Imunocell®

Mycophenolate Mofetil

Back on Track

BPI

Summary of Product Characteristics

I- Trade name

Imunocell® 500 mg tablets

II- Qualitative and quantitative composition

Each tablet contains 500 mg Mycophenolate mofetil (MMF)

Excipients: Microcrystalline cellulose, magnesium stearate, povidone, croscarmellose sodium, colloidal anhydrous silica, tab coat.

III- Pharmaceutical forms and presentations

Imunocell®: Film coated tablets, box of 50.

IV- Therapeutic indications

Imunocell® is indicated as a prophylactic treatment for the prevention of allogenic renal, hepatic, or cardiac transplant rejection.

Imunocell® should be used in combination with cyclosporine and corticosteroids.

V- Posology and method of administration

Use in renal transplant:

Adults: oral **Imunocell®** should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1.0 g administered twice daily (2 g daily dose).

Children and adolescents: the recommended dose of mycophenolate mofetil is 600 mg/m^2 administered orally twice daily (up to a maximum of 2 g daily). **Imunocell®** tablets should only be prescribed to patients with a body surface area greater than 1.5 m^2, at a dose of 1 g twice daily (2 g daily dose). **Imunocell®** tablets should only be prescribed to patients with a body surface area of at least 1.25 m^2. Patients with a body surface are of 1.25 to 1.5 m^2 may be prescribed **Imunocell®** tablets at a dose of 1.5 daily dose. Patients with a body surface area greater than 1.5 m^2 may be prescribed **Imunocell®** tablets at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Children (< 2 years): there are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dose recommendations and therefore use in this age group is not recommended.

Use in cardiac transplant:

Adults: oral **Imunocell®** should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Children and adolescents: no data are available for pediatric cardiac transplant patients, therefore use in this patients group is not recommended until further data to support this is available.

Use in hepatic transplant:

Adults: intravenous mycophenolate should be administered for the first 4 days following hepatic transplant, with oral **Imunocell®** initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Children and adolescents: no data are available for pediatric hepatic transplant patients, therefore use in this patients group is not recommended until further data to support this is available.

Use in elderly (65 years):

The recommended dose of 1.0g administered twice a day for renal transplant patients and 1.5g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Use in renal impairment:

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml min-1 – 1.173 m^{-2}), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Use in severe hepatic impairment:

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes:

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dose reduction or interruption of **Imunocell®** is not required. There is no basis for **Imunocell®** dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

VI- Contraindications

Imunocell® is contra-indicated in patients who are hypersensitive to mycophenolate mofetil, mycophenolic acid, or any other component in this medication.

VII- Special Warnings and Precautions

Patients receiving mycophenolate mofetil as a part of an immunosuppressant therapy are at an increased risk of developing lymphomas and other malignancies particularly of the skin.
This risk is not specific to mycophenolate mofetil but to all other immunosuppressant regimes involving drug combinations, and is usually related to the treatment duration and intensity.
Immunosuppression also increases susceptibility to infection. In controlled studies on prophylaxis of rejection, lymphoproliferative disease or lymphoma developed in 0.6-1% of patients taking mycophenolate mofetil with other immunosuppressant agents as compared with 0 and 0.3% of patients in control groups.
In 3 controlled studies on prophylaxis of rejection, the rate of fatal infections in patients receiving mycophenolate mofetil plus other immunosuppressant agents was similar (<1%) to that in patients receiving control therapy plus other immunosuppressant agents. Up to 1.5% of patients receiving mycophenolate mofetil for prophylaxis of rejection developed severe neutropenia (ANC < 500/µl). The neutrophil count of patients receiving mycophenolate mofetil should be monitored.
Mycophenolate mofetil should be interrupted or dose reduced in case neutropenia develops (ANC < 1.3x103/µl), appropriate diagnostic tests performed and patient treated as required.
Gastrointestinal hemorrhage and perforations have rarely been observed in patients treated with mycophenolate mofetil. However, mycophenolate mofetil has been associated with an increased incidence of gastrointestinal side effects, thus it must be administered with caution in patients with severe active disease in the digestive tract.
Higher plasma MPA and MPAG AUCs were observed in patients with severe chronic renal failure (glomerular filtration rate < 25ml/min/1.73m^2) receiving a single dose of mycophenolate mofetil, compared to healthy subjects or patients with less severe renal failure. Such patients must be carefully monitored and must not receive more than 1g of mycophenolate mofetil twice daily.
In post-transplant patients with delayed graft function, mean MPA AUC0-12 was comparable to, but MPAG AUC0-12 was 2-3 fold that seen in post-transplant patients without delayed graft function. No dose adjustment is recommended for these patients, however they should be carefully observed.
Concomitant administration of mycophenolate mofetil with azathioprine is not recommended.
Caution should be exercised on concomitant administration of mycophenolate mofetil with other drugs affecting entero-hepatic recirculation due to the significant reduction of MPA AUC by cholestyramine and consequently efficacy.

