1552/39-kinetics *Chlorcycloguanil: pharmacokinetic analysis of plasma and bone-marrow samples from a two-day (oral gavage) study in the mouse.*
- Lapdap 1/01 *Chlorproguanil: pharmacokinetics after one and seven oral (gavage administration) doses in rats.*
- 1552/36-kinetics *Chlorproguanil/dapsone and chlorcycloguanil: pharmacokinetic analysis of plasma samples from a 28-day oral (gavage) toxicity study in the rat.*
- 1552/66-kinetics *Chlorproguanil/dapsone: pharmacokinetic analysis of plasma samples from a 9 week oral (gavage administration) study in the male rat with a 4 week recovery period.*
- 1552/27-kinetics *Chlorproguanil and dapsone: pharmacokinetic analysis of plasma samples from a seven-day (oral gavage) repeated-dose toxicity study in the rabbit for each test article individually and in combination.*
- 1552/81-kinetics *Chlorproguanil/dapsone: pharmacokinetic analysis of plasma samples from a 7 day repeated dose toxicity study in the rabbit for each test article individually and in combination (lower doses).*
- 1552/40-kinetics *Chlorproguanil and dapsone: pharmacokinetic analysis of plasma samples from an embryo-foetal development study in the rabbit.*

### **Clinical study reports**

- Report 001 SB-433372/RSD-101LL2/1 *A multicentre, double-blind, phase III study comparing the safety and efficacy of chlorproguanil/dapsone (daily for three days) versus sulfadoxine/pyrimethamine (single dose) in the treatment of uncomplicated falciparum malaria in children in Africa.*
- Report 001 Tables.

- Report 002 SB-433372/RSD-101LL3/1 A 2-part, open, cross-over study to determine the relative bioavailability of chlorproguanil/dapsone after administration as three formulations and to study the potential for pharmacokinetic interaction of chlorproguanil and dapsone in healthy male volunteers.
- Report 002 protocol No: 99-029 A 2-part, open, cross-over study to determine the relative bioavailability of chlorproguanil/dapsone after administration as three formulations and to study the potential for pharmacokinetic interaction of chlorproguanil and dapsone in healthy male volunteers.
- Report 002 Appendix A (26/09/00).
- Report 003 SB-433372/RSD-101LL4/1 A single centre open phase II study to evaluate the safety and efficacy of chlorproguanil/dapsone (daily for three days) in the treatment of uncomplicated falciparum malaria in adults in Africa.
- Report 003 Tables Report 004 SB-433372/RSD-101LL5/1 A single centre open phase II study to evaluate the pharmacokinetics, safety and efficacy of chlorproguanil/dapsone (daily for three days) in the treatment of uncomplicated falciparum malaria in children aged three months to twelve years in Africa.
- Report 004 Tables.
- Report 005 SB-433372/RSD-101KHH/1 A rising-dose tolerance study in healthy human subjects, examining increasing doses of chlorproguanil with a constant dose of dapsone.
- Report 005 Tables.
- Report 005 Table 15.13.
- Report 005 Table 15.14.
- Report 006 SB-433372/RSD-101KHT/1 A double-blind randomised comparison of chlorproguanil/dapsone (daily for three days) with pyrimethamine sulfadoxine (single dose) as treatment for consecutive episodes of uncomplicated falciparum malaria in children.
- Report 006 Prior concomitant listings and tables Report 007 SB-433372/RSD-101KHX/1 A double-blind randomised comparison of chlorproguanil/dapsone (daily for three days) with pyrimethamine sulfadoxine (single dose) as treatment for consecutive episodes of uncomplicated falciparum malaria in children.
- Report 007 Prior concomitant listings and tables Report 008 SB-433372/RSD-101LL6/1 A single centre open label study to assess the safety and efficacy of chlorproguanil/dapsone (daily for three days) in the treatment of uncomplicated falciparum malaria in children aged three months to twelve months.
- Report 008 Tables.
- Report SB-433372/RSD-101N4N/1 Population pharmacokinetic modelling of the antimalarial chemotherapy 'Lapdap'.

