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Dear Jorge:

Application for inclusion of paromomycin in the WHO Model List of Essential Medicines

As a result of the successful product development by OneWorld Health, the Bill & Melinda Gates Foundation, Gland Pharmaceuticals, and WHO/TDR, Paromomycin IM Injection was granted regulatory approval in India for treatment of visceral leishmaniasis in August 2006. The pursuit of regulatory approval in other VL-endemic countries will begin shortly.

Paromomycin IM Injection is a safe, effective and inexpensive treatment for this neglected disease, including for cases resistant to other drugs. We hope the WHO will decide to include Paromomycin IM Injection in the List of Essential Medicines. As well as wider acceptance in India, we anticipate that inclusion will assist licensing of paromomycin in other countries, both alone and in combination, in the years ahead.

From inception, Paromomycin was developed to be the least expensive antileishmanial drug available, precisely because patients who suffer from VL are so desperately poor. Paromomycin itself is inexpensive because it is fermented and it has been off-patent for many years. As you know, OneWorld Health (San Francisco, [IOWH]) is a not-for-profit company, and does not receive any financial return whatsoever from drug sales. The research, development and technology transfer costs were provided through grants to IOWH from the Bill and Melinda Gates Foundation (Seattle). Gland Pharmaceuticals Ltd. (Hyderabad) produces paromomycin IM injection on an at-cost basis. WHO/TDR does

not benefit financially from this product. As demonstrated comparatively at the rear of this document, paromomycin is the least expensive VL cure available anywhere in the world.

Because paromomycin was first marketed in 1959 and has been used in dozens of countries for decades as an injectable antibiotic, much is known about its safety profile: paromomycin's adverse events are predictable and mirror those of other marketed aminoglycosides such as gentamicin. *This prior marketing is a major advantage in the decision of whether to prescribe or recommend paromomycin for the treatment of leishmaniasis.*

We have been urged to make this application by Médecins Sans Frontières – Holland and MSF's Campaign for Access to Essential Medicines, who have assisted us in this application.

We have kept this application rather brief. We do have a wealth of additional supportive data on every aspect of paromomycin, which we would be delighted to share with WHO on request during the consultation period that follows this application. In this document we have not cited nor appended published references, but can easily provide these on request.

I do hope this application will be successful, and remain,

Yours sincerely

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cc to
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Application for inclusion of Paromomycin IM Injection in the WHO Model List of Essential Medicines

1. Summary statement of the proposal

Indication: Visceral Leishmaniasis

1 (a) Visceral leishmaniasis is a neglected disease of developing countries

Visceral leishmaniasis (VL), a lethal protozoal vector-borne disease, affects a large rural poor population in South Asia and the Horn of Africa.

1 (a) Inadequacies in the current medicines for VL on the WHO Model List of Essential Medicines

In the main list of the WHO Model List of Essential Medicines, only meglumine antimoniate is listed as a treatment for VL, as an example of the class of pentavalent antimonial drugs. In the *complementary list* are listed amphotericin B and pentamidine. There are major shortcomings of these medications.

Pentavalent antimonials (sodium stibogluconate and meglumine antimoniate) are historically (since the 1940s) the therapeutic mainstay for VL, but they have significant toxicity. Resistance to antimonials, which have historically been the first-line of treatment for VL in Bihar and adjoining States, is now reported in up to 60% of patients in some areas of Bihar. Deaths have been attributed directly to the antimonial drugs.

Pentamidine is toxic and has (since the 1980s) lost its initial level of efficacy and is no longer a recommended alternative treatment for VL.

Amphotericin B, though highly effective, is expensive, must be infused IV over 6 hours, is associated with fever/chills/rigor, can be nephrotoxic, and requires close clinical and laboratory monitoring with hospitalization. The drug is not suitable for use in regular field conditions.

1 (b) Problems with other medicines for VL which are not included on the WHO Model List of Essential Medicines

Liposomal amphotericin B (AmBisome®) has excellent of safety and efficacy; however, its cost is unaffordable in most VL-endemic countries. Like amphotericin B, AmBisome requires IV infusion, which is not feasible in remote settings.

The oral drug miltefosine is relatively expensive and is teratogenic. Women of childbearing potential have to use effective contraception for 3 months due to the long half-life of the drug.

1 (c) Paromomycin

The approved regimen is paromomycin (base) 11 mg/kg IM for 21 days. (equivalent to paromomycin sulfate 15 mg/kg IM for 21 days used in the Phase III trial).

Note to reviewers: The Phase III clinical trial, VLPM01, which forms the basis of our submission for approval of Paromomycin IM Injection to treat (VL), used a drug product with a nominal strength of 500 milligrams (mg) of paromomycin sulfate per milliliter (mL) and a dose of 15 mg of paromomycin sulfate per kilogram (kg). We will market a drug product, Paromomycin IM Injection, with a concentration of 375 mg of paromomycin per mL at a recommended dose of 11 mg of paromomycin per kg.

It is important to note that, with this product, the composition of the formulation, and the strength and dosage, in terms of paromomycin, are essentially the same as that used in the Phase III clinical trial VLPM01. The reason for our label change is as follows:

Aminoglycoside antibiotic active pharmaceutical ingredients (APIs) are, in most cases, isolated during the manufacturing process as sulfate salts, and the sulfate load varies from batch to batch. Consequently, for consistency of potency from batch to batch, dosage forms of aminoglycoside antibiotics are labeled as per base, not salt form, to accurately reflect the concentration of active moiety. This is true almost without exception for all of the aminoglycosides currently in use (gentamicin, amikacin, tobramycin, etc.; United States Pharmacopoeia [USP] and product labeling for each dosage form).

The paromomycin sulfate API is fermented and purified by Antibioticos (Milan) and contains amounts of sulfate that can vary by as much as 10% or more. Therefore, to align our manufacturing practices with current industry standards, we propose to manufacture and label Paromomycin IM Injection so that each batch contains the same amount of base molecule. So while the product still contains approxinately 500 mg paromomycin sulfate (+/- 10%), the product contains exactly 375 mg/ml paromomycin base.

How does this label change impact the effective dose?

15 mg/kg paromomycin sulfate was effective in India in our Phase III clinical trial and is effective in MSF's hands in South Sudan in combination with SSG. This salt dose of 15 mg/kg is equivalent to 11 mg/kg of base. *Throughout the remainder of this document, 11 mg/kg paromomycin will be discussed as the effective dose.*

1 (d) Devlopment of paromomycin for VL

Paromomycin, an aminoglycoside antibiotic, was first marketed in 1959 and has an extensive and well-characterized safety profile. It is the only aminoglycoside with anti-protozoal activity. Its anti-leishmanial activity was first described in 1968. In 1986 a proof-of-concept study in Kenya confirmed the clinical efficacy of paromomycin in patients with VL. An additional study in Africa and several Phase II WHO/TDR-sponsored studies in India demonstrated efficacy in the treatment of VL using either Paromomycin IM Injection alone, or in conjunction with sodium stibogluconate. Studies demonstrated a dose-response with paromomycin sulphate at 12, 16, or 20 mg/kg daily for 21 days. In 2002 the Institute for One World Health (iOWH) received funding from the Bill & Melinda Gates Foundation to sponsor a randomized, controlled Phase III clinical trial with WHO/TDR as a co-sponsor. The large Phase III study, conducted in 2003-4, at four WHO/TDR trained clinical sites in Bihar, formed the basis for the product licence in India, and the source of comparative data on efficacy and safety.

Paromomycin has been marketed in various dose formulations around the world since 1959: parenteral (IV or IM), oral capsules, and topical (cream or ointment). Oral paromomycin is used to treat giardiasis (*Giardia lamblia*), amebiasis (*Entamoeba histolytica*), and cryptosporidiosis (*Cryptosporidium parvum*). Topical paromomycin is currently used to treat Old World cutaneous leishmaniasis (*L. major, L. tropica, L. aethopica*).

