SSG&PM

Sodium Stibogluconate & Paromomycin Combination Therapy

NOW AVAILABLE

Shorter-course, cost-effective treatment for visceral leishmaniasis

Recommended as
First-line Treatment for Visceral Leishmaniasis in East Africa

by WHO Expert Committee on the Control of Leishmaniases

SSG&PM IN BRIEF

• AN IMPROVED TREATMENT OPTION

The **Sodium Stibogluconate & Paromomycin (SSG&PM) combination treatment** is a new, **improved treatment option** for visceral leishmaniasis (VL) – also known as Kala Azar – for Africa. The treatment is **now available** and is a shorter-course coadministration of both drugs, which are given intramuscularly.

In March 2010, **the World Health Organization (WHO) Expert Committee on the Control of Leishmaniases recommended SSG&PM** as first-line treatment for VL in East Africa.

SSG&PM is now **recommended as first-line treatment in Northern Sudan and Southern Sudan** and is being used to treat patients in the field.

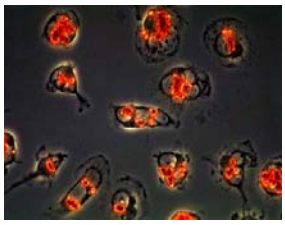
• MAIN ADVANTAGES OF SSG&PM

- SSG&PM has been shown in clinical trials to be as safe and effective as the current standard treatment of SSG alone for 30 days in East Africa.
- SSG&PM has a significantly shorter treatment duration than that of the standard treatment (**17 days *versus* 30 days**).
- The total drug cost of the SSG&PM combination is lower than the cost of SSG alone.
- Reduction of treatment duration means cost savings to both health providers and patients.
- Reduction of treatment duration is also critical to increasing patient turnover during outbreaks.

• A COLLABORATIVE PARTNERSHIP

The development of SSG&PM is the result of a collaborative partnership over a period of six years between DND*i*, the Leishmaniasis East Africa Platform (LEAP, see further), and other partners including the National Control Programmes of Kenya, Sudan, Ethiopia, and Uganda, as well as Médecins Sans Frontières (MSF) and the World Health Organization (WHO). The partnership reflects the benefits of South-South and North-South collaboration in making a new treatment available to patients in need.

DISEASE BACKGROUND



WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?

- 500,000 cases of visceral leishmaniasis (VL) [1]
- 1.5 million cases of cutaneous leishmaniasis (CL)[1]
- Approx. 50-60,000 deaths due to VL[1]
- 2,357,000 DALYs[1]

It is difficult to estimate the accurate incidence and case-fatality rate of VL due to frequent misdiagnosis and lack of surveillance systems.

HOW IS LEISHMANIASIS TRANSMITTED?

More than 20 species of the kinetoplastid protozoan parasite *Leishmania* can be transmitted to humans via some 30 species of phlebotomines sandflies.

WHAT ARE THE SYMPTOMS?

Leishmaniasis occurs in several forms, the two most common of which are:

- VL: characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anaemia. VL is life threatening.
- CL: characterized by lesions on the skin, which can either be self-healing or become chronic. CL is generally not life threatening.

WHERE DOES LEISHMANIASIS OCCUR?

Leishmaniasis occurs in 98 countries with 350 million people at risk.[1] VL affects poor populations living in remote areas of around 70 countries across Asia, East Africa, South America, and the Mediterranean region. The seven most affected countries, which represent over 90% of new cases, are Bangladesh, Brazil, Ethiopia, India, Kenya, Nepal, and Sudan.

VISCERAL LEISHMANIASIS TREATMENTS

WHAT ARE THE CURRENT TREATMENTS FOR VL AND THEIR LIMITATIONS?

The number of treatment options has increased in the past decade, but each treatment still has numerous drawbacks. Mostly they are difficult and lengthy to administer, toxic, and expensive. Resistance is an increasing problem.

- Pentavalent antimonials: toxic and increasingly ineffective due to resistance; requires 30-day, hospital-based parenteral treatment.
- Amphotericin B: dose-limiting toxicity; 15-20 day, hospital-based intravenous treatment.
- Liposomal amphotericin B (AmBisome®): effective, but expensive[2].
- Paromomycin: registered in India only, requires 3 weeks of intramuscular administration.
- Miltefosine: first orally available drug registered in India but expensive[2] and teratogenic.

WHAT ARE THE PATIENTS' TREATMENT NEEDS FOR VL?

Patients with VL need a treatment which is oral, safe, effective, low cost, and of short course.

(1) *Control of the Leishmaniases: Report of a Meeting of the WHO Expert Committee on the Control of Leishmaniases*, Geneva, 22-26 March 2010. WHO, Geneva, 2010.

