1. BACKGROUND

Malaria caused by *P. falciparum* is a major public health concern in the developing countries. It is estimated that more than 300 million people are affected by malaria with 2-3 million deaths each year\(^1\).

More than a billion women live in malaria transmission areas and are thereby exposed to the risks of malaria when pregnant\(^2\). *Plasmodium falciparum* malaria in pregnancy is associated with deleterious consequences to the mother and fetus. Maternal and fetal mortality, abortion, stillbirth, premature labour, birthweight reduction, maternal/fetal anemia are all known complications of falciparum malaria.

In certain areas of the globe, *P. falciparum* has become resistant to most of the available antimalarials. The search for alternative regimens have been slow and treatment options for pregnant women are now very limited. In the northern border of Thailand, quinine, clindamycin and artesunate are the only drugs currently prescribed for the treatment of uncomplicated falciparum malaria\(^3\).

Artemisinin (ATM) derivatives include compounds such as artemisinin, arteether, artemether, dihydroartemisinin and artesunate, each of which differs in the extent to which it has been tested and developed, but for

\(^3\) McGready et al. (1998).
which certain elements, including safety, must be viewed in the context of the class.

ATM analogues are developmental toxicants in the rat and rabbit. The effects in preclinical studies were dominated by embryo-lethality and late resorptions and a few instances of morphological abnormalities, all under circumstances not related to maternal toxicity.

All the ATM analogues have been associated with embryo-lethality over a narrow dose range. General experience has shown that morphological abnormalities and embryo-lethality are part of a continuous spectrum. A small change in dose or other factors may favour the occurrence of one over the other.

In addition to the predominant embryo-lethality there were instances of effects on the development of the cardiovascular system, the axial skeleton and limbs, but they do not suggest the nature of the toxic action. It is not possible to predict from the animal findings the exact nature of the harmful effects in women. However, the predominant experimental findings do suggest that if there were similar clinical effects, they were likely to become apparent during the first trimester of pregnancy, e.g. as early loss of pregnancy or difficulty in becoming pregnant.

The clinical information collected thus far is encouraging in not showing any evidence of harm to mothers or fetuses at any stage of pregnancy\(^4\).

The numbers of women studied after dosing during the first trimester of pregnancy being small, any conclusion about safety in them can only be of

limited power and there has been no study designed specifically to examine the early pregnancy loss.

A much larger number of women have been followed after treatment during the second and third trimester and there is greater confidence in the safety of treatment during that period, based on clinical findings and the results of animal experimentation.

Studies of babies born to mothers dosed during pregnancy or lactation have not shown evidence of physical or neurological abnormalities during development and this is supported by the results of the appropriate animal experiments.

It is important that pregnant women with malaria are treated, because of its serious adverse effects on the mother and the fetus, and the public health risk of continuing gametocyte transmission in the community.

There is clear evidence of benefits to the mother and the foetus of treating pregnant women for falciparum malaria with ATMs.

A recent expert meeting reviewed all the experimental evidence on the developmental toxicity of the ATMs and considered reasonable that these drugs should continue to be available for the treatment of women with malaria, irrespective of their pregnancy status. However, further clinical and experimental work is to be done to clarify the extent and nature of adverse developmental actions of these drugs. The group recommended that a clinical monitoring programme be established to assess the outcomes of pregnancy of women treated with antimalarial drugs.
This document aims at describing the framework for postmarketing risk assessment programme of the ATMs in pregnancy.

2. RISK ASSESSMENT STRATEGY - GENERAL COMMENTS

The objectives of a postmarketing risk assessment programme\(^5\) are to detect adverse events not previously observed, improve understanding of the potential severity of previously anticipated risks, detect events resulting from drug interactions or drug effects in particular populations, and assess the potential for causal relationships.

No single approach to postmarketing risk assessment is sufficiently comprehensive to permit full evaluation of all important safety concerns. Consequently, a postmarketing risk assessment program for the ATMs in pregnancy should be based on the integration of safety information obtained from different sources.

*Spontaneous reports*\(^6\) are inherently retrospective, and although they may be useful in identifying clusters of distinct rare outcomes, because of their potential for bias, they should not be used alone to identify increases in prevalence rates of adverse events.

*Epidemiology studies*, such as cohort studies and case control studies, have a potential for bias in patient selection and in ascertaining outcomes and exposures. When well conceived and well conducted, these studies can provide data sources of adequate size to examine relatively rare events and

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\(^5\) “Managing the risks from medicinal products use - creating a risk management framework”, report to the FDA commissioner from the Task Force on Risk Management, May 1999
to investigate specific pregnancy safety concerns in depth. *Population-based surveillance* systems can experience under-reporting of outcomes and do not link specific maternal exposures to fetal anomalies.

