MEMORANDUM

From: Director, GMP To: Secretary, Expert Committee on the Selection and Use of Essential Medicines
Date: 7 February 2011

Our ref: Attention:
Your ref: EML 2011 Through:
Originator: PO/cj Subject: Preparation for the 18th Meeting of the Expert Committee for the Selection and Use of Essential Medicines (21-25 March 2011, Accra, Ghana)

Further to your memorandum dated 13 January 2011, please find enclosed our recommendations on the three specific antimalarial medicines:

- Inclusion: Artesunate + amodiaquine fixed-dose combination -- Adults and Children
- Inclusion: Dihydroartemisinin + piperaquine -- Adults and Children
- Not inclusion: Pyronaridine + artesunate fixe-dose combination -- Adults and Children

Please do not hesitate to request for more information if required.

With many thanks for your continuous collaboration and support.

Dr Robert Newman

ENCLS: (3)
APPLICATION FOR THE INCLUSION OF ARTESUNATE-AMODIAQUINE FIXED
DOSE COMBINATION IN THE WHO ESSENTIAL MEDICINES LIST

The WHO Global Malaria Programme supports the availability of fixed dose formulations of
antimalarial medicines, as this simplifies treatment regimens, and improves patients' adherence to
treatment and reduces the potential selective use of antimalarial medicines as monotherapy.
Artesunate plus amodiaquine is one of the artemisinin-based combination therapies (ACTs)
recommended by WHO for the treatment of uncomplicated falciparum malaria since 2001 (see

Up to 2008, only co-blistered packaging of the individual medicines was available and thus
included in the WHO Guidelines for the Treatment of Malaria (1st Edition 2006). The application
for inclusion in the EML of the same fixed-dose combination was first submitted in May 2007 by
Sanofi. Since at the time this formulation did not undergo any regulatory assessment, and was not
yet evaluated by the WHO technical committee for malaria chemotherapy, WHO/GMP at that
time did not recommend it for inclusion in the model list.

In 2008, the safety and efficacy of the fixed dose formulation was evaluated by the WHO
technical committee for malaria chemotherapy and found to be suitable for public health use,
leading to the inclusion of artesunate-amodiaquine fixed formulation in WHO Guidelines for the
Treatment of Malaria, (2nd Edition 2010, see

The specific formulation which is submitted for inclusion in the WHO EML has been
prequalified by the WHO Prequalification programme in October 2008 and it is presently the only
ACT with a shelf life of 3 years as against other ACTs which have a shelf life of 2 years. The
treatment regimen of the specific FDC of the application complies with the target dose of 4
mg/kg/day artesunate and 10 mg/kg/day amodiaquine once a day for 3 days, with a therapeutic
dose range between 2–10 mg/kg/day artesunate and 7.5–15 mg/kg/dose amodiaquine as
recommended by the last edition of the WHO Guidelines for the Treatment of Malaria.

This fixed dose formulation is already being used extensively both in the public and private
sectors in many malaria endemic countries where it is progressively displacing the non-fixed
formulations of artesunate+amodiaquine.

Based on all of the above, the department supports the inclusion of this formulation in the WHO
Model List of Essential Medicines
APPLICATION FOR THE INCLUSION OF DIHYDROARTESMISININ PLUS PIPERAQUINE FIXED DOSE COMBINATION IN THE WHO ESSENTIAL MEDICINES LIST

The WHO Global Malaria Programme supports the development of new ACT treatments for the management of malaria. It also recommends antimalarial medicines be made available as fixed dose and child friendly formulations, as this simplifies treatment regimens, improves patients’ adherence to treatment and reduces the potential selective use of antimalarial medicines as monotherapy.

Dihydroartemisinin plus piperaquine (DHA+PPQ) is a new ACT treatment option which has been evaluated for its efficacy, safety and public health significance at the last review of the WHO Guidelines for the Treatment of Malaria, and listed and recommended as one of the treatment options for the management of uncomplicated malaria (2nd Edition 2010, see http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf).

Although this application was made by a manufacturer whose product is currently in the phase of submission for registration by a stringent regulatory authority, the Global Malaria Programme supports the inclusion of this formulation in the WHO Model List of Essential Medicines for the following reasons:

- DHA+PPQ from several another manufacturers (same strength and formulation ratio) already exist on the market and are registered for use in several malaria endemic countries.
- DHA+PPQ is already deployed as first line or second line treatment of malaria as per the National treatment policies of several malaria endemic countries (e.g. Cambodia, China and Viet Nam). In some parts of these countries, because of resistance to combination partners of several ACTs, this combination is the only effective treatment choice for the management of uncomplicated falciparum malaria.
- As part of the global efforts for artemisinin resistance containment this formulation is recommended as 1st-line treatment of uncomplicated falciparum malaria in the zone 1 of the containment (see http://whqlibdoc.who.int/publications/2008/9789241596817_eng.pdf

Since this antimalarial medicine is available on the market with regulatory approval in several countries, and the inclusion in the Model List is not product specific, based on the above considerations WHO/GMP recommends support the inclusion of DHA+PPQ in the WHO Model List of Essential Medicines.
APPLICATION FOR THE INCLUSION OF PYRONARIDINE TETRAPHOSPHATE/ARTESUNATE FIXED DOSE COMBINATION TABLETS AND GRANULES IN THE WHO ESSENTIAL MEDICINES LIST

The WHO Global Malaria Programme supports the development of new antimalarial medicines, and in particular artemisinin based combination therapies (ACTs) in which the combination partner is novel and has not been much exposed or used as monotherapy. However, the GMP Department cannot support this particular application for the following reasons:

- Pyronaridine /artesunate has not yet been evaluated by any drug regulatory authority and is not available on the market
- Its efficacy and safety have not yet been reviewed by the WHO technical committee for malaria chemotherapy, and is not recommended for use in the WHO Guidelines for the Treatment of Malaria
- The medicine has been deployed so far only in clinical trials.

Though a promising antimalarial medicine, it is premature for inclusion in the WHO Model List of Essential Medicine.