

PANIMUN BIORAL™

1. Introduction

Cyclosporine (Cyclosporine A) is a lipophilic polypeptide composed of 11 amino acids. It is potential immunosuppressor, which has given positive results in human kidney and bone marrow transplants to prevent and treat rejection & GVHD and in a series of diseases of autoimmune origin.

Panacea Biotec has developed a **self-micro emulsifying pre-concentrate of Cyclosporine – Panimun Bioral™** that on dilution with aqueous fluids (like water) forms a microemulsion without significant input of energy. The modified formulation is more consistent and has a predictable concentration time profile as compared to conventional formulation. Also the formulation has shown better bioavailability and reduction in inter and intra patient variability of all pharmacokinetic parameters.

2. Panimun Bioral™ Drug delivery system

Microemulsions are theoretically defined as dispersions of insoluble liquids in a second liquid that appears clear and homogeneous to the naked eye. Microemulsions are frequently called solubilized systems because on a microscopic basis they seem to behave as true solutions.

2.1 Major Components

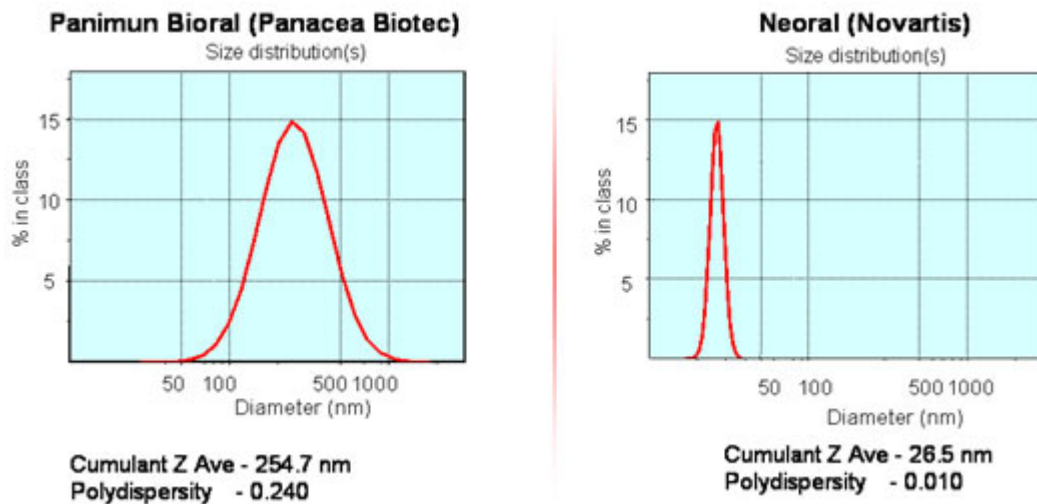
- ▪ A hydrophilic solvent
- ▪ A surfactant with high HLB value
- ▪ A co-surfactant with a low HLB value
- ▪ A lipid
- ▪ A hydrophobic drug

The SMEDDS system can be further formulated into:

- ▪ Oral drink concentrate

- ▪ Soft gelatin capsules
- ▪ Hard gelatin capsules

Panimun Bioral™ is bioequivalent to the Reference Listed Drug - Neoral (Novartis) even at an average particle size in the range of 150 to 350 nm (when measured by photon correlation spectroscopy using Malvern Zetasizer).



3. Clinical Experience

- ▪ In a double blind, randomized, crossover study conducted in 12 healthy male volunteers who were administered either of the formulations in a dose of 10mg/kg, **Panimun Bioral™** was found to be bioequivalent to reference formulation Sandimmun Neoral
- ▪ **Panimun Bioral™** or reference formulation was administered in a dose of 180 mg in 18 volunteers at a two-way crossover, randomized design. There was no significant difference in the bioavailability parameters of both the formulations

- ▪ Eighteen healthy male volunteers were administered two oral dosage forms (oral solution and soft gelatin capsules) of **Panimun Bioral™** in a single dose, two-way, non-crossover study. Both the preparations were bioequivalent, with relative bioavailability from soft gelatin capsules was of 102.28%
- ▪ **Panimun Bioral™** and Sandimmun Neoral were evaluated in different transplant centers using both volunteers as well as renal transplant patients. All these centers have reported that both products are bioequivalent
- ▪ The bioavailability of two cyclosporine formulations (**Panimun Bioral™** and Sandimmun Neoral) was compared in 10 adult patients of ESRD on maintenance hemodialysis by Enzyme Multiplied Immunoassay Technique (EMIT) after 6.5 days of Cyclosporine at a dose of 5mg/kg in two divided doses. The C_{max} , T_{max} , AUC, $T_{1/2}$ of both preparations were comparable with no significant difference. Other studies conducted at multi centers throughout >India have also shown similar pharmacokinetics in healthy male volunteers of the two preparations
- ▪ Another single blind randomized, crossover study was conducted by in which 12 healthy volunteers were enrolled and who were administered 300 mg of **Panimun Bioral™** and reference formulation (Sandimmun Neoral). Analysis of variance did not reveal any significant differences between the bioavailability parameters even after log transformation of the data. Confidence intervals on the ratio of test / reference was within the FDA specified limits of 0.8 – 1.25. Both the formulations were bioequivalent and safe
- ▪ **Panimun Bioral™** trough levels at different post transplant periods in 103 renal transplant patients were determined using HPLC assay over a period of two years. The trough levels concentration changes versus dose reductions were not markedly different after 2-4 weeks and remained within therapeutic range. Stabilized concentrations were achieved after first month

