OneWorld Health, a drug development affiliate of PATH

Paromomycin Intramuscular Injection

Safe, effective, and affordable treatment for visceral leishmaniasis

Visceral leishmaniasis (VL), or kala-azar, is a neglected and deadly infectious disease that is transmitted through the bite of a sand fly. It affects the visceral organs, causing chronic fever, weight loss, and anemia. If left untreated, VL is nearly always fatal, especially in children. VL is endemic in 79 countries, primarily in the developing world. The population at risk is estimated at 200 million; 20,000 to 40,000 people are believed to die from VL each year. Until recently, the only available therapies were expensive for the most vulnerable, poor populations—from US$20 to $250—and could be toxic or ineffective.

Paromomycin, an off-patent aminoglycoside antibiotic, is an established drug with an extensive history of use and a well-characterized safety profile. OneWorld Health (OWH), a nonprofit drug development program dedicated to discovering and advancing lifesaving medicines for neglected diseases, developed paromomycin intramuscular injection (PMIM) as an effective, inexpensive, and safe treatment for VL and worked with leading clinical researchers and the Indian pharmaceutical company Gland Pharma to manufacture and distribute the treatment. The cost of a course of treatment with PMIM is less than US$20, significantly lower than other currently approved VL therapies.

A number of studies are evaluating PMIM for use in combination with other treatments as a key tool in global VL elimination strategy.

WORLD HEALTH ORGANIZATION RECOMMENDATIONS FOR PMIM

The World Health Organization (WHO) recommends the use of PMIM as preferred combination therapy to treat both forms of VL[1]:

- Anthroponotic visceral leishmaniasis (AVL), which is caused by *Leishmania donovani* and primarily seen in South Asia (India, Nepal, and Bangladesh):
  - PMIM with miltefosine (10 days).
  - Liposomal amphotericin B (single dose infusion) with PMIM (10 days).
- Visceral leishmaniasis, caused by *Leishmania donovani* and primarily seen in East Africa (Ethiopia, Eritrea, Kenya, Somalia, Sudan, and Uganda):
  - Pentavalent antimonials with PMIM for 17 days (most preferred therapy).

MANUFACTURING CAPACITY

Gland Pharma has the capacity to manufacture 65,000 PMIM ampoules per day, provided it has adequate supply of the active pharmaceutical ingredient.

PMIM REGISTRATION STATUS

PMIM is registered with the National Drug Development agencies of India (2006), Nepal (2012), and Uganda (2012).

PMIM is included on the Essential Medicine Lists of the World Health Organization (2007), Bangladesh, Ethiopia, India, Nepal, Sudan, and Uganda.

Registration for PMIM is ongoing in Bangladesh, Ethiopia, Kenya, and Sudan.

Patients in a kala-azar clinic, India. Photo by Jonathan Torgovnik©.

ESTIMATED TOTAL USAGE OF PMIM SINCE 2009*

An estimated 24,000 VL patients have been treated with PMIM since 2009 through studies and public health programs, with 2,300 in South Asia and the rest in Africa.

*Based on supply of PMIM from Gland Pharma.

CURRENT STUDIES WITH PMIM

India: OWH will be initiating a clinical study to assess the feasibility of using PMIM in combination with other VL treatments in several sites in the Indian state of Bihar. This is part of a series of studies on optimal VL treatments within the public and private sectors being done in partnership with the Drugs for Neglected Diseases *initiative* (DND*i*) and TDR, the Special Programme for Research Training in Tropical Diseases.[2]

Bangladesh: OWH completed a clinical study in Mymensingh District on PMIM as a monotherapy. DND*i* is currently employing PMIM in ongoing, large-scale combination studies in the same district.

Nepal: OWH will implement a public health access study using PMIM in combination with other VL treatments at several government health centers in endemic areas in Nepal beginning in late 2012.

PARTNERS

- Bill & Melinda Gates Foundation
- Drugs for Neglected Diseases *initiative* (DND*i*)
- Leishmaniasis East Africa Platform (LEAP)
- Gland Pharma
- Governments of Bangladesh, India, and Nepal
- i+ solutions
- IDA Foundation
- Médecins Sans Frontières
- Special Programme for Research Training in Tropical Diseases (TDR)
- World Health Organization

ACKNOWLEDGEMENTS FOR PMIM

In 2012, WHO removed all restrictions on the import of PMIM from Gland Pharma and announced that it will begin to procure PMIM for the treatment of VL.

In 2011, Dr. Mounir Cristo Lado Lugga, Director of Endemic Tropical Diseases, Ministry of South Sudan, acknowledged PMIM's lifesaving role in South Sudan at the Leishmaniasis East Africa Platform (LEAP)[3] meeting in Nairobi.

In 2010, LEAP completed a multicenter, multi-country clinical trial in Kenya, Ethiopia, Sudan, and Uganda, sponsored by DND*i*. The LEAP 0104 study evaluated the use of paromomycin in a shorter 17-day course in combination with the VL drug sodium stibogluconate (SSG) as an improved treatment for VL. The study demonstrated that sodium stibogluconate and paromomycin (SSG&PM) combination therapy is as safe and effective as the SSG standard monotherapy with the advantage of offering a shorter and cheaper treatment course.[4] In March 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as a first-line treatment for VL in East Africa.[5]

For more information on PMIM, contact Dr. Raj Shankar Ghosh at info@path.org.

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Headquartered in South San Francisco, OneWorld Health is a nonprofit drug development program with a mission to discover, develop, and deliver safe, effective, and affordable new treatments for diseases disproportionately affecting people in the developing world. For more information, please visit www.oneworldhealth.org.

OneWorld Health is an affiliate of PATH, an international nonprofit organization that transforms global health through innovation. To learn more about PATH, visit www.path.org.

[1] WHO Technical Report Series 949. Control of the Leishmaniases: report of a meeting of the WHO Expert Committee on the control of Leishmaniases. Geneva, 22-26 March 2010. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_949_eng.pdf/. Accessed April 23, 2012.
[2] OneWorld Health website. Available at www.oneworldhealth.org/press_releases/view/pr_1320949017. Accessed April 23, 2012.
[3] Launched in 2003 with the support of DND*i*, LEAP brings together scientists and institutions in East Africa to develop clinical trial capacity to bring new treatment options to neglected VL patients in the region. Member countries include Sudan, Ethiopia, Uganda, and Kenya.
[4] Musa AM, Younis B, Fadlalla A, et al. (2010) Paromomycin for the treatment of visceral leishmaniasis in Sudan: A randomized, open-label, dose-finding study. *PLoS Negl Trop Dis* 4(10): e85. Available at: www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0001674.
[5] SSG&PM co-administration (VL in Africa). DND*i* website. Available at: www.dndi.org/portfolio/new-vl-treatments-ssg-pm.html. Accessed April 23, 2012.