*Pregnancy registries* are recognized as one method for ascertaining major risks associated with a drug or biologic exposure during pregnancy. For products known to adversely affect pregnancy outcomes or the developing fetus, the registry model may be used to estimate the magnitude of risk. A registry may also be used to identify factors that modify risk and to identify and quantify long-term effects such as delayed development, other neurological impairments, or any effects that might be detected in older children previously exposed in utero.

A pregnancy registry collects and analyzes reports of pregnancies exposed to a product or agent and actively obtains follow-up information on these pregnancies including outcome of the pregnancy and the infant. Voluntary reports are elicited from patients and healthcare providers based upon both identification of pregnancy and documentation of exposure at some time prior to and/or during pregnancy. At the time of registration, information is collected on the drug exposure, maternal disease status, and other factors that may affect pregnancy outcome. For prospective reports, pregnancies are followed and outcomes may be obtained using a variety of approaches, including maternal interviews, medical record abstraction or a combination of these methods.

Pregnancy registries are particularly important for products with a high use pattern in women of childbearing age because they are used to treat either chronic medical conditions or conditions with a high incidence in women. In

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addition, pregnancy risk information, particularly comparative information, is critical for products indicated for medical conditions that are caused or exacerbated by pregnancy such as asthma, diabetes, and hypertension. Pregnancy risk information is also important for products used in the treatment of conditions associated with high morbidity or mortality where treatment cannot be discontinued during pregnancy, such as some anti-infective or antiepileptic agents.

Pregnancy registries may also be useful to evaluate products suspected of causing harm during pregnancy based on animal reproductive toxicology studies, structure-activity relationships, pharmacological class, or human case reports.

ATM derivatives fulfill a number of these criteria; they are: 1) products expected to be used commonly by women of reproductive potential; 2) they are likely to be continued during pregnancy because they are necessary for a condition associated with high morbidity or mortality and 3) they are products suspected of adverse effects in human pregnancy based on findings from laboratory animal studies.

The figures below have been adapted from a report to the FDA commissioner from the Task Force on Risk Management entitled “Managing the risks from medicinal products use - creating a risk management framework”.

DRAFT PROTOCOL FOR MONITORING SAFETY OF ARTEMISININS IN PREGNANCY

Risk Management

(Rx Products)

Complex System for Managing the Risks of Medical Products

(Rx Products)
3. GENERAL OBJECTIVES

1. Estimate the magnitude of risk associated with the use of ATMs and other antimalarials in pregnancy
2. Identify and quantify immediate and long term effects of exposure to ATMs in pregnancy

4. SPONTANEOUS REPORTING

Information on suspected serious adverse events (notably, in this specific case, congenital abnormalities, fetal and maternal deaths) will be obtained via a pharmacovigilance system. The structure of this system is currently under design and is subject of a separate report. District Investigative Teams will evaluate each suspected report and this information will be integrated with that of pregnancy registries.

5. EPIDEMIOLOGICAL STUDIES

Further epidemiological studies will be needed to evaluate the possible association of ATMs with early pregnancy loss. This is a specific safety concern related to the preclinical studies demonstrating fetal resorption and lack of the data from use in the first trimester. Alternative designs, such as time-to-pregnancy studies, will need to be considered.

(Further information to be included after discussion with clinical experts mentioned by MG)
6. PREGNANCY REGISTRY

An active, prospective multi-centre surveillance system is to be established with enrollment of a representative, heterogenous study population. The registry is to include reports from different countries - Bangladesh, Zanzibar, Senegal and other countries introducing ATMs where prospective monitoring in pregnancy is feasible.

Multi-centre, international studies are logistically complex and require adaptations to country-specific differences in languages, medical practices, and rates of therapeutic abortions. Data collection instruments will need to be validated in the various research settings.

As malaria is associated with an increased risk of adverse pregnancy outcomes, a comparison to a healthy population without this condition may result in bias. Consequently, the selected comparison group involves pregnant women exposed to other antimalarials.

A. Patient Recruitment

A network of sentinel sites in the selected countries will aim at recruitment of all pregnant women with exposure to antimalarials. The successful implementation of this initiative will depend on the collaboration of WHO, local regulatory agencies and health authorities and pharmaceutical companies to promote awareness among healthcare providers and the public.