## **2. Documents provided by the MHRA of the United Kingdom**

- Clinical part of MHRA assessment report considered by the Committee of Safety of Medicines, United Kingdom (Lapdap Part IV.doc).
- Applicant's (GSK) responses to requests for amendments to Summary of Product Characteristics before finalization.

- Final Summary of Product Characteristics approved by MHRA for paediatric-strength tablets (same as for 80/100 tablets except formulation).
- Pre-finalization supplementary assessment report of MHRA.
- Final patient information leaflet approved by MHRA.

### **3. Documents provided by WHO**

#### **Publications**

- Allouche A et al. Comparison of chlorproguanil–dapson with sulfadoxine–pyrimethamine for the treatment of uncomplicated falciparum malaria in young African children: double-blind randomised controlled trial. *The Lancet*, 2004, 363:1843–1848 (publication of study 001 of the GSK regulatory dossier).
- Färnert A et al. Polyclonal *Plasmodium falciparum* malaria in travellers and selection of antifolate mutations after proguanil prophylaxis. *American Journal of Tropical Medicine and Hygiene*, 2002, 66:487–491.
- Hastings MD et al. Highly pyrimethamine-resistant alleles of dihydrofolate reductase in isolates of *Plasmodium falciparum* from Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2002, 96:674–676.
- Looareesuwan S, Imwong M, Wilairatana P. Chlorproguanil–dapson for malaria in Africa; commentary. *The Lancet*, 2004, 363:1838–1839.
- Mookherjee S et al. Identification and analysis of dihydrofolate reductase alleles from *Plasmodium falciparum* present at low frequency in polyclonal patient samples. *American Journal of Tropical Medicine and Hygiene*, 1999, 61: 131–140.
- Ochong E et al. Molecular monitoring of the Leu-164 mutation of dihydrofolate reductase in a highly sulfadoxine/pyrimethamine-resistant area in Africa. *Malaria Journal*, 2003, 2:46.
- Taylor WRJ, White NJ. Antimalarial drug toxicity; a review. *Drug Safety*, 2004, 27:25–61.
- Wichmann O et al. Molecular surveillance of the antifolate-resistant mutation 1164L in imported African isolates of *Plasmodium falciparum* in Europe: sentinel data from TropNetEurop. *Malaria Journal*, 2003, 2:17.
- Wilairatana P et al. Poor efficacy of antimalarial biguanide–dapson combinations in treatment of acute, uncomplicated, falciparum malaria in Thailand. *Annals of Tropical Medicine and Parasitology*, 1997, 91:125–132.

#### **WHO documents**

- *Background and objectives of the WHO technical consultation to review of safety of chlorproguanil/dapson for treatment of uncomplicated falciparum malaria in Africa*, WHO unpublished document, 2004.
- *Proposed terms of reference for the review of the safety of chlorproguanil/dapson ('Lapdap') commissioned by WHO RBM in collaboration with EDM*, WHO unpublished document, 2004.

- WHO/RBM information note on chlorproguanil/dapsone (Lapdap) for ministries of health of malaria endemic countries, WHO unpublished document, September 2003.
- WHO, UNICEF. *The Africa malaria report 2003*, WHO unpublished document WHO/CDS/MAL/2003.1093.
- WHO fact sheet on artemisinin-based combination therapy, WHO unpublished document, April 2004.
- WHO map of national malaria treatment policies in Africa, WHO unpublished document, June 2004.
- *Assessment of the safety of artemisinin compounds in pregnancy—report of two information consultation in 2002*, WHO unpublished document WHO/CDS/MAL/2003.1094.

### **Other documents**

- Bukirwa H et al. Chlorproguanil-dapsone for treating uncomplicated malaria. *The Cochrane Library* 2005; 2:1–29. Comments on the Cochrane systematic review by Professor P. Winstanley (letter to WHO/RBM of 28 June 2004).
- Coleman PG et al. A threshold analysis of the cost-effectiveness of artemisinin-based combination therapies in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene* (in press).
- East African Network for Monitoring Antimalarial Treatment. Published database on SP resistance in Africa. (Available from [www.eanmat.org](http://www.eanmat.org), updated June 2004).
- Krudsood S et al. Artesunate–dapsone–proguanil treatment of falciparum malaria; genotypic determinants of therapeutic response (draft).

