NECT

Nifurtimox-Eflornithine Combination Therapy

NOW AVAILABLE

A Major Step Forward in Treating
Patients Suffering from Deadly Sleeping Sickness

Improved treatment for sleeping sickness

included in WHO Essential Medicines List

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NECT IN BRIEF

• AN IMPROVED TREATMENT OPTION

The Nifurtimox-Eflornithine Combination Therapy (NECT) is a new, improved treatment option for stage 2 (advanced stage) Human African trypanosomiasis (HAT) also known as sleeping sickness. The treatment is now available and is a simplified coadministration of nifurtimox, which is given orally, and eflornithine, which is given intravenously.

In May 2009, the World Health Organisation (WHO) included NECT in the Essential Medicines List (EML). This means NECT is now an option for the treatment of stage 2 HAT.

In July 2009, the Democratic Republic of the Congo (DRC) has placed an order with WHO for the first NECT kits to treat 6000 patients.

• MAIN ADVANTAGES OF NECT

The clinical trial results demonstrated that NECT has a comparable efficacy and a favourable safety profile to eflornithine monotherapy, the best previously available treatment for stage 2 HAT.

NECT is easier to administer, with a reduced number of intravenous infusions of eflornithine (14 instead of 56) and a shorter treatment period (10 days instead of 14). This proofs to be more convenient for patients and puts fewer burdens on the health staff, logistics and infrastructure.

NECT is cost-effective, reducing the cost of drugs and medical equipment and the cost of transport of the kit as well as the cost of hospitalisation.

• A COLLABORATIVE PARTNERSHIP

The development of NECT is the result of a collaborative partnership over a period of six years between DND*i*, Médecins Sans Frontières, Epicentre, HAT platform, the Swiss Tropical Institute (STI), the national control programmes from the Democratic Republic of the Congo (DRC) and Republic of Congo, with the support of the World Health Organization (WHO), with drugs donated by sanofi-aventis and Bayer Schering Pharma AG.

BACKGROUND ON DISEASE

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a life-threatening tropical parasitic disease. 60 million people are at risk in 36 countries that lie mostly in sub-Saharan Africa. HAT mainly affects those in poverty-stricken, remote, rural areas.

WHAT IS THE ANNUAL IMPACT OF HAT?

50,000-70,000 cases [1]
48,000 deaths (2)[2]
1,525,000 DALYS [3]
Large proportions of communities can be affected by HAT, with serious social and economic consequences. Epidemics at the end of the 20th century infected up to 50% population in several villages across rural Africa.

HOW IS HAT TRANSMITTED?

Transmitted to humans by tsetse flies, HAT is caused by two sub-species of the kinetoplastid protozoan parasite, Trypanosoma brucei: *T. b. gambiense* (west and central African), *T. b. rhodensiense* (east and southern African).

WHAT IS THE CURRENT PATIENT TREATMENT NEED?

Available treatments are few, old, and stage-specific. Stage 1 treatments, pentamidine and suramin, are fairly well-tolerated but still require injections and are mostly ineffective in stage 2. For stage 2 (where most patients are diagnosed and thus treated), 2 available treatments exist:

- melarsoprol, an arsenic derivative that is painful, toxic (killing 5% of those who receive it), and increasingly ineffective (up to 50% resistance and treatment failure).
- eflornithine, difficult to administer, requires trained health staff and constant hospitalization (requiring 56 infusions of 2 hours each over 14 days), and resistance is an increasing concern.

WHERE DOES HAT OCCUR?