Material will be prepared for registry announcements, to recruit patients into the registry and to provide answers to questions anticipated from
responding healthcare professionals and patients. Accurate, current information on what is known about the product and its use during pregnancy will be included.

In an effort to avoid incomplete and misleading information, the registry will recruit and enroll women presenting to different health units, as demonstrated in the diagram. Women identified through the general pharmacovigilance system will also be followed.
B. Eligibility requirements

1. Woman with confirmed pregnancy (either through palpable fundus or positive pregnancy test)
2. Consent by patient or parent/guardian (if patient younger than 18).
3. Presence of one or more of the following conditions:
   a. History of antimalarial drug use during current pregnancy
   b. Positive malaria smear (clinical diagnosis of malaria)

Eligibility requirements might vary from country to country (e.g. married status) and these will need to be noted in the country specific protocols. If possible, a log of all patients refusing consent should be kept.

Prenatal testing (e.g. targeted ultrasound, chorionic villous sampling and amniocentesis) is not routinely available in the countries where the study is likely to take place, therefore, there is a low likelihood of enrolment of women with prior knowledge of pregnancy outcomes.
C. Data collection at enrollment

Once eligibility is determined and the patient consents to enroll in the study, baseline information on the patient, her pregnancy, the drug exposure, and medical conditions will be collected.

A draft data collection form is attached (Form A). The suggested minimal data elements to be obtained for each pregnancy exposure are highlighted (non-essential items marked in ‘blue text’). As mentioned in section 6, the forms will need to be modified according to the study settings. Although much of the information can be obtained upon interview and examination of the mother, medical record abstraction or an interview with the patient’s primary healthcare provider is strongly recommended to confirm information obtained. Care will be taken to ensure that the information is ascertained in an unbiased manner.

Recruiters will be instructed to reinforce the fact that the patient should report important events relating to pregnancy from the time of assessment until delivery.

D. Patient follow-up

The number and frequency of contacts should balance the burden to the patient and local health system with the desire to collect precise and detailed information on exposure and risks.

It is critical that all of the women enrolled in the study are followed in the same manner, regardless of their characteristics. Losing track of a particular subgroup of women, if the reason they are lost is in some way related to
their pregnancy outcome, can bias the study results. Additionally, losing a large proportion of study participants will invalidate an otherwise well designed registry.

A total of four visits to the woman and offspring are planned. Patients will be visited 7-30 days following recruitment to obtain updated exposure and risk factor information, as well as to assess the status of pregnancy, identify spontaneous abortions and elective terminations, and any medical reasons for elective termination.

Another visit is to occur as soon as possible after the expected delivery date. During this visit, general information regarding the delivery will be obtained and the newborn will be examined for major and minor congenital anomalies. Any abnormalities identified on this evaluation will need to be confirmed by specifically trained personnel (for example, District Investigative Team).

At 30-days after delivery, patients will be visited to determine if the child is alive. An additional visit is to take place between 6-18 months post-delivery for an assessment of developmental milestones.

The data collection forms have been devised for use by personnel with minimal training (forms B to E). All forms will need to be revised and validated in the research settings.
E. Study outcomes

- Proportion of anomalies in live-born, stillborn, late fetal deaths (ATM vs. other antimalarials) stratified by exposure interval, dose
- Determination of effect on fetal viability in second and third trimester and inadvertent exposures in first trimester (ATM vs. other antimalarials)
  - Proportion of Spontaneous Abortions
  - Proportion of Intrauterine death/Stillbirths
- Determination of neonatal and maternal mortality (ATM vs. other antimalarials)
- Determination of proportion of children with low birth weight (LBW) (ATM vs. other antimalarials)
- Assessment of developmental delays (ATM vs. other antimalarials)

As discussed, the current design will not address the issue of fetal resorption in first trimester (alternative designs, specific studies to be considered).

F. Statistical considerations

A total of 684 exposed pregnancies will be needed to detect a clinically significant difference in the proportion of major congenital abnormalities (100% increase; RR=2) with 80 percent power at the 0.05 level of significance. This sample size was calculated taking into account an estimated population rate of major birth defects of 3/100 liver births\(^7\). An

equal number of pregnancies should be enrolled in each group (unexposed or comparison drug)\textsuperscript{8}.

As the outcome of concern occurs only in live born infants, it is worth to consider that these may only represent approximately 50 to 60 percent of all prospectively enrolled pregnancies, considering the expected prevalence of spontaneous abortions, elective terminations and fetal deaths/stillbirths.