Carcinogenicity, mutagenicity, impairment of fertility: In studies in the rat and mouse, mycophenolate mofetil was not tumorigenic. In experimental models, mycophenolate mofetil did not demonstrate mutagenic activity. Mycophenolate mofetil has no effect on fertility of male rats. In a female fertility and reproduction study conducted in rats, malformations (principally of the head and eyes) occurred in the first-generation (F1) offspring in the absence of maternal toxicity. No effects on fertility were identified in the treated females (P1 females) or in the first-generation offspring (P2 females or P2 males).
Laboratory tests: Full blood counts should be performed weekly during the first month, twice monthly during the second and third months of treatment, then monthly throughout the first year.

Pregnancy and lactation

It is recommended that **Imunocell®** therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning **Imunocell®** therapy, during therapy, and for six weeks following discontinuation of therapy. Patients should be instructed to consult their physician immediately should pregnancy occur.
The use of **Imunocell®** is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available. **Imunocell®** should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus. There is limited data from the use of mycophenolate mofetil in pregnant women. However, congenital malformations including ear malformations i.e. abnormally formed or absent external/middle ear have been reported in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
Mycophenolate mofetil has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolate mofetil in breast-fed infants, **Imunocell®** is contraindicated in breast-feeding mothers.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamics profile and the reported adverse reactions indicate that an effect is unlikely.

VIII- Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Aciclovir: higher acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir in comparison to the administration of acyclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8%) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids with magnesium and aluminium hydroxides: absorption of mycophenolate mofetil was decreased when administered with antacids.

Cholestyramine: following single dose administration 1.5g of mycophenolate mofetil to normal healthy subjects pretreated with 4 g three times a day (TID) of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA. Caution should be used during concomitant administration because of the potential to reduce efficacy of **Imunocell®**.

Medicinal products that interfere with enterohepatic circulation: caution should be used with medicinal products that interfere with enterohepatic circulation because of their potential to reduce the efficacy of **Imunocell®**.

Ciclosporin A: ciclosporin A (CsA) pharmacokinetics were unaffected by mycophenolate mofetil. In contrast, if concomitant ciclosporin treatment is stopped, an increase in MPA AUC of around 30% should be expected.

Ganciclovir: based on the results of a single dose administration study of recommended doses of oral mycophenolate and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in which **Imunocell®** and ganciclovir or its prodrugs, e.g. valganciclovir are co-administered, the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Oral contraceptives: the pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by co-administration of mycophenolate.

Rifampicin: in patients not also taking ciclosporin, concomitant administration of Mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC0-12h) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust **Imunocell®** doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sirolimus: in renal transplant patients, concomitant administration of mycophenolate mofetil and CsA resulted in reduced MPA exposures by 30-50% compared with patients receiving the combination of sirolimus and similar doses of **Imunocell®**.

Sevelamer: decrease in MPA Cmax and AUC0-12 by 30% and 25%, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e.graft rejection). It is recommended, however, to administer **Imunocell®** at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There is no data on mycophenolate mofetil with phosphate binders other than sevelamer.

Trimethoprim/sulfamethoxazole: no effect on the bioavailability of MPA was observed.

Norfloxacin and metronidazole: in healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin and metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

Tacrolimus: in liver transplant recipients initiated on mycophenolate mofetil and tacrolimus, the AUC and Cmax of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by trough tacrolimus level. In renal transplant patients, the tacrolimus concentration did not appear to be altered by mycophenolate mofetil. However, in hepatic transplant patients, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g taken twice [BID] a day, morning and evening) were administered to patients taking tacrolimus.