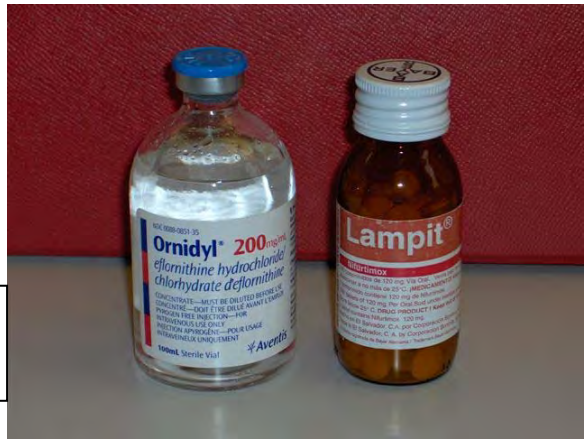
Of the 36 countries considered endemic for HAT, the 7 most affected countries represent 97% of all reported cases (see map). The Democratic Republic of the Congo (DRC) alone accounts for 2/3 of reported cases[4]. HAT primarily occurs in the poor and rural areas of Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.

WHAT ARE THE SYMPTOMS AND PRESENTATIONS?

HAT occurs in two stages:
Stage 1 - the haemolymphatic phase - includes non-specific symptoms like headaches and bouts of fever (generally goes undiagnosed without active HAT surveillance).
Stage 2 - the later, neurologic phase - occurs when the parasite crosses the blood-brain barrier (BBB) and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and, ultimately, results in death without effective treatment.

[1] World Health Organization (WHO). Wkly Epidemiol Rec. 2006:81;71-80.
[2] The World Health Report. Geneva; 2004. Available from http://www.who.int/whr/2004. Accessed Aug 12, 2008.
[3] DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.
[4] Simarro PP, Jannin J, Cattand P. PLoS Med. 2008;5:e55.

NIFURTIMOX-EFLORNITHINE COMBINATION THERAPY (NECT)



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With the ultimate goal to enable a WHO recommendation on the use of the nifurtimox-eflornithine combination therapy (NECT), the NECT project has shown that the combination is as effective and safe as standard eflornithine monotherapy, but easier to use, and safer than melarsoprol (highly toxic though still widely used in 50 % of patients with stage 2 HAT in 2008).
Begun originally in 2003 as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville), this study was extended, as of 2004, to additional sites in the DRC by DND*i* in collaboration with Epicentre, MSF, STI and the national HAT control programmes of the DRC.

This multi-centre clinical study, which enrolled 287 patients and was completed in 2008, compared the safety and efficacy of NECT, a coadministration of the oral drug nifurtimox and the intravenous drug eflornithine, with eflornithine monotherapy, the current first-line treatment for stage 2 *T. b. gambiense* HAT. As is requisite to establish efficacy in this disease, patients were actively followed up for 18 months after treatment.

The study conclusively demonstrated that NECT is as well-tolerated and efficacious as eflornithine. At the end of 2008, the final efficacy and safety results of the Phase III study were available and led to DNDi's submission of NECT for inclusion on the WHO Essential Medicines List (EML). The final results were published in The Lancet on July 4th, 2009 and were presented by Epicentre during the 2008 meetings of the American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org. The Essential Medicine List (EML) application and support statements of the HAT community are available on the website of the WHO EML.

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In May 2009, WHO announced that NECT had been included on the Essential Medicines List (EML). According to the WHO, NECT can now be used to treat patients and will provide an opportunity to improve the management of HAT cases. The WHO has already made preparations for the arrival of this improved therapeutic opportunity and is working to ensure that patients have access to NECT by providing appropriate training and supplying the drugs and necessary equipment to disease-endemic countries.

In July 2009, the Democratic Republic of the Congo (DRC) has ordered the first NECT kits to treat patients. Furthermore, DND*i* and partners are conducting a field study, which began enrolling patients in April 2009, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children. With a target of a minimum of 620 patients, by August 2009 already 150 people have been enrolled on five sites.

MAIN ADVANTAGES OF NECT

Nifurtimox-Eflornithine Combination Therapy – NECT, is an improved combination treatment for stage 2 HAT consisting of a co-administration of nifurtimox and eflornithine. While nifurtimox is given orally at a dose of 15 mg/kg/day, every 8 h for 10 days, eflornithine is given by intravenous infusion 400 mg/kg/day every 12 h for 7 days.