- ▪ In a retrospective study for CyA dose and trough levels by HPLC and its correlation with graft and patient survival conducted in 127 renal transplant patients of Indian origin receiving CyA (**Panimun Bioral™**) in two divided doses, it was concluded that lower doses of CyA were able to generate sufficient blood levels required for long term immunosuppressive therapy in Indian transplant recipients
- ▪ A retrospective analysis of 37 renal transplant patients stabilized on **Panimun Bioral™** for more than 3 months was done in patients who had stable graft function. The dose of Cyclosporine decreased over time from first to third month i.e. 8.2 ± 0.46 to 4.77 ± 0.23 mg/kg/ day
- ▪ In eleven male renal transplant recipients with stable graft function who were switched on **Panimun Bioral™** in 1:1 dosage conversion from stable individualized dosage regimen of the reference formulation, there were no episodes of graft dysfunction after conversion and the utilization of 1:1 conversion between the two formulations yielded comparable steady state concentration
- ▪ The suitability of limited sampling strategy i.e. 1, 3 and 5 hours after dosing with **Panimun Bioral™** or reference formulation was shown in 5 patients of haemodialysis receiving blood transfusion. Both the formulations in a dose of 5mg / kg were given in two divided doses and it was inferred that the 3-point sampling required few sampling points and was cost effective; with similar bioavailability of both the formulations
- ▪ In a study conducted in 146 patients to evaluate the cost of CyA (**Panimun Bioral™**) from time of renal transplant till current status, it was concluded that the cost of CyA decreased from Rs. 11,904 per month immediately after transplant to Rs. 5799 per month after 80 weeks of renal transplant
- ▪ In a study to evaluate the CyA(**Panimun Bioral™**) dose in 127 renal transplant patients of Indian origin studied retrospectively, it was concluded that lower doses

of CyA were able to generate sufficient blood levels required for long term immunosuppression in Indian transplant recipients

- ▪ In an open labeled prospective trial was conducted to evaluate the safety and efficacy of CyA(**Panimun Bioral™**) in 15 young patients with aplastic anaemia where CyA (**Panimun Bioral™**– 100 mg/ml) was administered at a dose of 5 mg / kg twice daily, it was concluded that the efficacy of CyA in the treatment of patients with aplastic anaemia resulted in 30.8% full remittance and 15.8% partial response at 12 weeks of monotherapy
- ▪ Renal transplant patients (36 diabetics and 67 non diabetics) receiving CyA (**Panimun Bioral™**) were retrospectively observed upto 1 year and it was concluded that diabetic renal transplant patients required the same dose of cyclosporine in the post transplant period as non-diabetic patients
- ▪ Cyclosporine trough levels were monitored at various post-transplant periods in renal graft recipients on microemulsion cyclosporine (**Panimun Bioral™**) and it was concluded that **Panimun Bioral™** was able to generate sufficient blood levels required for long-term immunosuppression therapy with cyclosporine

4. IPR Status

The SMEDDS system is patented in all major countries across the globe including:

- ▪ United States : US 5945398, US 6008191CIP, US 6187747CIP, US 6346511 CIP
- ▪ Europe : EP 982035, EP 985412, EP 1151755
- ▪ Japan : JP 2942556
- ▪ Australia : AU 716855

5. Development Status

- ▪ Commercialized in the Indian market

- CTD compilation under process for regulated markets

6. Product Presentation

Panimun Bioral™ 100mg

Cyclosporine Capsules

Each soft gelatin capsule contains

Cyclosporine 100mg

Panimun Bioral™ 50mg

Cyclosporine Capsules

Each soft gelatin capsule contains

Cyclosporine 50mg

Panimun Bioral™ 25mg

Cyclosporine Capsules

Each soft gelatin capsule contains

Cyclosporine 25mg

Panimun Bioral™

Cyclosporine Oral Solution

Each ml of Panimun Bioral solution

contains

Cyclosporine 100mg