Other interactions: co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

Live vaccines: live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

IX- Undesirable effects

The following undesirable effects cover adverse reactions from clinical trials:
The principal adverse reactions associated with the administration of mycophenolate in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting and there is evidence of a higher frequency of certain types of infections.

Malignancies:

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Lymphoproliferative disease or lymphoma developed in 0.6% of patients receiving mycophenolate (2g or 3g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3.6% of patients; other types of malignancy occurred in 1.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1year, but less than 3 years.

Opportunistic infections:

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load .The most common opportunistic infections in patients receiving mycophenolate (2g or 3g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were Candida mucocutaneous, cytomegalovirus (CMV) viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%.

Children and adolescents:

The type and frequency of adverse reactions in a clinical study, which recruited 92 pediatric patients aged 2 to 18 years who were given 600 mg/m2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate twice daily. However, the following treatment-related adverse events were more frequent in the pediatric population, particularly in children under 6 years of age, when compared to adults: diarrhea, sepsis, leucopenia, anemia and infection.

Elderly patients (65 years):

Elderly patients (65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving **Imunocell®** as part of a combination immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals.

Other adverse reactions:

Adverse reactions, probably or possibly related to mycophenolate, reported in 1/10 and in 1/100 to < 1/10of patients treated with mycophenolate in the controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients are listed in the following table.

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (1/10); common (1/100 to <1/10); uncommon (1/1,000 to < 1/100); rare (1/10,000 to <1/1,000); very rare (1/10,000), not known (cannot be estimated from the available data).Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

Adverse reactions, probably or possibly related to Mycophenolate, reported in patients treated with Mycophenolate in renal, cardiac and hepatic clinical trials when used in combination with ciclosporin and corticosteroid

System organ class	Frequency	Adverse drug reactions
Investigations	Very common	-
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased
Cardiac disorders	Very common	-
	Common	Tachycardia
Blood and lymphatic system disorders	Very common	Leukopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leukocytosis

Nervous system disorders	Very common	-
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenicsyndrome, dizziness, headache, paraesthesia, dysgeusia
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleura effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, Diarrhea, nausea
	Common	Gastrointestinal hemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
System organ class	**Frequency**	**Adverse drug reactions**
Renal and urinary disorders	Very common	-
	Common	Renal impairment
Skin and subcutaneous tissue disorders	Very common	-
	Common	Skin hypertrophy, rash, acne, alopecia
Muscoloskeletal and Connective tissue disorders	Very common	-
	Common	Arthralgia
Metabolism and nutrition disorders	Very common	-
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia,hypophosphataemia, hyperuricaemia, gout, anorexia
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection,bronchitis,pharyngitis, sinusitis, fungal skin infection, skin Candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common	-
	Common	Skin cancer, benign neoplasm of skin

Vascular disorders	Very common	-
	Common	Hypotension, hypertension, vasodilatation
General disorders and Administration site conditions	Very common	-
	Common	Edema, pyrexia, chills, pain, Malaise, asthenia
Hepatobiliray disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Psychiatric disorders	Very common	-
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia

X- Overdosage

Cases of mycophenolate mofetil overdosage have been reported in humans. MPA and MPAG are usually not removed by hemodialysis, however when plasma concentrations of MPAG are high (>100µg/ml) small amount of MPAG can be removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants such as cholestyramine.

XI- Pharmacological properties

Pharmacodynamic properties

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

Pharmacokinetic properties

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate is correlated with MPA concentration.

The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to intravenous mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration. MPA at clinically relevant concentration is 97% bound to plasma albumin.

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 - 12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.
A negligible amount of substance is excreted as MPA (< 1% of dose) in the urine. Orally administered radiolabelled mycophenolate mofetil results in complete recovery of the administered dose; with 93% of the administered dose recovered in the urine and 6% recovered in the faeces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100mg/ml), small amounts of MPAG are removed.

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and Cmax approximately 40% lower compared to the late post-transplant period (3 - 6 months post-transplant).

Renal impairment:
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml-min-l-l.73 m-2) were 28-75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3-6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function:
In patients with delayed renal graft function post-transplant, mean MPA AUC (0-12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2-3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of **Imunocell®** does not appear to be necessary.