Availability of eflornithine and nifurtimox

Drug name (generic)	Drug name (proprietary)	Manufacturer	Supplied in
Eflornithine (DFMO)	**Ornidyl®**	**sanofi-aventis**	Glass bottles (200 mg/ml in 100 ml bottles). Eflornithine must be diluted before use. Once diluted, eflornithine can be stored in the fridge for up to 24 hours.
Nifurtimox	**Lampit®**	**Bayer Schering Pharma AG**	Glass bottles, each containing 100 tablets of 120 mg.

EFFICACY AND SAFETY

NECT is similar in efficacy and has a favourable safety profile:

A randomised, controlled clinical trial with 287 patients enrolled was completed in six years. It compared the safety and efficacy of NECT, a co-administration of the oral drug nifurtimox and the intravenous drug eflornithine with eflornithine monotherapy, the current first-line treatment for stage 2 HAT.

- A cure rate of more than 96 % was shown to be comparable between the two treatments.
- Patient follow-up 18 months after the treatment was at 93%. This is an excellent percentage given the remoteness and difficulty of access in the areas where the study was conducted.
- The trial conclusively demonstrated that NECT is as well-tolerated as eflornithine monotherapy.

Resistance less likely to develop:

- The two drugs have different modes of action, thus the risk of resistance is smaller as a mutual protection is expected.

Less toxic than melarsoprol:

- NECT is a less toxic, more efficacious treatment than melarsoprol which is estimated to kill up to 5 % of treated patients, and has a documented high level of resistance. In 2008, this drug was still used for 50 % of the patients suffering from stage 2 HAT.

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Reduced risk of infections:

- With NECT the number of intravenous infusions has come down from 56 (with eflornithine monotherapy) to 14. This reduces the risk of infection linked to repeated intravenous infusions considerably – particularly also since the treatment needs to be implemented in remote areas with limited health infrastructure capacities.

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EASIER TO ADMINISTER AND TRANSPORT

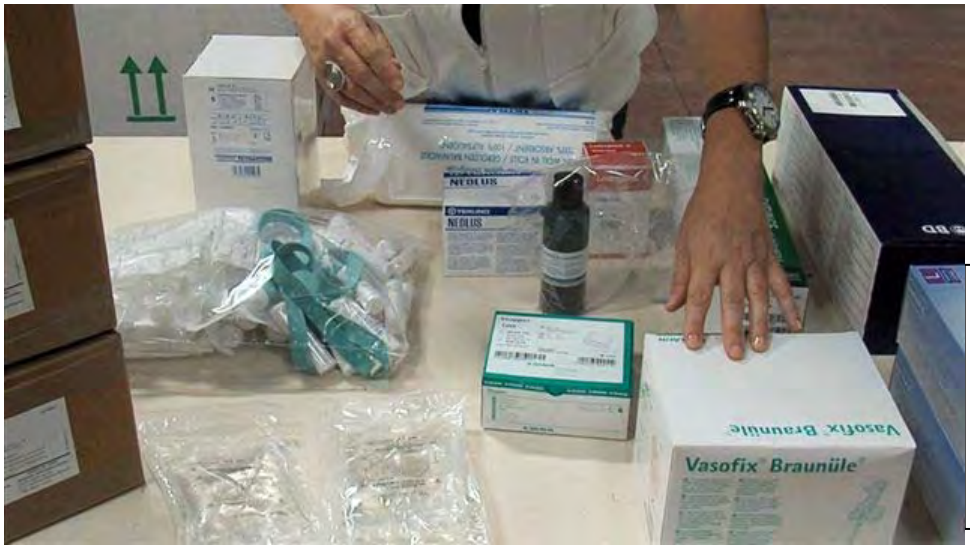
Reduced number of intravenous infusions:

- The number of infusions has come down from 56 to 14 compared to eflornithine monotherapy.