1 (e) Efficacy and Safety of paromomycin in VL

Efficacy: The Phase III clinical study (666 subjects) showed paromomycin has comparable efficacy (final cure rates at 6 months) to amphotericin B (94.6% vs. 98.8%, respectively; CI 6.9%; p <0.00007; non-inferiority test). Paromomycin provides a shorter treatment (21 days) than amphotericin B, sodium stibogluconate, or miltefosine (each 28-30 days). The IM route is suited for developing countries where IV infusions are not practical.

Safety: The Phase III study showed that no paromomycin –treated subjects developed protocol-defined nephrotoxicity, as opposed to 7 subjects (4.2%) in the amphotericin B group (p<0.0001). Paromomycin does not require laboratory monitoring of renal function.

State-of-the-art high frequency audiometry demonstrated transient and clinically insignificant threshold shifts from baseline during paromomycin treatment in 7 (1.6%) subjects, and 6 of the 7 cases were at high frequency, above the speech range. All 7 cases were reversible and returned to baseline levels at follow-up (at or before 6 months). At the dose and duration demonstrated to be effective for VL in India (11 mg/kg IM for 21 days), treatment with paromomycin does not require audiometric testing.

Overall, a smaller proportion of the subjects in the paromomycin group (59.8%) reported an adverse event (AE) than did the subjects in the amphotericin B group (66.9%). The severity of Grade 3 and Grade 4 AEs was lower overall in the paromomycin treatment group (2.2%) vs. 6.6% in amphotericin B treatment group. (P-value = 0.01).

Good Laboratory Practices (GLP) reproductive and developmental toxicology studies in two animal species (rat, rabbit) have shown that paromomycin is not teratogenic and does not affect fertility, implantation, delivery of live fetuses, or perinatal and postnatal development; thus, it can be safely used in females of child-bearing potential. This outcome is consistent with the class of aminoglycosides.

1 (f) Cost comparisons

Cost comparisons show that Paromomycin IM Injection is much cheaper than other medicines used for VL. Considering the costs of the medicine alone, at the recommended dosage of 11 mg per kg per day x 21 days, the cost per average VL patient (weight 35 kg) is Euros 4.19 (USD 5.09). The cost per death averted is Euros 4.23, the cost per VL patient cured is Euros 5.55 and the cost per disability-adjusted life year gained is of approx. Euros 0.2 (see Table 4 at rear of document).

1 (g) Regulatory status

The Government of India licensed Paromomycin IM Injection for the treatment of VL in August 2006 to our Global GMP Manufacturer, Gland Pharma Ltd., Hyderabad, India.

On 29 March 2005 the FDA granted Orphan Drug designation to paromomycin for the treatment of VL under the sponsorship of iOWH.

On 11 April 2005 the EMEA Committee for Orphan Medicinal Products granted Orphan Drug designation for iOWH to use paromomycin sulfate in the treatment of VL.

2. Name of the focal point in WHO submitting the application

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3. Name of the organization(s) consulted and/or supporting the application

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4. International Nonproprietary Name (INN, generic name) of the medicine

Paromomycin sulfate

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Paromomycin IM Injection is an individual medicine for visceral leishmaniasis. (Other members of the aminoglycoside group lack the anti-leishmanial activity of paromomycin.)

6. Information supporting the public health relevance

6 (a) Visceral leishmaniasis – disease burden.

Visceral leishmaniasis (VL), the most severe form of leishmaniasis is a lethal systemic infection caused by various species of *Leishmania* parasites; the infection is transmitted between humans (anthroponotic foci) by sand flies, and in some regions there is a canine reservoir (zoonotic foci). Also known as kala-azar, this disease causes chronic fever, weight loss, splenomegaly, hepatomegaly, and anemia. Once symptomatic, VL is almost always fatal if left untreated. Of the approximately 500,000 new cases of VL occurring annually, 90% are found in India, Bangladesh, Nepal, Sudan, and Brazil. Half of the VL patients in the world are estimated to live in and around Bihar state, India. Anthroponotic foci of Indian Subcontinent and East Africa are those of highest priority as they lead to periodic and deadly epidemics. VL patients most affected in this region have limited access to affordable treatments. In the most endemic areas of North Bihar, India, more than 80% of the VL patients earn less than US$ 216 per year. Safe, effective, and affordable treatments for VL in endemic regions are urgently needed, particularly in formulations that can be stored and administered in rural settings and applied in an elimination program for the Southeast Asian region.

6 (b) Inadequacy of existing medicines for VL

Pentavalent antimonials; Sodium stibogluconate and meglumine have been in use since the 1940s for VL, and are the only anti-leishmanial medicine currently in the main list of WHO Model List of Essential Medicines. Sodium stibogluconate, or sodium antimony gluconate, is sold under the brand name Pentostam ® (Glaxo Wellcome, UK). There are also generic forms manufactured by a number of pharmaceutical producers in India and China (Gluconate Ltd, Calcutta, India ('Stibonate'), Albert David Ltd, Calcutta, India and Shandong Xinhua, China). Meglumine antimoniate is sold under the brand name Glucantime ® (Rhodia do Brasil, Santo Andre, Brazil; Sanofi-Aventis, Paris, France) and it is manufactured as a generic by some other producers. Pentavalent antimonials are difficult to manufacture uniformly; there is ample evidence of the manufacturing of substandard generic preparations. Analysis of generic forms of sodium stibogluconate and meglumine antimoniate showed that these preparations can contain up to 10-15% of trivalent antimony, which is outside specifications and could have toxic effects. In studies where some generic preparations of pentavalent antimonials were used, high toxicity with fatalities have been reported. The presence of excess trivalent antimony may be responsible in part, and osmolarity might also be a factor related to toxicity.
These drugs are generally given by IM injections, which are painful, partly because the drug is irritant, and partly because large volumes are given. The regimen used for VL is 20 mg/kg daily for 28-30 days, so that an average VL patient (35 kg) will receive a 7ml IM injection daily. If given IV, ~25% develop thrombophlebitis at IV injection sites. Antimonials are unsafe in patients with renal or hepatic failure. In pregnant VL patients, antimonial treatment is associated with foetal loss. During treatment of large numbers of VL patients in the Sudan with pentavalent antimony, death rates of 4.8 to 20% were seen, and an unknown proportion of these deaths may be drug-related. When compared to miltefosine in a randomised trial of 580 VL patients, sodium stibogluconate patients had a significantly higher mortality (10%) during treatment than miltefosine patients (2%). The majority of patients will experience a range of adverse effects: lethargy, headache, nausea, vomiting, metallic taste, or pruritus. Toxicities include electrocardiographic changes and QTc prolongation; elevation of serum amylase and liver enzymes; arthralgia and myalgia; thrombocytopenia; leukopenia; anorexia and thrombophlebitis.

Among patients treated with pentavalent antimonials 20 mg/kg/day for 28 days, 58-83% had myalgias or arthralgias, 10-28% had abdominal pain, nausea or vomiting, 21% had headache, 10-50% developed elevation of liver transaminases, and almost 100% developed hyperamylasaemia. Electrocardiograph changes occur in >50% of patients; these are generally benign, though QTc prolongation is an indication to stop treatment. Sudden deaths which have all the characteristics of cardiac arrest are occasionally noted. Patients should ideally be hospitalised during systemic pentavalent antimonial therapy, and blood tests and ECGs performed twice weekly. Rare side effects of pentavalent antimonials are arthritis, rashes, hepatitis and cytopenias. Some patients with tremors or ataxia have been seen in the Sudan.
HIV co-infected patients are especially prone to pancreatic toxicity, and fatal pancreatitis has been repeatedly reported. In a study of 44 patients with AIDS and VL who were treated with meglumine antimoniate, 14% developed cardiotoxicity, 30% biochemical pancreatitis, and 5% renal impairment, In another study of 25 AIDS patients with visceral leishmaniasis who received meglumine antimoniate, 40% developed hyperamylasaemia, 20% acute pancreatitis (3 of these 5 patients died), 12% renal impairment, 8% leukopenia and 8% T wave inversion.
Pentavalent antimonials have progressively become less effective because of the emergence of resistant strains of *Leishmania donovani.* Primary resistance occurs increasingly in regions where antimonials have been extensively (mis) used. In the most endemic districts of Bihar State, India, 30-65% of visceral leishmaniasis patients show primary unresponsiveness to antimonials, and they are not recommended as first line therapy any longer in this region.