Hepatic impairment:
In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Children and adolescents:
Pharmacokinetic parameters were evaluated in 49 pediatric renal transplant patients given 600 mg/m2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate at a dose of 1 g BID in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

Elderly patients (65 years):
Pharmacokinetic behavior of mycophenolate in the elderly has not been formally evaluated.

Oral contraceptives:
The pharmacokinetics of oral contraceptives were unaffected by co administration of mycophenolate. A study of the co administration of mycophenolate (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05
mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate on the ovulation suppressing action of the oral contraceptives. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and progesterone were not significantly affected.

Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2-3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients as the recommended clinical dose of 2 g/day and 1.3-2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day.

Two genotoxicity assays (in vitro mouse lymphoma assay and in vivo mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamics mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other in vitro tests for detection of gene mutation did not demonstrate genotoxic activity.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg·kg^{-1}·day. The systemic exposure at this dose represents 2-3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3-2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients.
In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg kg^{-1} day^{-1} caused malformations (including anophthalmia, agnathia and hydrocephaly) in the first generation offspring in the absence of maternal toxicity.
The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg·kg^{-1}·day^{-1} (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg·kg^{-1}·day^{-1} (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels, are approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure).

The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population.

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA)
http://www.emea.eu

Evaluation of a new generic MMF formulation according to FDA rules and regulations in healthy volunteers, adult renal transplant patients: a Bioequivalence, clinical and pharmacodynamic study.

Introduction:

The general trend for public prescription of drugs, especially ones intended for chronic use, has shifted in the past few years from brand name to generics.The use of generic immunosuppressive drugs is increasing worldwide especially in Asian countries and the United State of America (USA)[1-10]. Beside the Asian countries currently there are generic forms for Cyclosporine (CYA) in the USA and for both Mycophenolate Mofetil (MMF) and CYA in Europe[11-16]. According to the FDA rules and regulations, all new drugs need proof that they are safe, tolerable and effective before they can be approved for marketing.The FDA also developed and issued explicit guidelines for a generic product's bioequivalency and stability, ensuring that products retain potency.The main rule is: if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product then it is equivalent and can be substituted (switchable) for that drug product.
Methods used to define bioequivalence as stated by the rule (FDA 21 CFR 320, 24) are:

1) **Pharmacokinetic/ Bioequivalence (PK) Studies in healthy volunteers,**
2) **Comparative clinical trials**
3) **Bioactivity or pharmacodynamic studies[17-19].**

Transmedical s.a.l has tested many of these generics prior to their commercial release.

The switchability of **Imunocell®** (Benta s.a.l, Beirut Lebanon) with the Innovator using all of the above FDA rules has been evaluated as follows:

1) PK; in a single oral dose comparative, bioavailability study
2) In a multicenter clinical study
3) Pharmacodynamic (intra cellular level)

The study was performed according to the Helsinki accord of medical ethics and monitored by the contract research organization (CRO) Transmedical s.a.l, (Beirut Lebanon, info@transmedicalsal.com) which is compliant with and EU audited for good clinical practice (GCP).

Materials and Methods:

The formulation tested were **Imunocell®** 500 mg (MMF) tablets batch number BT035, lot number 3002, manufactured by Benta s.a.l Lebanon on 12/2007 expiry date 12/2009 batch number 3002 and Innovator's 500 mg (MMF) tablets batch number M1507 (for the healthy volunteers) manufactured by the Innovator's mother company on 12/2006 expiry date 12/2009 and batch number M1886B01 expiry date 11/2010 (for the clinical study).
The study was carried out in accordance with the basic principles defined in the U.S. 21 CFR Part 312.20, the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, Somerset West, 1996) and the ICH harmonized tripartite guideline regarding Good Clinical Practices.
At the time of screening the patients were required to read, discuss, sign and date the Arabic translation of the informed consent in the presence of the principle investigator.
All subjects/patients were assured that they can withdraw from the study at any time without providing any reason for their action.

1) The bioequivalence (PK) study[27]:

Study design:
This was a double blind, (investigator and subject) balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioavailability study of tablets of **Imunocell®** (MMF 500 mg) tablet manufactured by Benta s.a.l Lebanon with that of Innovator's tablets containing MMF 500 mg, manufactured by Innovator's mother company, in healthy, adult, human subjects under fasting conditions.