- With NECT the treatment is shortened to 10 days instead of 14. This makes NECT a treatment that is far more practical and more convenient for the patients.

Administered during the daytime:

- The infusions are reduced to twice a day instead of four times - one every 6 hours. The treatment can be administered during daytime. The patient does not require night time treatment, which puts less pressure on medical staff. NECT is therefore a far more suitable treatment for the remote and resource-poor settings where HAT is being treated.



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Volume and weight of treatment divided by half:

- To make the treatment more accessible, a treatment kit has been designed and is distributed by WHO, in collaboration with MSF Logistique. The kit, which consists of the medicines and all the materials needed for the proper administration of NECT, can contain 4 full treatments in an approx. 36 kg package as opposed to the current 2 full treatments per kit with eflornithine monotherapy.

- The volume per treatment also has come down to 37.5 dm3 instead of 85 dm3. This is a tremendous advantage in terms of logistics, especially when it comes to transport to remote areas in places such as the DRC.

Comparison between kit eflornithine (DFMO) and kit NECT

	KIT DFMO	KIT NECT
Number of treatments/kit	*2*	***4***
Volume/ treatment	*85 dm3*	***37.5 dm3***
Weight/ treatment	*19 kg*	***9 kg***

(Source WHO /MSF-Logistique)

COST-EFFECTIVE

Cost of treatment cut in half, available at 222.5 €:

- With less eflornithine, less intravenous infusion equipment, and infusion fluids used, the cost of a NECT treatment has been reduced by 50 %.

Comparison between kit eflornithine and kit NECT (estimation)

	KIT DFMO	**KIT NECT**
Cost of medicines	720 €	**773 €**
Cost of material	173 €	**117 €**
Total cost of kit	893 €	**890 €**
Treatment/kit	2	**4**
Cost treatment/patient	446.5 €	**222.5 €**

(Source WHO/ MSF Logistique)

Cost of transport less than half due to reduced weight and volume:

- The cost of transportation per patient goes down by half, since one kit can contain 4 full treatments instead of the 2 full treatments for eflornithine monotherapy. Sending 1 treatment of eflornithine from the MSF Logistique warehouse in France to Kinshasa in DRC costs 21.7 Euros. The cost of transport for 1 treatment of NECT is only 9.4 Euros.

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Cost of hospitalisation significantly reduced:

- With NECT, drugs have to be administered only during 12 hour a day instead of 24 hours. The patients receive their 2 injections during day time. This reduces the cost for medical staff dramatically.
- A patient treated with NECT needs to stay in hospital for 10 days instead of 14 when treated with eflornithine monotherapy. This also necessitates less staff time to administer and monitor the treatment.

PUBLICATIONS

"Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non inferiority trial", Priotto G, Kasparian S, Mutombo W, Ngouama D, et al.,Lancet, 4 July 2009;. 374 (9683): 56 – 64.

"*Three drug combinations for late-stage Trypanosoma brucei gambiense sleeping sickness: a randomized clinical trial in Uganda"*, Priotto G, Fogg C, Balasegaram M et al., Public Library of Science (PLoS) Clin. Trial 2006, 1:e39.

"Nifurtimox plus eflornithine for late-stage sleeping sickness in Uganda: a case series", Checchi F, Piola P, Ayikoru H, et al., PLoS Negl Trop Dis 2007, 1:e64.

"Nifurtimox-eflornithine combination therapy for second-stage Trypanosoma brucei gambiense sleeping sickness a randomised clinical trial in Congo", Priotto G, Kasparian S, Ngouama D, et al., 'Clin Infect Dis 2007; 45:1435-42.