(2) Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007.

SSG&PM COMBINATION THERAPY TREATMENT

BACKGROUND

In East Africa, most VL patients are treated with pentavalent antimonials (SbV). Two compounds are in clinical use: meglumine antimoniate (or Glucantime®) and sodium stibogluconate (SSG or Pentostam®). SbV are administered parenterally at a dose of 20 mg/kg/day, for up to 30 days. Intramuscular injections are the most common administration route, and are associated with intense local pain and systemic adverse effects.

Paromomycin (PM) is an aminoglycoside that was originally developed as a broad spectrum parenteral antibiotic. Minor nephrotoxicity, less than 1% reversible ototoxicity, and only minor hepatotoxicity are reported. The combination of SSG and PM was tested in the late 1990s in India to tackle the growing problem of SSG resistance in Bihar State. However, due to the declining efficacy of the standard SSG in India, further development of this combination was not pursued for the region. The Institute of OneWorld Health (iOWH) developed and registered (2006) PM as a monotherapy treatment (given for 21 days) in India. In the meantime, in order to respond to a medical emergency in the field, combination therapy of SSG and PM was used in Southern Sudan by MSF prior to the DND*i* study launched in 2004 (see below). Other available anti-leishmanials include oral miltefosine given for 28 days and liposomal amphotericin B, given as an IV infusion. Evidence on the use of the two latter treatments in East Africa remains limited.

In East Africa, standard SSG monotherapy has retained its efficacy. However, the treatment remains problematic due to toxicity and lack of feasibility associated with the long treatment regimens required. Furthermore, unlike in India, paromomycin was not registered in the region. Therefore, parallel to this, DND*i*, in collaboration with regional partners in East Africa (Leishmaniasis East Africa Platform, LEAP), commenced in 2004 a phase III trial comparing:

- SSG standard treatment for 30 days *versus*
- PM alone for 21 days *versus*
- SSG&PM combination for 17 days.

The trial results (see below) led to the successful development of the combination treatment.

The treatment is administered as follows:

- SSG (20mg/kg) given intramuscularly once a day for 17 days
  given concurrently with
- PM (15m/kg sulphate dose, 11mg/kg base dose) given intramuscularly once a day for 17 days.

LEAP 0104: A MULTI-COUNTRY CLINICAL TRIAL

In 2010, the Leishmaniasis East Africa Platform (LEAP) completed a multi-centre, multi-country clinical trial (LEAP 0104) sponsored by DND*i* in Kenya, Ethiopia, Sudan, and Uganda. The **LEAP 0104 study involved over 1100 VL patients** and showed that a short-course combination of PM (15mg/kg/day) and SSG (20mg/kg/day) had a similar safety and efficacy profile (efficacy at 6 months follow up post-treatment > 90%) as the standard SSG monotherapy treatment (SSG 20mg/kg/day for 30 days). The trial also demonstrated that the use of PM (15 or 20 mg/kg/day) alone for 21 days resulted in significantly lower efficacy. Thus the use of the combination will be critical to prolonging the use of both drugs in the region, particularly PM.

Moreover, this combination of SSG&PM has the additional **advantage of being a shorter course** (17 days) and **cheaper treatment than the standard treatment** of SSG alone for 30 days. From 22 to 26 March 2010, the **World Health Organization convened an expert committee** meeting that **recommended the use of the combination of SSG&PM as a first-line regimen for the treatment of visceral leishmaniasis (VL) in the East African region**. Following this, the **Ministries of Health in Sudan recommended the use of this therapy to treat VL**. Registration of paromomycin, for use in combination with SSG for VL in the region, is now underway and is expected to be completed by the end of 2011. Nonetheless, implementation at the field level has already commenced in Sudan.

MAIN ADVANTAGES OF SSG&PM

- To date, SSG&PM combination treatment offers **a real cost-effective option**, particularly since other alternatives such as miltefosine or liposomal amphotericin B remain unregistered, require high treatment doses, and are costly or unfeasible in the local healthcare setting.
- The **cost of drugs for SSG&PM is 44 USD**. This compares favourably to the alternative monotherapies of SSG for 30 days (nearly 56 USD), liposomal amphotericin B 20mg/kg total dose (252 USD) or miltefosine for 28 days (150 USD).
- SSG&PM offers **a shorter treatment duration** than SSG or miltefosine. It is also **feasible to administer in the primary healthcare setting**.
- The combination of SSG&PM has the potential to prolong the life of both drugs.