The objective of the study:
To compare the pharmacokinetic profile of the sponsor's product:
Imunocell® 500 mg relative to that of Innovator's 500 mg tablets (containing 500 mg of Mycophenolate Mofetil, MMF) manufactured by Innovator's mother company, in healthy, adult, human subjects following the administration of 500mg (one tablet) single dose under fasting conditions.

Parameters measured:
Cmax: Maximum measured plasma concentration following each treatment.
AUC_{0-t}: The area under the plasma concentration versus time curve from time zero to the last measurable time point as calculated by linear trapezoidal method.
T_{max}: Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.

Data analysis:

The untransformed and in-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} will be subjected to Analysis of Variance (ANOVA). ANOVA model will include sequence, subjects nested into sequence, period and formulation effects. An F-test will be performed to determine the statistical significance of the effects involved in the model at a probability level of 5% (p=0.05).

The patients:

In all 24 healthy subjects were included with the following demographic data:

Sex						
Number of male			14			
Number of female			10			
AGE			**Height**		**Weight**	
Min	21		150		50	
1st Quartile	31.75		158.8		62.25	
Median	36		165		69.5	
Mean	36.75		165		71.25	
3rd Quartile	41.25		172.2		78.5	
Max	51		187		95	
95 % confidence interval	33.38051	40.11949	160.9943	168.9224	66.04511	76.45489
std. deviation	7.979594		9.387685		12.32618	

Healthy was ascertained by medical history, demographic data, physical examination, and clinically normal laboratory profiles. Subjects with a history of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunological, dermatological, neurological, or psychiatric diseases were excluded. In addition, subjects with a history or presence of alcoholism or drug abuse within the past year, other immunosuppressive agents, or chronic infections were also excluded.

The randomization was generated using a statistical software SAS® version 9.1.3. All the subjects were divided into blocks of equal size such that allotment of sequences 'A -B' and 'B-A' will be balanced within each block. Thus, random allocation of drug products (or formulations) was balanced over the period and sequence. In each period, subjects was administered either of the test or reference product, according to the randomization schedule.

The Test and Reference Product were assigned with the randomization code (A or B). The randomization code was available only to the Principal Investigator from the Biostatistician and was opened by the Principal Investigator only after the pharmacokinetic data has been completed. The study personnel involved in dispensing and the study Monitor were accountable for ensuring compliance to randomization schedule.

The subjects, who were housed in a clinical facility which is GCP compliant and is audit by the EU inspectors, were given a single oral dose of 500 mg with a washout period of 7 days.

Pharmacokinetic profiles of blood Mycophenolic Acid (MPA) concentration–time profile included blood levels at : 0, 20, 40, 1, 1h:20 min, 2h, 3h, 4h, 6h, 8h, 10h, 12h and 24 hours following each dose. The samples were collected through an indwelling vein cannula placed in the forearm of the subjects. Subjects were fasted overnight before dosing and for at least 2 hours thereafter. Water was not permitted for 1 hour before and 1 hour after dosing but was allowed at all other times. Plasma was isolated and MPA concentration determined using a high-performance liquid chromatography and a validated enzyme-linked immunosorbent assays–based method (kit lot number A15793 expiry date 30/11/2009 Transmedical s.a.l Beirut, Lebanon). The first blood sample collection was prior to a saline drip. All food for quantity and quality was kept the same in both periods for all subjects. The analysis of subject's samples was performed using a calibration curve with quality control standards, distributed throughout each batch. A set of quality control samples was analyzed before and after subject's samples in each period. The parameters analyzed were: Cmax maximum measured plasma concentration following each treatment; AUC_{0-t}; the area under the plasma concentration versus time curve from time zero to the last measurable time point as calculated by linear trapezoidal method; Tmax, time of maximum measured plasma concentration. If the maximum value occurred at more than one time point, Tmax was defined as the first time point with this value. The following laboratory parameters were performed during the study, in each period and at beginning and end of the study: urinanalysis, hematology, and biochemistry parameters. The study medication was administered only to those subjects with a clinically acceptable value upon pre-dose laboratory assessments. To monitor safety, sitting blood pressure and heart rate determinations were performed.