### **TDR research proposals for phase-IV studies on Lapdap in Africa**

- Effectiveness of chlorproguanil–dapsone (Lapdap) through home management approach for treatment of uncomplicated malaria in children.  
*Objectives:*
  - (i) to examine the effectiveness of chlorproguanil-dapsone (Lapdap) with a home-management approach to clinical and parasitological cure rates;
  - (ii) to document adverse reactions to Lapdap.
- Safety monitoring of chlorproguanil–dapsone (Lapdap) and sulfadoxine–pyrimethamine in a resource-limited country (Ghana).  
*Objectives:*
  - (i) to find ways to obtain information on suspected adverse reactions to Lapdap and SP from users and suppliers of the drugs in the community and in health-care institutions;
  - (ii) to monitor intensively the safety of Lapdap and SP;
  - (iii) to relate reported adverse events associated with Lapdap use to data on consumption obtained from wholesalers and dispensers;

- (iv) to assess risk factors for haemolysis and other adverse events associated with Lapdap and SP.
- Assessment of safety of Lapdap and co-artemether in the treatment of acute uncomplicated malaria: effect of host factor.
 

*Objectives:*

  - (i) to determine the rate and degree of haemolysis in patients given Lapdap and in those given co-artemether;
  - (ii) to evaluate the effects of erythrocyte G6PD deficiency and sickle-cell gene on haemolysis due to Lapdap administration;
  - (iii) to determine parasitological and clinical responses to Lapdap.
- Effectiveness of and pharmacovigilance for Lapdap and co-artemether used for treatment of uncomplicated falciparum malaria in northeastern United Republic of Tanzania.
 

*Objectives:*

  - (i) to estimate clinical, haematological and parasitological responses;
  - (ii) to assess community compliance with and acceptability of Lapdap and co-artemether use;
  - (iii) to document the frequency and type of potential drug-related adverse events;
  - (iv) to determine the prevalence and monitor development of *dhfr* and *dhps* gene mutations;
  - (v) to estimate the cost-effectiveness of use of drugs in programme setting.
- Safety of Lapdap in the treatment of young children with uncomplicated malaria in Nouna, Burkina Faso.
 

*Objectives:*

  - (i) to determine serious adverse events (in particular, haemolysis in G6PD deficiency) during treatment of young children with uncomplicated malaria with chlorproguanil-dapsone (Lapdap);
  - (ii) to determine other adverse events during treatment of young children with uncomplicated malaria with Lapdap.
- An operational study of Lapdap (chlorproguanil-dapsone) as treatment for uncomplicated falciparum malaria in Malawi.
 

*Objectives:*

  - (i) to assess the tolerability and safety of Lapdap in an unselected patient care setting;
  - (ii) to evaluate the clinical effectiveness of Lapdap in all age groups, with the exception of pregnant women;
  - (iii) to evaluate the cost-effectiveness of Lapdap in all age groups, with the exception of pregnant women;
  - (iv) to evaluate the effect of level of resistance to SP on the effectiveness of Lapdap over one year;
  - (v) to determine the prevalence of mutations in the genes that encode the

target proteins *dhfr* and *dhps*, before and after exposure to Lapdap in an operational setting.

- Safety and effectiveness of Lapdap and co-artemether for uncomplicated malaria under actual conditions of use.

*Objectives:*

- (i) to compare the effectiveness of Lapdap and co-artemether for treatment of uncomplicated malaria under actual conditions of use;
  - (ii) to investigate the acceptability of Lapdap and co-artemether, compliance with the recommended regimens, and their effects on treatment success;
  - (iii) to determine the safety of treatment of G6PD-deficient and normal malaria patients;
  - (iv) to compare the effects of Lapdap and co-artemether on the transmissibility of *P. falciparum* after treatment;
  - (v) to determine the frequency of molecular markers of SP resistance before and after treatment and investigate any effect on the efficacy of Lapdap of infection with parasites carrying SP-resistance markers;
  - (vi) to determine the cost-effectiveness of the two treatments.
- Study of *P. falciparum* resistance to chlorproguanil-dapsone (Lapdap) in children with uncomplicated malaria.