Amphotericin B (desoxycholate) intravenous (IV) infusion is the treatment of choice in regions with antimony resistance. It should be noted that amphotericin B is not licensed for VL in any country. Amphotericin B is included on the *complementary list* of the 2005 WHO Model List of Essential Medicines. However, amphotericin B therapy requires 4–5 weeks of hospitalization and fifteen 6-hour IV infusions requiring intensive clinical and laboratory monitoring and adverse events that require significant clinical management. During the paromomycin Phase III study, 76.5% patients treated with amphotericin B required concomitant medications during treatment.

Pentamidine is included on the *complementary list* of the 2005 WHO Model List of Essential Medicines. Pentamidine is not licensed for VL in any country. Pentamidine is not currently recommended in any national or NGO treatment programme for VL. Published experience with pentamidine is limited, and regimens vary. One recommended regimen is pentamidine isethionate 4 mg/kg body IM on alternate days for 15 injections over 30 days. Prolonged courses (for example, where pentamidine is given until the patient is cured) and lower doses (2 mg/kg on alternate days) have also been used. Reported cure rates vary, with initial parasitological cure being achieved in >90% of patients, often after 33 or more injections. There are reports that in Bihar, the same area where antimonial resistance is common, resistance to pentamidine is also increasing. Reported minor side effects with pentamidine included an uneasy feeling during intravenous injection (12%), intestinal disturbances (6%), cellulitis (5%), abscess formation (1%), and allergic manifestations (2%). Major reactions to pentamidine included hyperglycemia (10%; reversible in 6% and irreversible in 4%), and delayed hypoglycemia (8%). Approximately 1% of VL patients will suffer fatal toxicity from pentamidine.

Liposomal amphotericin B. This medicine is not included on the 2005 WHO Model List of Essential Medicines. Treatment of VL with liposomal formulations of amphotericin B (AmBisome®, Gilead Sciences, USA), although shorter in duration (5 days) and safer. Ambisome is approved for the treatment of VL in the United States, India and perhaps a few other countries. The main limitations to the use of AmBisome are that it requires IV infusions, and that remains unaffordable in VL-endemic countries.

Miltefosine. This medicine is not included on the 2005 WHO Model List of Essential Medicines. Miltefosine (Impavado) is the first effective oral therapy for VL, and is licensed in several countries. Miltefosine has a risk for developing drug resistance due to its long half-life (approximately 150 hours). It has demonstrated teratogenicity in animals and is associated with significant gastrointestinal adverse events (nausea and vomiting), thus limiting its acceptance in some patients. Women of childbearing potential have to use effective contraception for 3 months. Though the oral route offers significant advantage, at the present time, *there is no pediatric dosage form* available for use in children, making accurate dosing a challenge.

7. Treatment details

SUMMARY OF PRODUCT CHARACTERISTICS

7.1. NAME OF MEDICINAL PRODUCT

Paromomycin IM Injection
Solution for Intramuscular (IM) Injection (375 mg/mL)

7.2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2-mL ampoule contains paromomycin sulfate equivalent to 750 mg of paromomycin.

7.3. PHARMACEUTICAL FORM

Paromomycin Injection is formulated as a sterile, aqueous solution for IM administration in a single-use 2-mL amber glass ampoule.

7.4. CLINICAL PARTICULARS

7.4.1 Therapeutic Indications

Paromomycin Injection is indicated for the treatment of Visceral Leishmaniasis (VL).

Paromomycin Injection has not been studied in patients with post-kala-azar dermal leishmaniasis (PKDL). The number of courses of paromomycin treatment that can be safely administered over a long PKDL therapy has not been determined.

Paromomycin Injection is not recommended for treatment as an antibiotic for patients with active bacterial infection.

7.4.2 Posology (Dosage) and Method of Administration

Paromomycin Injection is administered IM, once-a-day, for 21 consecutive days. The recommended IM dosage for patients (5 kg and above) with normal renal function is 11 mg/kg/day paromomycin base (equivalent to ~ 15 mg/kg/day paromomycin sulfate). The patient's pretreatment body weight must be obtained for calculation of the correct dosage. Refer to the *Dosage Guide for Patients with Normal Renal Function* for the recommended dosage and injection volume.

Calculation for determining dosage:

A: Patient's Weight (kg) × 11 (mg/kg) = Patient's Dosage (mg)

B: Patient's Dosage (mg) ÷ 375 (mg/mL) = Patient's Dosage (mL)

(Simple calculation for 11 mg/kg dose:

0.03 ml × patient's weight (kg) = IM injection volume

Injection volume would differ if dose was not 11 mg/kg)

Dosage Guide for Patients with Normal Renal Function
(Administer Dosage Once-a-Day for 21 Days)

For Patient Weighing (kg)	Dose (11 mg/kg/day) (mL)	For Patient Weighing (kg)	Dose (11 mg/kg/day) (mL)	For Patient Weighing (kg)	Dose (11 mg/kg/day) (mL)
5	0.1	32	0.9	59	1.7
6	0.2	33	1.0	60	1.8
7	0.2	34	1.0	61	1.8
8	0.2	35	1.0	62	1.8
9	0.3	36	1.1	63	1.8
10	0.3	37	1.1	64	1.9
11	0.3	38	1.1	65	1.9
12	0.4	39	1.1	66	1.9
13	0.4	40	1.2	67	2.0
14	0.4	41	1.2	68	2.0
15	0.4	42	1.2	69	2.0
16	0.5	43	1.3	70	2.1
17	0.5	44	1.3	71	2.1
18	0.5	45	1.3	72	2.1
19	0.6	46	1.3	73	2.1
20	0.6	47	1.4	74	2.2
21	0.6	48	1.4	75	2.2
22	0.6	49	1.4	76	2.2
23	0.7	50	1.5	77	2.3
24	0.7	51	1.5	78	2.3
25	0.7	52	1.5	79	2.3
26	0.8	53	1.6	80	2.3
27	0.8	54	1.6	81	2.4
28	0.8	55	1.6	82	2.4
29	0.9	56	1.6	83	2.4
30	0.9	57	1.7	84	2.5
31	0.9	58	1.7	85	2.5

7.4.3 Contraindications

Paromomycin Injection is contraindicated in those patients who have demonstrated or have shown hypersensitivity to any of its constituents or to other aminoglycosides. Discontinue use if an allergic reaction occurs.

Paromomycin Injection is contraindicated in patients with renal insufficiency. (This is because the drug is not metabolized – it is 100% renally excreted unchanged in urine and the technology to adjust for renal dysfunction is generally not available in VL-endemic regions of the world.)

7.4.4 Special Warnings and Special Precautions for Use

In cases where paromomycin does not lead to a VL cure at or before 6 months, **do not repeat paromomycin therapy**. Instead, switch to another anti-leishmanial drug.

A minimum 3-month window of time is required between each course of paromomycin treatment for VL because specific tissues, namely the kidney and ear, slowly eliminate aminoglycosides.

Aminoglycosides as a class have an inherent potential for causing ototoxicity and nephrotoxicity.

The United States (US) Food and Drug Administration (FDA) class labeling for parenteral aminoglycoside antibiotics lists the following adverse events in a boxed warning: ototoxicity (neurotoxicity manifested as auditory toxicity), nephrotoxicity, and neurotoxicity manifested as numbness, skin tingling, muscle twitching, and convulsions. Neuromuscular blockade and respiratory paralysis have been reported following high doses of aminoglycosides.

7.4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Paromomycin Injection has only been studied as a monotherapy. It is recommended that Paromomycin Injection not be combined with other anti-leishmaniasis therapies at this time, pending studies of combination therapy. Combination with any other aminoglycosides, such as gentamicin, streptomycin, etc. should be avoided.