DONORS & PARTNERS

Donors

Thanks to continuous support from public and private donors, DND*i* was able to provide 4.6 million Euros (€) in support of the clinical research phase, including 1 million € from the HAT Platform and 1.6 million € from the European Union (EU) as well as the support from

- the Ministry of Foreign and European Affairs (MAEE)-France
- the Spanish Agency of International Cooperation for Development (AECID) –Spain
- the Department for International Development (DFID) – United Kingdom
- Médecins Sans Frontières (Doctors Without Borders)
- the Medicor Foundation –Liechtenstein
- and the European Union - Framework Programme 5 and 6

Partners

• HAT platform

About HAT Platform

The HAT platform is a scientific and technical regional network dedicated to the Human African Trypanosomiasis (HAT). Its main objective is to set up a pool of highly qualified regional skills through relevant training in order to facilitate clinical trials and develop new diagnostics and treatment tools against the disease. Founded in 2005, this network, available to all, is composed of members from the HAT national control programmes of 7 endemic countries (Democratic Republic of Congo, Angola, Uganda, Sudan and Republic of Congo, Central African Republic, and Chad) in partnership with STI, DNDi, MSF, Epicentre, WHO, FIND, ITMA, and KARI-TRC. The contribution of the HAT platform in facilitating the NECT trials illustrates the key role that experts and partners from endemic countries play in defining strategies to succeed and particularly tackle the challenges of conducting and monitoring trials in remote areas.

• Epicentre

About Epicentre

Epicentre is a non-profit organisation created in 1987 by Médecins Sans Frontières, which groups health professionals specialised in public health and epidemiology. In 1996, Epicentre became a World Health Organization Collaborating Center for Research in Epidemiology and Response to Emerging Diseases. Epicentre's team carries out operational and clinical research from its offices in Paris (headquarters), Geneva, and Brussels, and a permanent research base in Mbarara, Uganda. Epicentre also offers its expertise to organisations requesting short-term field epidemiologic studies in developing countries. Epicentre designs and organises training sessions for Médecins Sans Frontières and other partners in public health and epidemiology. Epidemiologists from Epicentre also give guest lectures and organise training modules in the field of applied epidemiology as part of university or diploma courses. Lastly, Epicentre has developed an expertise in the development and field installation of software applications for the management of health information. For more information, please consult: http://www.epicentre.msf.org/.

• Médecins Sans Frontières (MSF)

About MSF

Doctors Without Borders/Médecins Sans Frontières (MSF) is an international medical humanitarian organization created in 1971. Today, MSF provides aid in nearly 60 countries to people whose survival is threatened by violence, neglect, or catastrophe, primarily due to armed conflict, epidemics, malnutrition, exclusion from health care, or natural disasters. MSF provides independent, impartial assistance to those most in need. MSF reserves the right to speak out to bring attention to neglected crises, to challenge inadequacies or abuse of the aid system, and to advocate for improved medical treatments and protocols. For more information, please consult www.msf.org.

• Swiss Tropical Institute (STI)

About STI

The Swiss Tropical Institute (STI) was founded in 1943 as an independent research institute and is an associated institute to the University of Basel. The STI has the mandate to contribute to the improvement of the health of populations internationally and nationally through excellence in research, services, and teaching and training. STI contributes effectively to bridge the

"translational gaps" in the R&D-process for drugs, vaccines and public health interventions between promising research outcomes and their validation and implementation for impact in resource limited economies. The institute has a long tradition, experience and track record in human African trypanosomiasis (HAT) in the endemic countries and has pioneered designing and implementing clinical research, studies and trials of all phases in HAT. Such pioneer studies include the IMPAMEL programme (improved application for melarsoprol) for second stage HAT and the DB289 phases II to III clinical trials in first stage HAT. The STI was the implementing partner in the NECT trial for 2 sites in DRC (Kasai) and monitored the trial in the 3 DRC sites. For further information, please consult www.sti.ch.