*Objective:*

To assess the influence of pre-existing SP resistance on the efficacy of Lapdap therapy by analysing point mutations in *dhfr* (Asn-108/Ile-51/Arg-59) and *dhps* (Gly-437/Glu-540) genes of parasites at the beginning of Lapdap therapy in relation to recrudescence and overall cure rates.

- Effectiveness and safety of Lapdap and potential development of *Plasmodium falciparum* resistance in Nigerian children.

*Objectives:*

- (i) to compare the effectiveness and safety of CD and SP in children with acute uncomplicated *P. falciparum* malaria;
- (ii) to evaluate the effectiveness and safety of CD in children with a clinical (presumptive) diagnosis of malaria;
- (iii) to assess the effectiveness and safety of CD in children in whom treatment of acute, symptomatic, uncomplicated *P. falciparum* infection with SP failed;
- (iv) to evaluate the relationship between susceptibility of parasites to components of CD in vitro, the presence of multiple mutations in the *dhfr* and *dhps* genes of *P. falciparum* and treatment outcomes in children treated with CD;
- (v) to develop a local area network for monitoring adverse drug reactions to CD and collate data on adverse events through a pharmacovigilance centre for antimalarial drugs.

- Effectiveness and safety of Lapdap in the treatment of uncomplicated malaria and selection of drug-resistant parasites.

*Objectives:*

- (i) to compare the effectiveness of CD with that of Amodiaquine/SP for the treatment of uncomplicated falciparum malaria;
- (ii) to evaluate the selection pressure on CD, using plasmodial genetic polymorphisms as predictors of antifolate drug resistance and clinical response to malaria.

***Working papers submitted by the reviewers before the meeting***

- Dr Siddika Mithani: Review of clinical reports and GlaxoSmithKline clinical expert report in relation to efficacy and safety of chlorproguanil–dapsonе.
- Dr Frank M. Sullivan: Report on chlorproguanil–dapsonе preclinical toxicology.
- Prof Chris J. van Boxtel: Risk–benefit analysis of chlorproguanil–dapsonе.

***Presentations given during the meeting***

- RBM: WHO technical consultation to review the safety of chlorproguanil/dapsonе for treatment of uncomplicated falciparum malaria in Africa; background, objectives and expected outcomes (presented by Dr A. Bosman).
- Dr Lucio Luzzatto: Review of preclinical and clinical study reports in relation to haematological toxicity.
- Dr Olugbemiro Sodeinde: Review of haematological toxicity.
- Professor Martin Danis: Review of clinical reports and GlaxoSmithKline clinical expert report in relation to efficacy and safety of chlorproguanil–dapsonе.
- Professor I. Ralph Edwards: Review of on-going and planned phase-IV studies with chlorproguanil–dapsonе.

***Additional documents distributed at the meeting***

- GSK replies to MHRA questions with specific reference to drug resistance (Q5), post-marketing surveillance in Africa (Q7) and G6PD labelling (Q2).
- *Lapdap product monograph developed with Africa in mind*. GlaxoSmithKline, 2003, 45 pp.
- Laboratory values from the GSK summaries of patients data as recorded at each visit during study 001.
- Mutabingwa T<sup>†</sup> et al. Chlorproguanil–dapsonе for treatment of drug-resistant falciparum malaria in Tanzania. *The Lancet*, 2001, 358:1218–1223.
- Sulo J et al. Chlorproguanil–dapsonе versus sulfadoxine–pyrimethamine for sequential episodes of uncomplicated falciparum malaria in Kenya and Malawi: a randomised clinical trial. *The Lancet*, 2002, 360:1136–1143 (publication of studies 006 and 007 of the GSK regulatory dossier).