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as cisplatin, cephaloridine, kanamycin, amikacin, neomycin, polymyxin B, colistin, reptomycin, tobramycin, vancomycin, and viomycin, should be avoided because of the possibility of additive toxicity.

The concurrent use of paromomycin with potent diuretics, such as ethacrynic acid or furosemide, should be avoided since these diuretics may by themselves cause ototoxicity. In addition, when administered intravenously (IV), diuretics may enhance aminoglycoside toxicity by increasing the aminoglycoside concentration in serum and in specific tissues.

Other factors that may increase patient risk of toxicity are dehydration and advanced age (may be associated with reduction in glomerular filtration rate).

Some drug interactions between aminoglycosides and other drugs have been reported, but their significance is unknown: digoxin, vitamin B6, aspirin, ketoralac, piroxicam, and ibuprofen.

7.4.6 Pregnancy and Lactation

<u>Pregnancy</u>

The use of Paromomycin Injection in pregnant women has not been studied.

GLP reproductive toxicology studies in two animal species (rat and rabbit) have shown that paromomycin is not teratogenic and does not affect fertility, implantation, or delivery of live fetuses.

Because aminoglycosides as a class cross the placenta, they may cause fetal harm when administered to a pregnant woman. Administration of aminoglycosides late in pregnancy may result in the accumulation of drug in fetal plasma and amniotic fluid. Streptomycin has been reported to cause complete irreversible bilateral deafness in children born to women who received the drug during pregnancy. Insufficient data are available regarding paromomycin to make specific recommendations regarding its use in pregnant women.

Lactation

The use of Paromomycin Injection in lactating women has not been studied. Based on a complete review of the use of paromomycin in humans, paromomycin can be used during lactation without adverse effects on mothers and infants (EMEA Committee for Veterinary Medicinal Products, Paromomycin Summary Report (2) 2000). The safety in nursing infants is consistent with low excretion into breast milk and negligible oral absorption of paromomycin (and all aminoglycosides).

7.4.7 Effects on Ability to Drive and Use Machines

No studies on the effects of Paromomycin Injection on the ability to drive and use machines have been performed.

7.4.8 Undesirable Effects

Because paromomycin was first marketed in 1959 and has been used in dozens of countries for dozens of years as an injectable antibiotic, much is known about its safety profile: paromomycin's adverse events are predictable and mirror those of other marketed aminoglycosides such as gentamicin. *This prior marketing is of primary importance in the decision of whether to prescribe or recommend paromomycin for the treatment of leishmaniasis. It would be very unlikely to observe any new adverse events with paromomycin that have not already been described for aminoglycosides over the past 50 years. .*

The most commonly reported adverse drug reactions are injection site pain, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, pyrexia, and an abnormal audiogram. These effects are usually mild to moderate and transient or reversible at the end of treatment. There were no age or gender differences noted in the incidence of adverse events that occurred in patients treated with paromomycin.

In a clinical trial of 500 patients treated at the recommended dosage, the following undesirable effects were observed:

- Very common side effects ≥10% of patients: mild injection site pain
- Common side effects 1–10% of patients: transient AST and ALT elevation, pyrexia, reversible abnormal audiogram
- Uncommon side effects 0.1–1% of patients included: vomiting, alkaline phosphatase elevation, blood bilirubin elevation, injection site swelling, ototoxicity, abscess, conductive deafness, proteinuria

Nephrotoxicity was not observed in any subjects at the recommended 11 mg/kg/day dose and duration for treating VL.

Ototoxicity was mild and reversible at the recommended 11 mg/kg/day dose and duration for treating VL. No clinical hearing loss was seen in any paromomycin treated patients; nor were any vestibular signs and symptoms noted.

7.4.9 Overdose

The consequences of aminoglycoside overdose are dependent on the dose administered, the patient's renal function, state of hydration, age, and whether other medications with similar toxicities are being administered concurrently.

Renal, auditory, and vestibular toxicities have been associated with aminoglycoside overdose.

Patients who have abnormal renal function and who are receiving other nephrotoxic drugs or are volume depleted are at greater risk for developing acute tubular necrosis when treated with aminoglycosides.

High-dose monotherapy of aminoglycosides could potentially cause neuromuscular blockade or respiratory paralysis may occur in patients with myasthenia gravis or Parkinson's disease following administration. Prolonged respiratory paralysis may also occur in patients receiving decamethonium, tubocurarine, or succinylcholine.

If paromomycin is ingested, toxicity would be unlikely as it is very poorly absorbed from an intact gastrointestinal tract; paromomycin has been marketed for decades as a 250 mg oral capsule for the treatment of giardiasis, amebiasis and general bowel sterilization.

Treatment of an aminoglycoside overdose: In managing an overdose, the initial intervention would be to establish an airway and ensure oxygenation and ventilation. Resuscitative measures should be initiated promptly if respiratory paralysis occurs. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts (IV calcium gluconate), but mechanical assistance may be necessary.

Patients who have received an overdose of aminoglycosides who have normal renal function should be adequately hydrated to maintain a urine output of 3 to 5 mL/kg/hr. Patients whose renal function is abnormal may require more aggressive therapy; hemodialysis may be beneficial.

7.5. PHARMACOLOGICAL PROPERTIES

7.5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Paromomycin is an aminoglycoside antibiotic with *in vitro* and *in vivo* anti-leishmanial activity against *L. donovani* and *L. infantum/chagasi*. Paromomycin has been shown to be highly efficacious in curing VL in Phase II clinical trials. In a large, multi-center, randomized Phase III clinical trial, 500 patients (321 males, 179 females; 188 < 15 years, 312 > 15 years) received paromomycin 11 mg/kg IM once a day for 21 doses; 166 patients (95 males, 71 females; 64 < 15 years, 102 > 15 years) received amphotericin B 1 mg/kg IV every other day for 15 doses. Based on final cure rates (6 months after end of treatment), paromomycin demonstrated highly statistically significant non-inferiority to amphotericin B, with a confidence bound 6.9%, (paromomycin 94.6%; amphotericin B 98.8%; p-value < 0.00007). In subgroup analyses, ***there were no differences in the paromomycin final cure rates:***

between male (95%) and female patients (94.4%), or

between adults (93.6%) and children (96.3%)

The mechanism of the anti-leishmanial activity of paromomycin remains uncertain. Experimental findings include a reduction in available cellular energy (cytosol or mitochondria), alteration of parasite membrane properties, and accumulation of paromomycin in lysosomes causing errors in protein synthesis. Paromomycin exhibits specificity for prokaryotic *versus* human ribosomes.

There have been no reported cases of naturally occurring resistance to paromomycin in VL due to *L. donovani* or *L. infantum/chagasi*.

7.5.2 Pharmacokinetic Properties

The bioavailablity of paromomycin in patients following IM administration is very high, approaching 100%, and is negligible following oral administration; thus, IM administration is required to treat systemic infections like VL. The average half-life of paromomycin in humans is 2–3 hours. Paromomycin is not metabolized —it is removed from the plasma by glomerular filtration and excreted unchanged in the urine; thus, accumulation can occur in patients with diminished renal function.

The population pharmacokinetics of IM paromomycin were characterized in 453 male and female VL patients who underwent clinical therapy for 21 days at the recommended dose of 11 mg/kg. All patients had normal renal function. The individual data were best described by a one-compartment population model with first-order absorption and first-order elimination. Paromomycin was absorbed quickly following IM administration, reaching peak plasma concentrations in 1 hour. The absorption half-life was ~ 20 minutes, and the elimination half-life was 2.6 hours. Paromomycin is not metabolized, but excreted unchanged in the urine. Mean peak (C_{max}) and trough (C_{trough}) plasma concentrations of paromomycin on Days 1, 8, 15, 21, and 22 were similar, indicating no accumulation of drug.

No significant differences in C_{max} or C_{trough} plasma concentrations were observed in patients less than 15 years of age vs. patients age 15 and older; likewise, no significant differences in C_{max} or C_{trough} plasma concentrations were observed for male vs. female patients.