- ## sanofi-aventis

About sanofi-aventis

Sanofi-aventis, a leading global pharmaceutical company, discovers, develops and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and New York (NYSE: SNY). Sanofi-aventis, through its Department Access to Medicines, has committed itself in the fight against sleeping sickness, signing an agreement with the WHO in 2001.
50 million dollars are granted to the WHO over 10 years to help develop training and diagnosis actions, treatment and research against HAT. NECT is in line with this and thanks to the common efforts of the WHO, MSF, DNDi, sanofi-aventis, and Bayer, a shorter and more easy-to-administer treatment of eflornithine combined with nifurtimox will represent an important improvement before the arrival of a new oral treatment, today in phase I.

- ## Bayer Schering Pharma AG

About Bayer Schering Pharma AG

Bayer Schering Pharma's engagement in the fight against African sleeping sickness: Clinical trials have shown that a combination therapy made up of drugs containing the active substances nifurtimox from Bayer Schering Pharma and eflornithine from sanofi-aventis is especially promising in the fight against this African disease. As a result, the WHO added this combination therapy to the list of "essential drugs" in May 2009.
The parasitic pathogen is transmitted by the bite of the tsetse fly and is particularly widespread among the poorest sections of the population in the rural areas of this region. In an agreement signed in September 2009, Bayer Schering Pharma has committed itself to supplying 400,000 tablets a year of the drug Lampit (active ingredient: nifurtimox) over a period of 5 years for the eflornithine-nifurtimox combination therapy. In parallel, sanofi-aventis is donating the same amount of its drug Ornidyl (eflornithine). The donation of these two drugs for the combination therapy will enable the WHO to equip a package for treating African sleeping sickness, which will provide not only drugs but also training to maximize access to the combination therapy. The donation of 400,000 tablets a year is equivalent to delivering 4000 bottles of 100 tablets.
Bayer Schering Pharma is a leading global specialty pharmaceutical company. Its research and business activities are focused on four areas: Diagnostic Imaging, General Medicine, Specialty Medicine and Women's Healthcare.

- ## World Health Organization (WHO)

About WHO

WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends. The HAT control and surveillance programme focuses on:
Provide wider accessibility of people at risk to diagnosis and treatment. WHO assists 'National Sleeping Sickness Programmes' (NSSCPs) to implement control activities and capacity building through in-service training and thematic workshops at national, regional, and international level. Reagents and equipment for screening and diagnosis and drugs for treatment are also provided.
Strengthened surveillance. This is achieved through mobile teams who travel through endemic areas and who are active in case-finding and the maintenance of network for passive surveillance. Good reporting is imperative to allow WHO to properly follow-up the epidemiological evolution of the disease at continental level.
Guidelines and policies. These are jointly elaborated with health services of endemic countries and delivered to national implementing bodies through coordination seminars. The main objective is to harmonize control strategies and make optimal use of available tools.

- **Drugs for Neglected Diseases initiative (DND*i*)**

About DND*i*

The Drugs for Neglected Diseases initiative (DND*i*) is an independent, not-for-profit product development partnership, working to research and develop new and improved treatments for neglected diseases such as leishmaniasis, human African trypanosomiasis (HAT) or sleeping sickness, Chagas disease, and malaria. DND*i* was founded in 2003 by the humanitarian organization Médecins Sans Frontières (MSF) along with five research institutions in Brazil, France, India, Kenya, and Malaysia. With the objective to address unmet patient needs for these diseases, DNDi has developed the largest ever R&D portfolio for the kinetoplastid diseases and has already made available two new antimalarial treatments: "ASAQ" in 2007 with sanofi-aventis, and "ASMQ" in 2008 with Brazil's Farmanguinhos. In May 2009, NECT has been added to the Essential Medicines List (EML) of the World Health Organization (WHO) based on the application submitted by DND*i* and supported by Epicentre and Médecins Sans Frontières (MSF). In September 2009, Fexinidazole, a promising new drug for the treatment of HAT has entered the Phase 1 of clinical trial.