2) The clinical study[27]:

The primary objective of the study is to compare pharmacokinetics of the new generic MMF formulation – **Imunocell**® 500 mg tablets after the switch from Innovator's original formulation 500 mg tablets in stable adult renal transplant recipients.

The secondary objective of the study is to evaluate the blood trough level (BTL) and the C_{max}.

The tertiary objective of the study is to evaluate the safety of the switch from Innovator's tablets to **Imunocell**® 500 mg tablets.

Vital signs, incidence of adverse events, changes in blood pressure and laboratory variables were assessed during each visit. The patients were selected according to the following criteria: first renal transplant, clinically stable with no rejection episodes for at least 6 months, and acceptable safety with/tolerance to Innovator's tablets. The maintenance immunosuppressive regimen for all patients was a Cyclosporine or Tacrolimus -based in combination with prednisone and MMF. Myocardial infarction within 6 months of enrollment was grounds for exclusion from the study. Any of the following occurring within the 14 days prior to the study was also considered grounds for exclusion: uncontrolled cardiac arrhythmia; any condition that might compromise gastrointestinal tract, kidney, or liver function; any condition that might influence MMF pharmacokinetics. Subjects who failed to complete the study were not replaced.

Demographic data:

In all, 16 (11 males and 5 females) were enrolled in and 16 completed the study (11 males and 5 females)

The demographic data of the patients

Sex	***Number of males***	11	
	Number of females	5	
Age	***Min***	32	
	1st Quartile	37	
	Median	46	
	Mean	60.25	
	3rd Quartile	62.5	
	Max	70	
	95 % confidence interval	63.4229	61.662
	std. deviation	9.08244	

On day 0, the patients who were receiving the commercially available Innovator's MMF were switched to the same Innovator's MMF (batch number M1886B01, expiration date 11/2010). On day 7 the first sparse sampling pharmacokinetics (BTL, 45minutes, and 75 post the dose), was performed and each recipient underwent hematologic testing, urinalysis, and serum biochemistry testing. On day 14, abbreviated pharmacokinetics testing was done over a 2-hour period (pre-dose, and then at 20, 40, 60, 80 and 120 minutes) following the dose. The MPA level in each blood sample was determined using a MPA kit (lot No. expiration date Transmedical s.a.l Beirut Lebanon).

On day 15, the patients were switched from Innovator's MMF tablets to equivalent dosages of **Imunocell®** tablets (batch numberT035, expired 12/2009). A second sparse-sampling pharmacokinetic testing, hematologic analyzing, urinalysis, and serum biochemistries was performed on day 21, and a second 2-hour period abbreviated pharmacokinetics testing on day 28 (blood drawn at same time points noted). In the morning of day 45, the patients were switched from **Imunocell®** back to equivalent dosages of Innovator's MMF. Additional BTL were measured on days 7, 18, and 35[20]. Safety parameters and blood levels for CYA or Tacro were monitored at each visit.

3) Pharmacodynamic study[27]:

The primary objective Is to compare the intra-cellular bioavailability "cellular pharmacokinetics" of the new generic **Imunocell®** 500 mg tablets after the switch from original formulation Innovator's MMF tablets in stable adult renal transplant recipients.
The secondary objective of the study is to evaluate at C0 and Cmax, of cellular pharmacokinetics and pharmacodynamic effects (defined by the total lymphocyte count) of both drugs **Imunocell®** and Innovator's MMF.
As the tertiary endpoints the following parameters were assessed:
- Physical examinations
- Vital signs
- Incidence of adverse events
- Changes in blood pressure
- Laboratory variables