The population estimate for the apparent clearance (CL/F) was 4.06 L/h (or ~ 0.107 L/h/kg). Inter-individual variability in CL/F was estimated to be 31%. The population estimate for the apparent volume of distribution (V/F) was 0.40 L/kg (or ~ 40% of body weight). The pharmacokinetics of paromomycin remained linear with time, and there was no evidence of drug accumulation over the 21-day course of therapy. The pharmacokinetics in VL patients were not influenced by age, gender, or pretreatment parasite counts, and were similar to the pharmacokinetics of paromomycin that have been reported in healthy adult volunteers, demonstrating that the disease does not alter the pharmacokinetics of paromomycin, in particular its renal excretion.

Based on these results, paromomycin can be safely administered IM on a body-weight (mg/kg) basis to male and female VL patients who have normal renal function, without the need for therapeutic monitoring or dose adjustment. Children (5 years and above) should receive the same mg/kg dose as adults.

7.5.3 Preclinical Safety Data

Preclinical toxicology data in mice, rats, guinea pigs, rabbit, dogs and monkeys suggest dose- and time-dependent ototoxic and nephrotoxic effects, which are rare in humans at the dose that is recommended to treat VL (i.e., 11 mg/kg, IM, once a day for 21 days).

Paromomycin had no effect on reproductive performance or upon embryofetal viability in a comprehensive reproductive toxicology program (Good Laboratory Practice (GLP)) that evaluated fertility and early embryonic development in male and female rats. Paromomycin did not affect implantation or delivery of live fetuses or show evidence of teratogenic potential in GLP embryofetal development studies in rats or rabbits.

Paromomycin was not mutagenic or clastogenic in a battery of GLP genotoxicity studies including the Ames assay (Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay), a forward mutation assay in Salmonella typhinormurium, the mouse lymphoma forward mutation assay, the human lymphocyte chromosomal aberration assay, or the in vivo mouse micronucleus assay.

In summary, reproductive and developmental toxicology studies in rats and rabbits have shown that paromomycin is not a teratogen and does not affect fertility, implantation, delivery of live fetuses, or perinatal and postnatal development. In addition, paromomycin is not genotoxic or mutagenic.

Carcinogenicity studies with Paromomycin Injection have not been performed.

7.6. PHARMACEUTICAL PARTICULARS

7.6.1 List of Excipients

Sodium Metabisulfite (IP) (antioxidant): 5 mg/mL
Disodium Edetate (Ph. IP) (chelating agent): 0.125 mg/mL
Water for Injection (IP) (solvent): 1 mL/mL

7.6.2 Incompatibilities

Paromomycin Injection should not be mixed with other injectable solutions.

7.6.3 Shelf Life

Two (2) years when stored below 30°C and protected from light.

(Stability data supporting a label change to a 3 year shelf life were submitted to the Drug Controller of India in June 2006 – awaiting response.)

7.6.4 Special Precautions for Storage

Store below 30°C. Protect from light. Do not freeze.

DO NOT STORE partially used ampoules for future patient use.

7.6.5 Nature and Content of Container

2-mL Type 1 amber glass ampoules, supplied in packs of 7 ampoules.

7.6.6 Instructions for Use and Handling, and Disposal

For single use only. Any unused paromomycin from opened ampoules should be discarded.

7.7. MARKETING AUTHORIZATION HOLDER

Gland Pharma LTD (D.P. Bally)
6-3-862 Ameerpet
Hyderabad 5000 016
India
Tel: +91-40-5562-1010
Fax: +91-40-2340-2229
Email: gland@glandpharma.com

MANUFACTURER

Gland Pharma Ltd
D.P Pally, Dundigal Post
Hyderabad-500043,
India

DEVELOPED BY

Institute for OneWorld Health
50 California Street, Suite 500
San Francisco, CA 94111
USA

with

WHO/TDR

Geneva, Switzerland

DISTRIBUTOR

In discussion with

Gland Pharma Ltd.

Hyderabad, India

and

International Dispensary Association

Amsterdam, Netherlands

8. Summary of comparative effectiveness

Several small WHO/TDR-sponsored clinical trials established that paromomycin was an effective treatment for VL. The best information on the effectiveness and safety of paromomycin comes from the large Phase III clinical trial sponsored by OneWorld Health with funding from the Bill & Melinda Gates Foundation. This randomized, controlled, phase III study compared paromomycin with amphotericin B, the present standard of care in Bihar. In four VL treatment centers in Bihar, 667 patients ages 5–55 with parasitologically confirmed VL were randomized in a 3:1 ratio to receive either paromomycin (n=502) 11 mg/kg intramuscularly daily for 21 days (paromomycin base; equivalent to 15 mg/kg for 21 days of paromomycin sulfate), or amphotericin B (n=165) 1 mg/kg intravenously every other day for 30 days. Final cure was assessed at 6-month follow-up. There was >99% follow-up at 6-months.

The ITT (intent-to-treat) analysis demonstrated a final cure rate of 94.6% for subjects in the paromomycin treatment group compared to a final cure rate of 98.8% for subjects in the amphotericin B treatment group (CI=6.9%, p=0.00007). In the pediatric subgroup, a highly statistically significant non-inferiority demonstration of paromomycin compared to amphotericin B was demonstrated (p-value =0.001).

Paromomycin cure rates for men and women were similar (94% and 95%, respectively) The analysis of the primary endpoint (final cure at 6 months) by gender showed that paromomycin was non-inferior to amphotericin B for both genders (males p-value =0.006; females p-value =0.002).

Sustained clinical improvement occurred during the treatment period with an associated decrease in fever, reduction in spleen size, weight gain, and increase in hemoglobin, WBCs, platelets, and albumin. Of the 449 patients in the paromomycin group with a new diagnosis of VL, 423 achieved final cure (94%), and of the 52 patients who were prior non-responders or who had experienced a prior relapse to antimonials and miltefosine, 51 patients achieved a final cure (98%). *Thus, paromomycin was effective in treating patients with VL regardless of their response to prior leishmanial treatment.*

In paromomycin-treated patients, time to achieve cure (21 days) represents a 30% decrease compared to amphotericin B (30 days). All clinical and laboratory parameters of improvement occur quickly with paromomycin and in the case of hemoglobin, a key indicator of clinical improvement, the level was higher in paromomycin patients at the end of treatment compared to amphotericin B treated patients. *In summary, this Phase III study conducted in Bihar, India on 667 patients with VL, demonstrated a highly statistically significant non-inferiority of paromomycin compared to amphotericin B overall, in the pediatric subgroup, and in the analyses by gender. In other words, paromomycin shows comparable efficacy to amphotericin B in all subgroups.*

The manuscript entitled “Injectable Paromomycin for Visceral Leishmaniasis in Bihar, India: A Multicenter Randomized Phase 3 Controlled Clinical Study” by Shyam Sundar, M.D., T.K. Jha, M.D., Chandreshwar P. Thakur, M.D., Prabhat K. Sinha, M.D., and Sujit K. Bhattacharya, M.D., has been submitted for publication to *New England Journal of Medicine (NEJM)*– the manuscript will be made available to the committee when it is published by NEJM or in another prominent journal.

9 Summary of comparative evidence on safety

9 (a) Estimation of the total patient exposure to date

Since 1962, at least 40 clinical publications have reported the use of paromomycin sulfate in different diseases. Initially, paromomycin was used for treatment of bacterial infections. It has also been evaluated for treatment of tuberculosis, and since 1990 paromomycin has been used in the treatment of cutaneous, mucosal, and visceral forms of leishmaniasis. Nine publications since 1990 have reported the results of clinical trials of the efficacy and safety of paromomycin in patients with VL. In combination with the iOWH Phase III study, efficacy and safety data in VL patients is available on over 1000 patients who received paromomycin either alone or in combination with sodium stibogluconate.

A post-approval Phase IV trial has been approved by the Government of India. The trial will begin patient enrollment in February 2007, and is expected to enroll between 1,350 and 2,000 additional VL patients in India.

