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The Secretary of the WHO Expert Committee on
The Selection and Use of Essential Medicines
Policy, Access and Rational use
Department of Medicines Policy and Standards
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To whom it may concern

We are happy to support DND's application for the inclusion of NECT, the co-administration of oral nifurtimox with iv eflornithine, into the WHO Model List of Essential Medicines for the treatment of second stage *T.b. gambiense* sleeping sickness (Human African Trypanosomiasis, HAT).

Standard treatment of second stage HAT still largely relies on the arsenic drug melarsoprol which may cause severe adverse drug reactions with a fatal outcome in about 5% of the treated patients, and for which an increasing number of treatment failures have been reported.

The newer and potentially safer alternative eflornithine suffers from a number of disadvantages which hampered the intended replacement of melarsoprol: Eflornithine monotherapy of HAT consists of a 14 day course of four daily infusions, resulting in the use of 56 necessary pouches of infusions fluids and seven changes of the iv lines. Despite the recent supply of fixed kits, the necessary logistics never had a realistic chance to become sustained by Ministries of Health and, therefore, the use of eflornithine remained rather limited to treatment centers entertained by NGOs. In the opinion of the experts at the Swiss Tropical Institute two other factors might have limited the expected large scale use of eflornithine monotherapy: On the one hand, the considerable number of infusion catheter changes in health facilities with limited professional capacity, and the obvious lack of stocks of ancillary antibiotics which would likely have led to a problematic rate of life threatening cases of septicemia. On the other hand, the use of eflornithine monotherapy bears the risk drug resistance development, and first reports of increasing rates of treatment failures have recently been brought up. Loosing the only drug in use for treatment of melarsoprol refractory patients is a daunting scenario.

Therefore, there is a high medical need for safer, more effective and easy to use alternatives. Since there are no new drugs for second stage HAT presently under clinical development, the idea to explore alternative treatment schedules and particularly, to combine currently available drugs, is highly justified.

Several trials assessing combinations of eflornithine, melarsoprol and nifurtimox were conducted in recent years. In all trials, the efficacy was better in the combination arm as compared to the monotherapies. In terms of safety, the combination of nifurtimox and eflornithine was clearly superior over any combination containing melarsoprol, and was therefore selected for further assessment. Eventually, a randomized, controlled, multi-center trial, NECT – nifurtimox-eflornithine combination therapy, was conducted in the Republic of Congo and the Democratic Republic of Congo comparing NECT with the standard eflornithine regimen.

HAT is a disease occurring in very remote areas of resource limited countries and, despite of its high socio-economic impact, the disease prevalence is often below 1% even in high endemic areas. This has essential implications on the conduct of clinical trials on this disease. Access to patients is difficult and clinical research infrastructure and professional capacity in those areas has not been maintained or never existed. In spite of those conditions, the NECT trial with 287 patients was conducted at a remarkably high quality standard. Before the initiation, significant staff training and laboratory improvement took place, the trial was continuously monitored according to the international standards of good clinical practice. An independent audit was performed by a certified specialist at Epicentre (clinical data management & statistics), the Pharmaceutical Medicine Unit of the Swiss Tropical Institute (contract research organization) plus at the field sites in the Republic of Congo and Democratic Republic of Congo. The audit reaffirmed the reliability, integrity and validity of the trial data.

The trial conclusively demonstrated the non-inferiority of the efficacy of NECT versus the standard eflornithine monotherapy, and it was well tolerated. Using the combination, the number of infusions can be reduced from 56 to 14. This reduces the necessary hospitalization time and the total amount of eflornithine by one third, and the necessary number of infusions by half. Under the conditions in many of the treatment centers, this is likely to have a positive impact on the frequency of nosocomial infections, but also on the compliance to the treatment schedule particularly because the drug applications at night time are no longer necessary.

The Swiss Tropical Institute has a longstanding experience in clinical research on sleeping sickness. In our experience, NECT is a significant improvement in the treatment of second stage *T.b. gambiense* HAT and it provides for the first time a true opportunity to replace melarsoprol as the first line treatment of the disease. In conclusion, we recommend the WHO's Expert Committee on the Selection and Use of Essential Medicines to adopt this new combination treatment into the WHO Model List of Essential Medicines.

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