AVAILABILITY AND COMPARATIVE COST OF SSG&PM

Drug name (generic)	Manufacturer	Supplied in	Cost per treatment (based on a patient weight of 35kg)
Sodium Stibogluconate	Albert David (generic) GSK (propriety)	30ml vial of 100mg/ml	55.8 USD for a 30-day treatment of 20mg/kg/day
Paromomycin	Gland Pharma (single supplier only)	2ml vial of 500mg/ml	15 USD for a 21-day treatment of 15mg/kg/day (sulphate dose; equivalent to 11mg/kg/ day base)
SSG&PM	See above	See above	44 USD for a 17-day treatment at the above daily doses

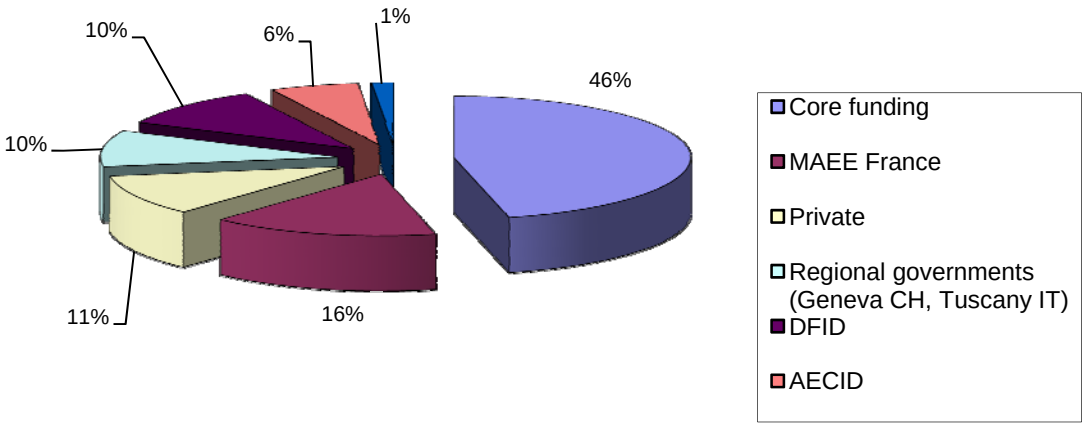
DONORS & PARTNERS

Donors

Thanks to continuous support from public and private donors since 2003, DND*i* was able to provide 8.6 million Euro (€) for the clinical research phase and for significant capacity building and infrastructure development for LEAP partners. In particular, support was granted from the following:

- Ministry of Foreign and European Affairs (MAEE) / France
- Médecins Sans Frontières (MSF) / international
- Region of Tuscany / Italy
- Spanish Agency of International Cooperation for Development (AECID) / Spain
- Republic and Canton of Geneva, Institution Department, International Solidarity / Switzerland
- Swiss Agency for Development and Cooperation (SDC) / Switzerland
- Dutch Ministry of Foreign Affairs (DGIS) / The Netherlands (as per January 2011)
- Department for International Development (DFID) / United Kingdom
- Medicor Foundation / Liechtenstein
- A Swiss public foundation and individual donors

Total budget for SSG&PM combination and capacity building: 8.6M € (2003-2010)



