

5 January 2006

New Hope for Malaria Patients in 2006

Dear Colleague,

We are delighted to inform you that the Drugs for Neglected Diseases Initiative (DNDi) and partners will be delivering two new fixed-dose artesunate-based combination therapies for malaria in 2006: **artesunate-amodiaquine** and **artesunate-mefloquine**. We are in the process of assembling the Quality, Pre-clinical and Clinical Registration files for these therapies, based on the development work of a consortium of public and private partners led by DNDi.

As you are aware, due to increasing resistance to monotherapy in the treatment of malaria, the WHO and national programmes have recommended the use of combinations of two anti-malarials, one of which should be an artemisinin derivative. DNDi's new artesunate-based combinations will soon be added to the arsenal of drugs to fight malaria. Both are easy to use (two tablets once a day for 3 days - adult treatment), available in paediatric formulations (one tablet once a day for 3 days), and offer the advantages of fixed-dose combination therapy, which could result in improved compliance, prevention of resistance, and reduction of transmission.

1. Artesunate-amodiaquine – AS/AQ

The pivotal clinical trial of AS/AQ carried out in Burkina Faso with the "Centre National de Recherche et de Formation sur le Paludisme" (CNRFP) is close to being concluded and includes infants and children, the population most susceptible to malaria in many regions of Africa. Other clinical activities, including pharmacokinetic investigations, are almost complete.

Meanwhile, DNDi has negotiated an agreement with one of the world's leading pharmaceutical companies, **sanofi-aventis**, to complete the manufacturing scale-up, registration, and distribution of this new product developed by DNDi. Sanofi-aventis will apply for WHO pre-qualification of the manufacturing site in Morocco and register the drug with the regulatory authorities of the countries concerned. It submitted the first marketing authorisation applications in December 2005.

The company has agreed to make AS/AQ available at cost price to the public sector, i.e., governments and government hospitals of disease-endemic countries, NGOs, and international not-for-profit organisations. The target price is less than US\$1 per adult treatment and 50 cents per paediatric treatment.

Sanofi-aventis will pay DNDi a licensing fee of 3% of net private sector sales for a period of 7 years. DNDi will use this payment to reduce the public-sector sale price of AS/AQ which, in addition, will be available patent-free and open to generic production immediately.

AS/AQ will be useful in countries and regions where resistance to amodiaquine has not yet developed to a significant degree, e.g., in many African countries and Indonesia.

2. Artesunate-mefloquine – AS/MQ

The WHO has recommended the use of AS/MQ combinations for malaria treatment in South East Asia and several countries in Latin America, where multi-drug resistance has been developing steadily. DNDi's pivotal Phase III clinical trials of AS/MQ were conducted

in Thailand in the first six months of 2005 by the Shoklo Malaria Research Unit, part of the Faculty of Tropical Medicine of Mahidol University, Thailand. The co-formulation was developed by **Farmanguinhos**, a state-supported drug development and manufacturing unit in Brazil.

The results of the 500-patient clinical study comparing AS/MQ with existing separate tablet formulations show a very high cure rate for patients in both groups – 94.1% for AS/MQ and 92.0% for the separate tablet formulation. The study included infants, children and adults. It will be complemented by pharmacokinetic and safety investigations of the new fixed-dose combination (FDC) and confirmation of biopharmaceutical quality.

Both the new FDC and the existing separate tablet formulation have similar safety profiles, with low and comparable rates of minor side effects, such as dizziness, lack of appetite, headaches, and sleep disturbance. The most commonly reported side-effect for mefloquine – early vomiting - is much lower for AS/MQ FDC (3%) than for the separate tablet formulation (8.4%).

Farmanguinhos, DNDi's partner in charge of pharmaceutical development, is committed to the production, registration and distribution of the drug in Brazil and Latin America. Meanwhile, DNDi is identifying pharmaceutical partners in Asia who will be able to manufacture and deliver AS/MQ at cost to the public sector – i.e., at a target price of \$2 to \$2.5 for the adult treatment.

In conclusion

By the end of 2006 these two new fast-acting artesunate FDCs will be registered for malaria treatment. If used properly, on a rational public health basis, they could be instrumental in saving countless lives lost to malaria every year.

It is now an acknowledged fact that the treatment of malaria cannot rely on a handful of drugs. We need not only more artemisinin combination therapies but also new chemical entities, and it is encouraging to see promising portfolios being developed along these lines by the Medicines for Malaria Venture and other initiatives.

Further information

If you wish to know more about DNDi's artesunate-amodiaquine and artesunate-mefloquine products please do not hesitate to get in touch with Dr Graciela Diap (gdiap@dndi.org) or Jaya Banerji (jbannerji@dndi.org).

Kind regards,

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