9 (b) Safety data from Phase III clinical trial

Both nephrotoxicity and ototoxicity are safety concerns for the aminoglycoside chemical class, and these were addressed in the large Phase III clinical trial. Safety endpoints included AEs, laboratory evaluations, vital signs, and audiometric assessments. Adverse events were graded using Common Toxicity Criteria (CTC). Nephrotoxicity was defined as an increase in serum creatinine level that was either double the baseline value and >2.0 mg/dL, or >2.5 mg/dL. Ototoxicity was defined as a confirmed shift from baseline in audiometric thresholds by either 25 dB or more at $\geq$ 1 of the tested frequencies (1–12 kHz), or 20 dB or more at two or more adjacent frequencies. This definition allowed for detection of hearing loss that, if confined to frequencies of 4 kHz or higher, would not interfere with daily communication.

Deaths during treatment: Three (3) deaths (0.5%) occurred during the treatment period, 2 occurred in the paromomycin group (0.4%) and 1 in the amphotericin B group (0.6%). One (1) patient with an undisclosed history of alcoholism received only 2 doses of paromomycin and died at home a few days after discharge. The other patient died from septicemia after receiving 11 doses of paromomycin. Neither death could be directly attributed to the study drug. The 1 death in the amphotericin B group resulted from gastroenteritis, and was not related to the study drug.

Seven (7) patients in the paromomycin group (1.4%) were discontinued from study drug because of AEs, 2 with Serious Adverse Events (SAEs) of elevated hepatic enzymes, and 5 for AEs: 2 with elevated hepatic enzymes, 2 with reversible ototoxicity, and 1 for injection site pain. These patients were subsequently discontinued from study drug and successfully treated with AmBisome® rescue medication. One (1) patient in the amphotericin B group (0.6%) experienced an SAE of bacterial pneumonia after 10 doses of study drug, and was subsequently a final cure.

Audiometric Tests: A total of 589 patients had evaluable audiometry data, 442 in the paromomycin group and 147 in the amphotericin B group. After testing and blinded review of the results by an expert audiologist, 7 paromomycin recipients (1.6%) and no amphotericin B recipients had confirmed threshold shifts defined as ototoxicity in the protocol. This ototoxicity rate, 1.6%, was not related to age, and was not statistically

different from the 0% rate in amphotericin B (P=0.20). Six (6) of the 7 cases were at high frequency, above the speech range, and all 7 cases were transient and reversible, returning to baseline levels at follow-up (at or before 6 months). Clinically, no patient reported any hearing loss, and no vestibular dysfunction was observed.

Renal Evaluation: No patients in the paromomycin group met the protocol-specified definition of nephrotoxicity, whereas 7 patients (4.2%) in the amphotericin B group did. To further examine potential nephrotoxicity using another set of laboratory criteria (creatinine elevation ≥50% of baseline and ≥1.4 mg/dL during treatment), a *post hoc* analysis demonstrated that 42 amphotericin B recipients (25.3%) experienced potential nephrotoxciity using this definition, while only 4 patients (0.8%) in the paromomycin group experienced this level of elevation in creatinine. Mean changes from baseline to eod of therapy in BUN and creatinine were statistically significantly higher in the amphotericin B group.

Adverse Events: Injection site pain (55.2%) was most the frequently reported AE in the paromomycin treatment group, and infusion reactions of fever, rigors, and vomiting at 56.6%, 23.5%, and 9.6%, respectively, were most frequently reported in the amphotericin B treatment group. Paromomycin injection site pain was mild in nature, rarely associated with swelling, and the vast majority were reported as CTC Grade 1 events (98.6%). One (1) paromomycin-treated patient (0.2%) discontinued therapy due to injection site pain and swelling.

Overall, the severity of AEs was lower in paromomycin-treated patients, with CTC Grade 3 and Grade 4 AEs occurring more frequently in the amphotericin B group compared to the paromomycin group (6.6% vs. 2.2%, P=0.01). Concomitant medication use was 76.5% in the amphotericin B treatment group compared to 14.4% in the paromomycin treatment group (P<0.001).

Other Laboratory Tests: Almost half the patients in both treatment groups entered the study with ALT or AST levels above normal, which is consistent with the published literature of significant hepatic involvement in 25–40% of VL patients. Of the 4 patients (0.8%) in the paromomycin group who developed elevations in ALT >5× upper limit of normal (ULN) during the study, 3 were discontinued from study drug and subsequently rescued, and 1 had a full course of treatment and achieved an initial and final cure. One of the 4 patients developed jaundice after 8 days of treatment and recovered after discontinuation of paromomycin; the patient's baseline elevations in alkaline phosphatase (533 U/L) and prothrombin time (20 seconds) suggested pre-existing liver disease.

In conclusion, paromomycin is an established drug with an extensive and well-characterized safety profile following about 30 years of use as an injectable antibiotic. It is still in use as an oral antibiotic and antiprotozoal throughout the world, with more than four decades of use as a human and veterinary product. The safety and efficacy profile demonstrated in the Phase III study and prior Phase II dose-ranging studies is excellent and establish that paromomycin given IM for the treatment of VL in India is safe and effective.

Although paromomycin is an old drug, it has never been licensed for use as an anti-leishmanial drug, so it brings to the field a brand new mechanism of action. Paromomycin is particularly advantageous because of its shorter duration of administration, very low cost and demonstrated safety and efficacy profiles in the

pediatric population, females of childbearing potential, and in patients with prior treatment failures. The existing health delivery system in India is ideal for the administration of the drug intramuscularly under directly observed therapy in a broad-reaching public health program, and local manufacturing of the compound in India at a very low cost aligns well with the needs of non-profit and government institutions with limited resources to provide effective treatment

9 (c) Safety data from other sources

We do not have access to the safety database of paromomycin when used as an injectable antibiotic because it is proprietary (now belongs to Pfizer). Several other sources of safety data are available, however.

The WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden) reported on paromomycin (used as an antibiotic) from the years 1972 through 2003. A total of 98 adverse drug reactions to paromomycin that occurred in 58 patients from 8 countries were reported. Only four of the 98 AE reports were for parenteral paromomycin in four patients (rash, dizziness, anaphylactic shock, and vision abnormality/vision blurred/injection site inflammation). During this 31-year time period, no reports of ototoxicity or nephrotoxicity were submitted.

Safety data from seven publications of the use of paromomycin in the treatment of VL in Africa and India are summarized in Table 1 (total number of patients 729).

Publications of paromomycin when used as an injectable antibiotic fail to provide informative safety data, primarily because the studies were performed in the 1960s and 1970s when such data was not generally included in publications.

Table 2 presents a summary of Farmitalia post-marketing safety data of paromomycin when used as an injectable antibiotic, world-wide, over 20 years (1959-1979),

Table 3 presents a summary of postmarketing data of paromomycin when used as an injectable antibiotic in Japan over 3 years (1970=1973).

Table 1: Published Studies of Injectable Paromomycin for Visceral Leishmaniasis

Citation	Disease/ Geography	Sample Size	Dosage and Schedule	Adverse Events
Chunge et al., 1990	VL Clinical trial; Africa	53 (1) 11 (2) 19 (3) 23	(1) IV/IM Sb^v 20 mg/kg/day × 20 days (2) IM paromomycin sulfate 14–16 mg/kg/day (equivalent to 10.5-12 mg/kg base) × 20 days (3) IV/IM Sb^v 20 mg/kg/day + paromomycin sulfate 14–16 mg/kg/day (equivalent to 10.5-12 mg/kg base) × 20 days	Incidence of AEs*: (1) 3/11 (27%) (2) 0/19 (3) 5/23 (22%) * nosebleeds, nausea; phlebitis at injection site. In (3), chest pain (with iron supplementation)
Seaman et al., 1993	VL Randomized clinical trial; Africa	134 (1) 67 (2) 67	(1) Sb^v 20 mg/kg/day IM × 30 days (2) Sb^v 20 mg/kg/day IM + paromomycin sulfate IM 15 mg/kg/day (equivalent to 11 mg/kg base) × 17 days	Death (1) 7% (2) 4% Oto- and nephrotoxicity not assessed
Thakur et al.,1992 *(Data included in final paper below)*	VL Clinical trial; India	22	IM paromomycin sulfate 12 mg/kg/day (equivalent to 9 mg/kg base) + Sb^v 20 mg/kg/day × 20 days	None observed.