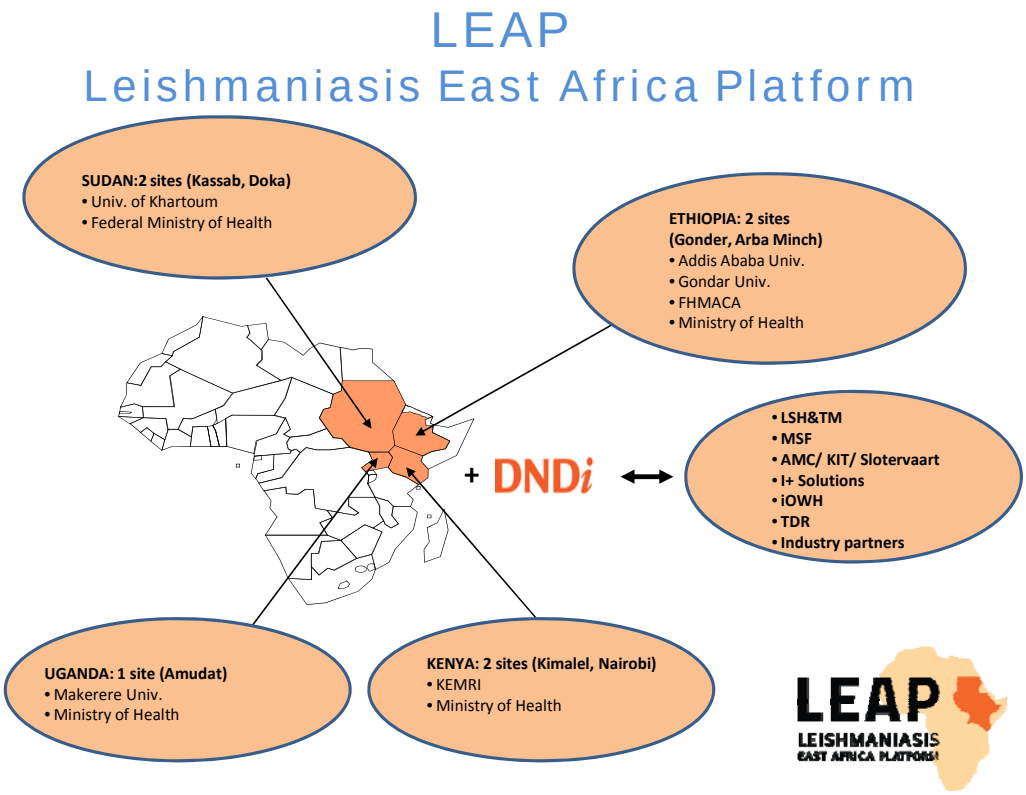
Partners

- **Institutional Partners**

In addition to LEAP and DND*i*, many partners have played a vital role in bringing SSG&PM to fruition. The London School of Hygiene and Tropical Medicine (LSH&TM) provided critical statistical and data management support and training. Médecins Sans Frontières (MSF) was involved as one of the investigating institutions and ran a trial site in Sudan. i+ Solutions and IDA Foundation were involved in procurement and logistics, and are currently involved in the registration of paromomycin. Gland Pharma and the Institute for OneWorld Health (iOWH) are supporting DND*i* in the supply and registration of paromomycin. The World Health Organization's Special Programme on Tropical Disease Research and Training (TDR) provided training and technical support.

- **LEAP Platform**

About LEAP
LEAP, the Leishmaniasis East African Platform, is a regional clinical research network whose goals are to: facilitate clinical testing and registration of new treatments for VL in the region (Ethiopia, Kenya, Sudan, and Uganda); evaluate, validate, and register improved options that address regional needs for VL; and provide capacity strengthening for drug evaluation and clinical studies in the region. Founded in 2003 in Khartoum, Sudan, LEAP incorporates partners from across the spectrum of clinical research and disease control organizations working in leishmaniasis-endemic countries in East Africa. LEAP is jointly hosted by the Kenya Medical Research Institute (KEMRI); the Faculty of Medicine, Addis Ababa University, Ethiopia; the Institute of Endemic Diseases, University of Khartoum, Sudan; and Makerere University, Kampala, Uganda. It includes DND*i*, MSF, WHO, and other partners working in VL in East Africa.



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

About DND*i*
The Drugs for Neglected Diseases *initiative* (DND*i*) is a patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable medicines for diseases that afflict millions of the world's poorest people. DND*i* focuses on developing new treatments for the most neglected patients suffering from diseases such as sleeping sickness (or human African trypanosomiasis), leishmaniasis, Chagas disease, and malaria and recently announced an expansion of its portfolio to include specific Helminth infections and paediatric HIV. DND*i*'s primary objective is to deliver six to eight new treatments by 2014 and to establish a strong R&D portfolio for these diseases.

PUBLICATIONS

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Geographical Variation in the Response of Visceral Leishmaniasis to Paromomycin in East Africa: A Multicentre, Open-Label, Randomized Trial by Hailu A, Musa A, Wasunna M, Balasegaram M, Yifru S, Mengistu G, Hurissa Z, Hailu W, Weldegebreal T, Tesfaye S, Makonnen E, Khalil E, Ahmed O, Fadlalla A, El-Hassan A, Raheem M, Muellerm, Koummuki Y, Rashid J, Mbui J, Mucee G, Njoroge S, Manduku V, Musibi A, Mutuma G, Kirui F, Lodenyo H, Mutea D, Kirigi G, Edwards T, Smith P, Muthami L, Royce C, Ellis S, Alobo M, Omollo R, Kesusu J, Owiti R, Kinuthia J, for the Leishmaniasis East Africa Platform (LEAP) group. *PLoS NTD*, 2010 October, 4(10):e709.

Combination therapy for visceral leishmaniasis by van Griensven J, Balasegaram M, Meheus F, Alvar J, Lynen L, Boelaert M. In *Lancet Infect Dis* 2010; 10: 184-94.

Developments in the treatment of visceral leishmaniasis by den Boer M. L, Alvar J, Davidson R. N, Ritmeijer K, Balasegaram M. In *Expert Opinion on Emerging Drugs*, 2009 Sept, 14; 3, 395-410.

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For the most neglected

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