Institute for OneWorld Health

A Nonprofit Pharmaceutical Company

Lessons Learned from the Registration of Paromomycin in India

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Paromomycin history (1)

- Broad spectrum **aminoglycoside antibiotic**

- First manufactured in **1959** by Farmitalia Carlo Erba (Italy) as an antibiotic
- **Multiple approvals** have been granted over the years as an antibacterial
- **Generic names include**: aminosidin sulfate, aminosidine sulfate, catenulin sulfate, crestomycin sulfate, estomycin sulfate, hydroximycin sulfate, monomycin A sulfate, neomycin E sulfate and paucimycin sulfate.

- **Trade names (parenteral) include**: Gabbromicina, Gabromicina and Gabromycin

Paromomycin History (2)

- Marketed internationally as a **parenteral antibacterial** agent and as **oral antiprotozoal** agent since the 1960's
- (> 40 years)

- Oral and injectable formulations marketed, but **only oral formulation** still available by the time the Phase 3 clinical trial in Visceral Leishmaniasis (VL) was planned

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Paromomycin History (3)

- **Late1980's-mid 1990's**: number of pilot clinical trials for safety & efficacy against kala azar with Pharmacia & Upjohn (P&U) donated injectable PM

- **1993-1997** : pre-clinical and clinical studies supported by TDR/University of Illinois/SoloPak Pharmaceuticals to expand the dossier

- **1997-today**: TDR/IDA developed new liquid filled GMP injectable PM dosage form which was proven to be bio-equivalent to P&U product.

- **2001** Institute for One World Health (iOWH) set up a new partnership with TDR/IDA

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Paromomycin: Project Objectives

- To **produce a safe and efficacious GMP injectable product** for VL treatment
- To **produce and submit a regulatory dossier** that meets international regulatory guidelines
- To produce a GMP finished product **to be available in the public sector of VL endemic countries** for the lowest cost possible per 21 day treatment course

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PM Chemistry, Pharmacy, Pre-clinical & PKs

- Source of GMP drug substance raw material:
  - **Antibioticos, Milan, Italy**
- Source of GMP drug product
  - **Pharmamed Parenterals Ltd (PPL), Malta**, for IDA, Amsterdam
  - 500 mg PM sulfate / ml - 2ml
- **All tests negative for mutagenicity & genotoxicity**
- **PKs**: HPLC, single dose IM assay to evaluate PM concentration in biological fluids of 16 HNVs at 12 or 15 mg/kg

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PM Safety data: use on infectious diseases

- Summary data for **2.397 patients treated with injectable PM for various infectious diseases**.
- Up to 2g/day for 30 days
- AEs; hearing function (0,4%), renal dysfunction (0,1%) not age-related

- **Japanese data on 2.220 patients**
- AEs: injection pain (4,2%), local rash (1,4%)

- **High safety profile**

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PM: Several phase II clinical trials with CRFs

- **In India, Kenya & Sudan**

- **VL randomised controlled trials:**
  - PM versus pentavalent antimonials (Sb5+)
  - PM + Sb5+ versus Sb5+ alone
  - Different doses of PM (12 to 20 mg/kg/day for 21 days)
  - >10 clinical trials

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GCP Bio-equivalence Study

- To demonstrate the **bio-equivalence between the "Old" and "New" formulations of PM**
- 16 HNVs randomised to 15 mg/kg of "Old" and "New" formulations
- **Higher peak (C max)** observed with the PPL Paromomycin product
- Higher peak don't affect toxicity profile of the drug
- **The two products were considered to be bio-equivalent**

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Phase 3 Clinical Trial

- Conducted in **Bihar State**, a VL highly endemic region in India
- **667 patients in 4 sites**
- Principal investigators (PIs) from KACE were **highly experienced leaders** in the treatment of VL. They provided guidance in protocol development
- To compare safety & efficacy of **paromomycin** to standard treatment in the region, **amphotericin B** in a randomised, open-label, controlled trial

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Registration Dossier

- **Summary of international marketing history**, including list of all countries in which paromomycin had ever been marketed
- **Discussion of product withdrawals** with focus on reasons for withdrawal (not safety related)
- **Summary of safety profile**, including Summary of Product Characteristics and reports from the WHO Uppsala Monitoring Centre database

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Registration Dossier

- **Phase 3 clinical study report** submitted to DCGI
- **Manufacturing information**, with reference to US pharmacopeial monograph for paromomycin active ingredient
- **Summary of nonclinical information**, primarily from the literature
- **Summary of published clinical studies**, including one pharmacokinetic study in humans

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Lessons Learned

- Important to **engage local clinical and regulatory experts before initiating development work**
- Helpful to capitalize on clinical investigators' and regulators' recognition of the **need for a new treatment for VL**
- Important to consolidate **extensive information** from previous use in **other indications and in other regions** to provide a thorough discussion of the risks and benefits of the drug
- Important to provide data showing the drug could be used **safely and effectively in the Indian population**

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Additional Registrations

- Registration dossiers in preparation for filing in **Bangladesh and Nepal**
- Rely on **Indian approval** and information from Indian dossier and safety information from recently completed **Phase 4 study (500 patients)** plus **PM inclusion in WHO, EML**
- Several meetings held with governments of both countries to reach agreement on **requirements for timely approval** of an important, new treatment for VL

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Thank you!

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