Citation	Disease/ Geography	Sample Size	Dosage and Schedule	Adverse Events
Thakur et al., 1995	VL Randomized open sequential design trial; India	136 (1) 96 (2) 40	(1) Paromomycin sulfate 12 mg/kg/day (equivalent to 9 mg/kg base) +: a. Sb^v 20 mg/kg/day b. Sb^v 10 mg/kg/day c. Sb^v 5 mg/kg/day (2) Paromomycin sulfate 6 mg/kg/day (equivalent to 4.5 mg/kg base) +: a. Sb^v 20 mg/kg/day b. Sb^v 10 mg/kg/day c. Sb^v 5 mg/kg/day (stopped after 40 subjects enrolled)	(1) All AEs: 11/96 (11%) (1a) 4/32 (13%): abdominal pain, nausea, GI hemorrhage, breast abscess (1b) 2/32 (6%): abdominal pain, gastroenteritis, fever (1c) 5/32 (16%): abdominal pain, vomiting, hearing disturbance, herpes (2) All AEs: 4/40 (10%) (2a) 2/13 (15%) : AE not specified (2c) 2/14 (14%) : AE not specified
Jha et al., 1998	VL Open-label randomized controlled Phase II clinical trial; India	120 (30 per arm)	(1) Paromomycin sulfate 12 mg/kg/day (equivalent to 9 mg/kg base) × 21 days (2) Paromomycin sulfate 16 mg/kg/ (equivalent to 12 mg/kg base) × 21 days (3) Paromomycin sulfate 20 mg/kg/day (equivalent to 13.5 mg/kg base) × 21 days (4) Sb^v 20 mg/kg/day × 30 days	(1) 1/30 (3.3%) : vomiting (2) 0/30 (3) 2/30 (6.7%): ototoxicity (4) 2/30 (6.7%): reversible myocarditis 1/30 (3.3%): epileptic seizure
Thakur et al., 2000b	VL Open label randomized Phase II clinical trial; India	149 (1) 52 (2) 48 (3) 49	(1) Paromomycin sulfate 12 mg/kg/day (equivalent to 9 mg/kg base) + Sb^v 20 mg/kg/day × 21 days (2) Paromomycin sulfate 18 mg/kg/day (equivalent to 13.5 mg/kg base) + Sb^v 20 mg/kg/day × 21 days (3) Sb^v 20 mg/kg/day × 30 days	(1) 0/52 (2) 0/48 (3) 1/49 (2%): cardiotoxicity Incomplete audiometric data
Thakur et al., 2000a	VL Open-label randomized controlled Phase II clinical trial; India	115 (1) 30 (2) 27 (3) 29 (4) 29	(1) Paromomycin sulfate 12 mg/kg/day (equivalent to 9 mg/kg base) × 21 days (2) Paromomycin sulfate 16 mg/kg/day (equivalent to 12 mg/kg base) × 21 days (3) Paromomycin sulfate 20 mg/kg/day (equivalent to 15 mg/kg base) × 21 days	None described. Renal toxicity not observed. Incomplete audiometric and ECG data.

Citation	Disease/ Geography	Sample Size	Dosage and Schedule	Adverse Events
			(4) Sb^v 20 mg/kg/day × 28 days	

Table 2: Adverse Events for Parenteral Paromomycin, 1959–1979

Indication	Dosage and Schedule	Adverse Events
Not specified		Ototoxicity (cochlear): 0.4% Renal toxicity: 0.12% Pain at injection site: 0.75%
Respiratory tract infections (n=865)	Newborns: 40–50 mg/kg/day IM × 15–30 days Children: 15–50 mg/kg/day IM × 15-30 days Adults: 0.5–2 g/day IM, 3–40 g intrapleural × 30 days, 0.5 g/day intrabronchial + 2 g/day IM × >10 days	Injection site tenderness: 1.6% Bilateral partial deafness: 0.1% Decrease in hearing: 0.2% Ear buzzing: 0.1% Hepatotoxic jaundice: 0.1% Allergy: 0.1% Albuminuria: 0.1%
Urinary tract infections (n=240)	Newborns: 40–50 mg/kg/day IM × 5–15 days Children: 20–40 mg/kg/day IM × 5–15 days Adults: 0.5–1.5 g IM × 2–20 days	Ear buzzing: 0.4% Renal hypofunction: 0.8%
Ob/Gyn and surgical infections (n=404)	Adults 1–2 g IM × 1–26 days + 1.5 g/day IP	Transient cochlear damage: 0.25%
Amebic liver abscess (n=212)	Adults 0.5–1.5 g IM × 10–40 days then 0.5 g × 4–34 days (many cases: also 0.5 g intrapleural × 32–103 days)	Decrease of hearing: 1.6% (both cases received 36 g IM + 16 g intrapleural)
Urethritis (n=189)	1 g IM × 2–5 days	Tenderness at injection site: 1.5%
Skin infections (n=188)	Newborns 40–50 m/kg/day IM × 5–15 days Children: 20–50 mg/k/day IM × 3–49 days Adults: 0.5–1.5 g IM × 3–49 days	None
Other infections (n=390)	Newborns: 40–50 mg/kg/day IM × 5–15days Children: 15–40 mg/k/day IM × 3–20 days Adults: 0.5–1.5 g IM × 2–30 days	Skin rash: 0.3% Injection site tenderness: 0.3% Hearing disturbances: 0.5%

Aminosidine injection = paromomycin injection

Data source: Farmaitalia.

Experience of Parenteral Paromomycin in Japan

Registered in Japan in 1968, parenteral paromomycin underwent a 3-year post-marketing surveillance, ending in June 1973. Table 3 presents the AEs associated with this period of post-marketing safety surveillance.

Table 3 : Post-Marketing Surveillance (Japan)

Adverse Events (AE)	Before Approval N (%)	After Approval N (%)	Total N (%)
Nausea/vomiting	1 (0.2)	3 (0.2)	4 (0.2)
Diarrhea/loose stools	—	2 (0.1)	2 (0.1)
Skin rash	4 (0.8)	1 (0.06)	5 (0.2)
Local rash	22 (4.4)	8 (0.5)	30 (1.4)
Injection site pain	9 (1.8)	85 (4.9)	94 (4.2)
Malaise	6 (1.2)	3 (0.2)	9(0.4)
Tinnitus	2 (0.4)	6 (0.3)	8 (0.4)
Overall AE incidence	**44/499 (8.8%)**	**108/1721 (6.3%)**	**152/2220 (6.8%)**

Data source: Farmitalia.

Two revisions were known to have been made to the package insert:

(a) September 1984 (both oral and parenteral paromomycin). The following was added to the section Careful Administration under Precautions for Use:
"Those for whom ingestion is not possible, those who are under parenteral alimentation, those who are in poor general condition, or the aged, must be carefully observed because symptoms of vitamin K deficiency may appear."

(b) September 1991 (parenteral paromomycin only). The following was added to the section Adverse Events under Precautions for Use:
"There may be rare occurrences of edema, proteinuria, hematuria, and abnormality in electrolytes such as in potassium."

Oral Paromomycin

Oral paromomycin remains on the market in many countries to date, with a range of indications, as noted below.

Humatin® (Parke-Davis) is marketed in Australia, Canada, Great Britain (GB), Germany, Italy, Spain, Switzerland, and the United States. Indications include bacterial enteritis, hepatic encephalopathy and coma, intestinal amebiasis, preoperative intestinal sterilization, and taeniasis.

Gabbromicina® (Pharmacia-Upjohn) is marketed in Belgium and Italy. Indications include amebiasis, bacterial intestinal infections, and giardiasis.

Gabromicina® (Pharmacia-Upjohn) is marketed in Hong Kong. Indications include amebiasis and bacterial infections.

