

## **Malaria Policy Advisory Committee**

### **Evidence Review Group (ERG) on the cardiotoxicity of antimalarial medicines**

#### **Terms of Reference**

##### **Background**

A prolonged QTc interval is a risk factor for ventricular tachyarrhythmias, such as [torsades de pointes \(TdP\)](#), which can cause sudden cardiac death, particularly when the QTc interval is over 500 msec. However, the relation between QTc prolongation and TdP is not entirely clear, as only some patients with prolonged QTc intervals develop life-threatening ventricular tachyarrhythmias. This could be related to genetic disorders, pathological conditions, or drug interactions with concomitant medications that prolong the QTc interval.

As a drug side effect, TdP has been a major liability, causing the withdrawal of medications from the marketplace. Yet, the relations between the drug-induced prolongation of QTc intervals and predictors of ventricular tachyarrhythmias that can cause sudden cardiac death are not well understood. Compounds that have been linked to clinical observations of TdP include [amiodarone](#), [fluoroquinolones](#), [methadone](#), [lithium](#), [chloroquine](#), [erythromycin](#), [amphetamine](#), [ephedrine](#), [pseudoephedrine](#), [methylphenidate](#) and [phenothiazines](#). Some antiarrhythmic medications, such as [sotalol](#), [procainamide](#) and quinidine, may induce TdP as a side effect. The following factors have been associated with an increased risk of TdP: hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, heart failure, left ventricular hypertrophy, hypothermia, subarachnoid hemorrhage and hypothyroidism.

The US-FDA is investing in a research programme designed to identify better predictors of drug-induced TdP, with the aim of progressively moving away from Thorough QT (TQT) study requirements for registration. This programme is expected to be completed over the next two years, and involves *in vitro* studies assessing the effects of drugs on multiple ion channels, as well as early clinical studies with exposure–response analysis using detailed ECG collection. The programme also includes ECG studies of multichannel block by multiple drugs in order to differentiate a pure hERG potassium channel block associated with a high torsade risk, and a combined hERG potassium channel and inward current block (calcium or late sodium) that may lower torsade risk (1).

##### **The case of antimalarial medicines**

Several quinoline antimalarial medicines are associated with a prolonged QTc interval, namely chloroquine, quinine, mefloquine and piperazine (in fixed-dose combination with dihydroartemisinin). WHO recommends all of these medicines for the treatment of malaria. Quinidine is associated with higher levels of cardiotoxicity and is no longer used for malaria treatment. Halofantrine causes a marked increase in QTc prolongation and has been associated with over 30 reports of sudden cardiac death. As a result, WHO does not recommend halofantrine for the treatment of malaria.

Many studies on the effects of antimalarials on prolonged QT intervals may systematically overestimate drug-induced effects when comparing pre- and post-treatment ECGs, as the resolution of fever and fasting (which influence the heart rate) are associated with the prolongation of the QTc interval. The QT should be corrected according to the heart rate, preferably using the Fridericia correction (QTcF), in order to improve the detection of patients at increased risk of ventricular arrhythmia.

Chloroquine belongs to the 4-aminoquinoline group and has been the most widely used antimalarial over the last 60 years. Several hundred tons have been dispensed for treatment and prophylaxis; in the past, it was even distributed as medicated salt. At higher doses, often in combination with other agents, it has also been used for the treatment of rheumatoid arthritis, systemic lupus erythematosus and other chronic conditions.

Piperaquine is a bisquinoline compound, also of the 4-aminoquinoline group. In the 1960s, it was deployed on a large scale in China, where an estimated 140 million adult doses were deployed for large-scale malaria prophylaxis, treatment and mass drug administration. In view of increasing levels of drug resistance and in line with WHO recommendations, dihydroartemisinin-piperaquine in fixed-dose combination is increasingly being deployed in malaria-endemic countries, including for mass drug administration<sup>1</sup>.

In 2011, based on findings from Thorough QT (TQT) studies, the European Medicine Authority gave marketing authorization to Eurartesim™, outlining a series of contraindications and requirements for ECG monitoring (SmPC available at:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/001199/WC500118113.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001199/WC500118113.pdf)).

### **Plan for WHO review of the cardiotoxicity of antimalarial medicines**

In collaboration with the WHO Department of Essential Medicines and Health Products, and following the EMA's and US-FDA's recommendations for experts, the WHO Global Malaria Programme consulted a small group of expert cardiologists and QTologists on how best to proceed with the review of the cardiotoxicity of antimalarial medicines.

Although more research is needed to identify the predictors of drug-induced TdP, the experts recommended that WHO analyse a large individual patient data series to document sudden cardiac death following drug exposure. Documented TdP in ECG recordings, even in a single case, should be taken as a strong indicator of the mechanisms of drug-induced death. The analysis should include not only the quinoline antimalarial medicines, but also concomitant medicines able to prolong the QTc interval (see: [www.qtdrugs.org](http://www.qtdrugs.org)). There was general consensus that the search and analysis of drug-associated "syncope" was unnecessary, as it would be influenced by too many confounders.

The WHO secretariat presented the rationale, objectives and proposed methods of the Evidence Review Group (ERG) at the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), held in June 2016 in Geneva. The advisory committee endorsed the objectives and proposed list of studies, and experts recommended the findings be presented at the next annual meeting in 2017.

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<sup>1</sup> Administration of antimalarial treatment to every member of a defined population or every person living in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals. Mass drug administration is usually performed in order to reduce the parasite reservoir of infection radically and thus reduce transmission in a population.

The specific objectives of the ERG meeting will be the following:

- To evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials (from data available to Vigibase, WWARN, Liverpool STM, and pharmaceutical companies);
- To assess the dose-response effect and risk factors of QTc prolongation from pharmacokinetic/pharmacodynamic (PK/PD) studies of the main ACTs used in Africa, i.e., artemether-lumefantrine, artesunate-amodiaquine and dihydroartemisinin-piperaquine
- To analyse the PK/PD effect of piperaquine in healthy volunteers compared to malaria patients, based on comparative clinical trials of dihydroartemisinin-piperaquine, artemether-piperaquine and artesunate-piperaquine
- To identify evidence gaps and provide recommendations for additional studies, including meta-analyses of individual patient dose-response effects and risk factors for QTc prolongation following exposure to different antimalarial medicines.

The conclusions of the ERG and draft recommendations will be presented to the Malaria Policy Advisory Committee (MPAC) in March 2017 and to the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) in April 2017.

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