MEMORANDUM

From:	Dr J. Alvar, CDS/NTD/IDM	**To:**	Coordinator, HTP/EDM/PAR and Secretary, Committee on the Selection and Use of Essential Medicines	**Date: 2 February 2007**
Our ref:		**Attention:**	Dr Suzanne Hill	
Your ref:		**Through:**	Coordinator, IDM Director, NTD 9/2	
Originator:	/jb	**Subject:**	REQUEST FOR ENTERING PAROMOMYCIN IN THE ESSENTIAL MEDICINE LIST	

In relation with the application of paromomycin (PM) to treat visceral leishmaniasis formulated by the institute of One World Health to be included in the EDL, the signer would highlight the pros- and contras- of this drug based in the extension of the disease, and the reduced panoply of available drugs (antimonials, amphotericin B, miltefosine, and now PM). Antimonials are in the EDL. Visceral leishmaniasis is present in 62 countries with an incidence estimated in 500,000 new cases per year, 50% of them in Bihar state, India. In most of the districts in Bihar north the Ganges River, resistance to antimonials reaches up to 60%.

PM is an aminoglycoside antibiotic marketed for more than 40 years for bacterial and protozoal infections, with extensive safety profile. To treat leishmaniasis, PM has to be given intramuscular PM IM injection (94.6% final cure rate when given for 21 days) and PK does not evidence of accumulation following repeat administration with normal renal function; no differences are found when comparing women, men and children according to phase III results. No teratogenic effect at therapeutic doses has been detected in rats and rabbits in regards to fertility, embryonic development, teratogen potential, and prenatal/postnatal development.

Aminoglycosides can produce ototoxicity, although PM IM injection phase III studies show that this drug has no relevant hearing effects (1,6% transient and reversible ototoxicity out of 442 treated patients; based on audiometry: 1/7 cases within the speech range). Injection site pain is common (55%). Liver transaminases can increase transiently, like all other anti-leishmania drugs.

PM IM injection in visceral leishmaniasis has been used in limited scale: a phase III multi-center trial including 442 patients from India and Sudan has shown higher efficacy in the former. In fact, in Sudan PM IM injection has to be used in combination with other anti-leishmania drug. Phase IV study has already started in India, including 2000 patients. PM IM injection has the FDA and EMEA orphan drug status, and it has been registered in India so far. Little bibliography is available on the use of this drug for visceral leishmaniasis.

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PM IM injection has to be administered during 21 days, a significant less duration than the rest of injectable or oral drugs (28 days), and the inoculum is 1 ml, much less than the other drugs making possible to be administered in primary health centers. PM resistance can not be ruled out in the future, in spite of the shorter treatment duration, the fact that compliance increases being an injectable drug when compared with oral drugs, and also considering its price. Indeed, the price of PM IM injection (US$10 for adults and 5 for children) make this drug much more affordable by control programs and also by the neglected people that commonly suffer this disease. Insufficient data are available regarding the use of PM IM injection in pregnant women, aspect that will be explored during phase IV study. Until we obtain the above-mentioned information, contraception is strongly advised if PM IM injection is to be used in childbearing age women.

Considering the above mentioned arguments, PM could be included in the EDL to be used in the Subcontinent India and in combination with other drug in Eastern Africa; further indications of its use can only be recommended when more experience is gained.

Dr J. Alvar