Additional trade names include Kapseal® (Great Britain, United States), Gabromycin® (Germany), Gabbroral® (Italy), and Pargonyl® (The Netherlands).

Topical Paromomycin

Topical paromomycin ointment (15%) is marketed by Teva Pharmaceuticals (Israel), bramd name Leshcutan. The sulfate salt of paromomycin is used to produce the product. It is prescribed to treat Old World cutaneous leishmaniasis, caused by several Leishmania species, including *L. major, L. tropica,* and *L. aethiopica.* The product is now being considered for approval in the United States for use by US Army soldiers in the Middle East.

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

In these calculations, we have considered only the costs of the medicines themselves. Data provided on 9th October 2006 by Margriet den Boer, MSc, MPharm, PharmD, Campaign for Access to Essential Medicines Médecins Sans Frontières.

10 (a) Range of costs of the proposed medicine

As shown in the Table 4, Paromomycin IM Injection is produced by a single manufacturer, Gland Pharamceuticals, Hyderabad, India.

Cost per ampoule: The cost per 2 ml ampoule of 500 mg/ml paromomycin sulphate (equivalent to 375 mg/ml paromomycin base) is Euros 0.38.

Cost per case: At the recommended dosage of 11 mg per kg per day x 21 days, the costs cost of VL treatment for the average patient (weight 35 kg) is Euros 4.19.

Cost per death averted: All cases of VL are eventually fatal if untreated. Among VL patients treated with Paromomycin IM Injection the mortality rate was 0.6%. The final cure rate was 94.6%, all failures survived and were successfully treated with amphotericin B which is the standard of care for resistant or relapsed VL in India. Thus the cost per death averted is Euros 5.55. This is exactly the same as the Cost per VL patient cured.Cost per disability-adjusted life year gained: The average age of a VL patient is 15 yrs, and life expectation after VL cure is normal without residual disability. Thus the cost per DALY gained is of the order Euros 0.2.

10 (b) Comparative costs

The comparative costs for other medicines used for VL are indicated in Table 4, below. Paromomycin IM Injection is less expensive than any other treatment for VL, and this outcome was deliberately sought from the start of the VL research and development program because patients who suffer from VL are so desperately poor. IOWH is a not-for-profit company, and does not receive any financial return whatsoever from drug sales. The research, development and technology transfer costs were provided through grants to IOWH from the Bill and Melinda Gates Foundation. Gland Pharma produces paromomycin IM injection on an at-cost basis. WHO/TDR does not benefit financially from this product.

Pentavalent antimonials. Costs vary according to the manufacturer. The costs per average VL patient (35 kg) are as follows: Pentostam (sodium stibogluconate, GSK) Euros 122.89, Glucantime (meglumine antimoniate, Aventis) Euros 43.50 and sodium stibogluconate (generic, Albert David) Euros 22.75.

Amphotericin B costs range (according to supplier) from Euros 16.49 (generic amphotericin B, Combinopharm) to Euros 45.9 (Fungizone, BMS) per average VL patient (35 kg).

Pentamidine costs were not available. Pentamidine is not currently recommended in any national or NGO treatment programme for VL, and is not licensed for the treatment of VL.

Liposomal amphotericin B. Estimated cost for an average 35 kg VL patient varies from Euros 347.64 to Euros 2,243.44, according to whether or not the supplier (Gilead) provides the medicine at a greatly reduced public sector price. Currently, this price is offered to MSF for treatment of VL patients in Africa.

Miltefosine costs vary according to whether the medicine is being purchased privately or is provided within an institutional programme. Within programmes, miltefosine costs Euros 57.3 for paediatric use (20mg/day/28 days) to Euros 70 per average 35 kg for adult use (100 mg/day/28 days) VL patient. However this differential pricing for public sector has not been applied in India so far. In India (private sector), miltefosine cost is currently Euros 110.

PRODUCT (INN, strength, formulation)	MANUFACTURER, country	BRAND NAME if any	Packaging	Shelf life	Price as quoted	Price Euro/unit	Price USD/unit	Standard treatment protocol	Price Euro/standard treatment protocol (35 kg)	Price USD/standard treatment protocol (35 kg)	Date of price info.	Source of price info.
amphotericin B injection 50 mg	Bristol Meyer Squibb US	Fungizone	1 vial	2 years	3,16 GBP	4,37	$5.22	1 MKD x 15 D (alt. days)	45,90	54,81	2006	BNF 52
amphotericin B injection 50 mg	Combinopharm Spain	---	1 vial	?	1,91 USD	1,57	$1.87	1 MKD x 15 D (alt. days)	16,49	20,03	2005	Sources and Prices… PLWHA 2005
liposomal amphotericin B 50 mg	Gilead US (public sector price Africa only)	AmBisome	1 vial	3 years	22,30 Euro	22,30	$26.55	4 MKD x 6 D (alt. days)	347,64	446,04	2005	Gilead
liposomal amphotericin B 50 mg	Gilead US	AmBisome	1 vial	3 years	96,69 GBP	133,55	$160,26	4 MKD x 6 D (alt. days)	2243,64	2692,20	2006	BNF 52
meglumine antimonate 85 mg/ml, 5 ml vial	Sanofi-Aventis France	Glucantime	5 amp	?	4,39 Euro (public sector price)	0,88	$1.05	20 MKD x 30 D	43,50	52,80	2005	Aventis
miltefosine 10 mg*	Zentaris Germany	Impavido	56 caps	4 years	57,30 Euro	1,02	$1.21	20 mg x 28 D	57,30	69,62	2005	Acteon Medeor Germany
miltefosine 50 mg*	Zentaris Germany	Impavido	56 caps	4 years	70 Euro	1,25	$1.49	100 mg x 28 D	70	85,05	2005	Zentaris
paromomycin 375 mg/ml, 2 ml	Gland Pharma India	Paromomycin IM injection	100 ampoules	2 years	47 USD	0,38	$0.45	11 MKD x 21 D	4,19	5,09	2006	Gland
SSG, 100 mg/ml, 100 ml vial	GSK UK	Pentostam	1 vial	3 years	40 GBP (public sector price)	58,52	$69.67	20 MKD x 30 D	122,89	149,31	2005	GSK
SSG, 100 mg/ml, 30 ml vial	Albert David India	SSG	1 vial	2 years	3,25 Euro	3,25	$3.87	20 MKD x 30 D	22,75	27,65	2006	IDA

Table 4: Costs of medicines for treatment of visceral leishmaniasis.
Data provided by Margriet den Boer, MSc, MPharm, PharmD, Campaign for Access to Essential Medicines Médecins Sans Frontières.

11. Summary of regulatory status of the medicine

11 (a) Regulatory status in country of origin – India

Paromomycin IM Injection was licensed in August 2006 as treatment for visceral leishmaniasis.

11 (b) Regulatory status in other countries

On 29 March 2005 the FDA granted Orphan Drug designation to paromomycin for the treatment of VL under the sponsorship of iOWH.

On 11 April 2005 the EMEA Committee for Orphan Medicinal Products granted Orphan Drug designation for iOWH to use paromomycin sulfate in the treatment of VL.

11 (c) Status for non-VL indications

Paromomycin has a history of more than four decades of use as a human and veterinary product, is an established drug with an extensive and well-characterized safety profile and is still in use (as an antibiotic and antiprotozoal) throughout the world, both as oral and injectable formulations. Teva Pharmaceuticals (Israel) markets topical paromomycin ointment for the treatment of cutaneous leishmaniasis.

12 Availability of Pharmacopoieal standards

Monographs for paromomycin sulfate are listed in the following Pharmacopoieas:
International
United States
Italian
Chinese.

13 Proposed new text for the WHO Model Formulary

FORMS	RATIONALE	ATC CODE	LISTING
2-mL ampoule containing paromomycin sulfate equivalent to 750 mg of paromomycin.	For the treatment of Visceral Leishmaniasis. Dose: 11 mg/kg paromomycin (equivalent to 15 mg/kg paromomycin sulphate) daily by IM injection for 21 days. Date added: 2006.		Main List