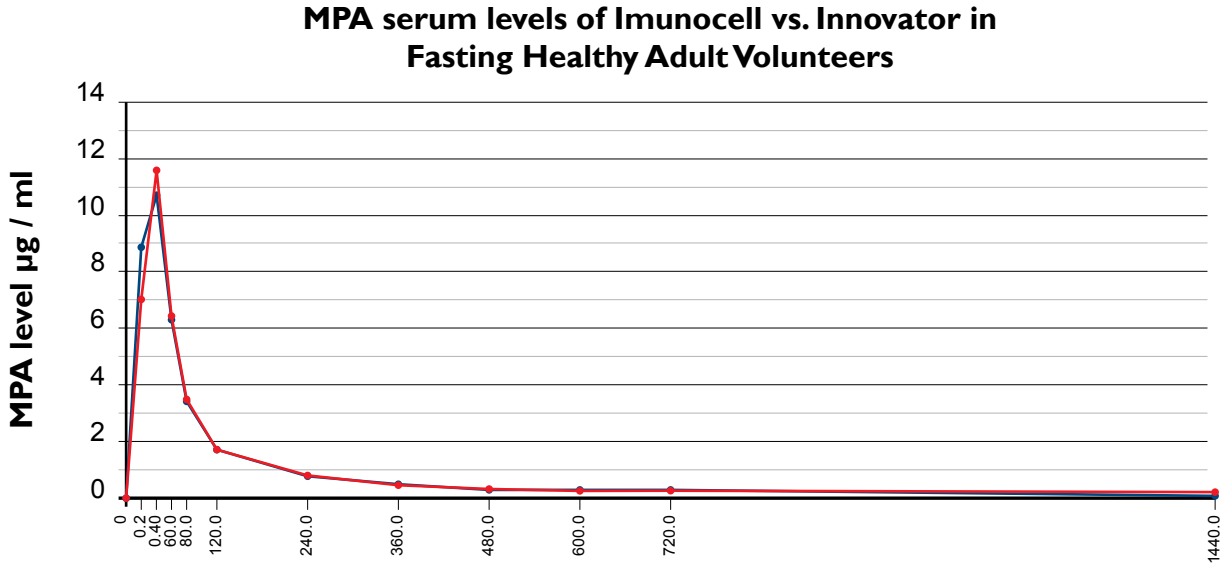
Methods:
MPA levels in the lymphocytes were determined using the method of Masri et al[21-23]. Briefly the lymphocytes were separated from 2 mls of EDTA blood using density gradient centrifugation on ficoll - hypaque, washed three times with PBS (Phosphate buffer saline). The cells were incubated 30µl of the patent cell extracting solution (MIRA solution). 20 µl of the extracts were used to measure the MPA levels using the MPA ELISA kits as described above. The individual cell concentration was calculated using the total number of lymphocytes and is expressed as ng/lymphocyte

Results:

The bioequivalence study[27]:

All the subjects and who were enrolled completed the study.
Pharmacokinetic profiles of both Innovator and Imunocell® were similar (Figure 1)

Figure1: Mean blood MPA concentrations plot for Innovator and Imunocell® 500 mg tablets in healthy volunteers:



	0	0.2	0.40	60.0	80.0	120.0	240.0	360.0	480.0	600.0	720.0	1440.0
Imunocell	0	8.92	10.77	6.26	3.46	1.73	0.81	0.5	0.36	0.38	0.29	0.05
Innovator	0	7.08	11.52	6.37	3.5	1.73	0.84	0.46	0.4	0.3	0.28	0.11

The area under curve (AUC), AUC extrapolated to infinity (AUC0-inf), rate of absorption (Tmax), extent of absorption (Cmax), half time (T1/2) of **Imunocell®** and Innovator's MMF were within the general 80-125 % FDA acceptance range (Table 1)

Table 1: of variance computed on logarithmically transformed values of AUC and C_{max} of **Imunocell®**

Source:	***Df***	***Sum of Sq.***	***Mean Sq.***	***F value***	***p-value***
Treatment	1	0.00005	0.00005	0.0142	0.9063
Period	1	0.00036	0.00036	0.1071	0.7466
Sequence	1	0.10401	0.10401	1.37361	0.2537288
Subject(Seq)	22	1.66585	0.07572	22.4127	
Residual	22	0.07433	0.00338		

90 % CI for ratio (reference) - (test) ---log AUC 0-t [%]	
Lower Bound	Upper Bound
97.22897	**103.26195**

Source:	***Df***	***Sum of Sq.***	***Mean Sq.***	***F value***	***p-value***	
Treatment	1	0.03402	0.03402	12.535	0.001837	**
Period	1	0.00224	0.00224	0.8247	0.373637	
Sequence	1	0.0001526	0.0001526	0.0011797	0.972907	
Subject(Seq)	22	2.84594	0.12936	47.6633		
Residual	22	0.05971	0.00271			

90 % CI for ratio (reference) - (test) ---log Cmax [%]	
Lower Bound	Upper Bound
102.6642	**108.3501**

Clinical Study[27]:

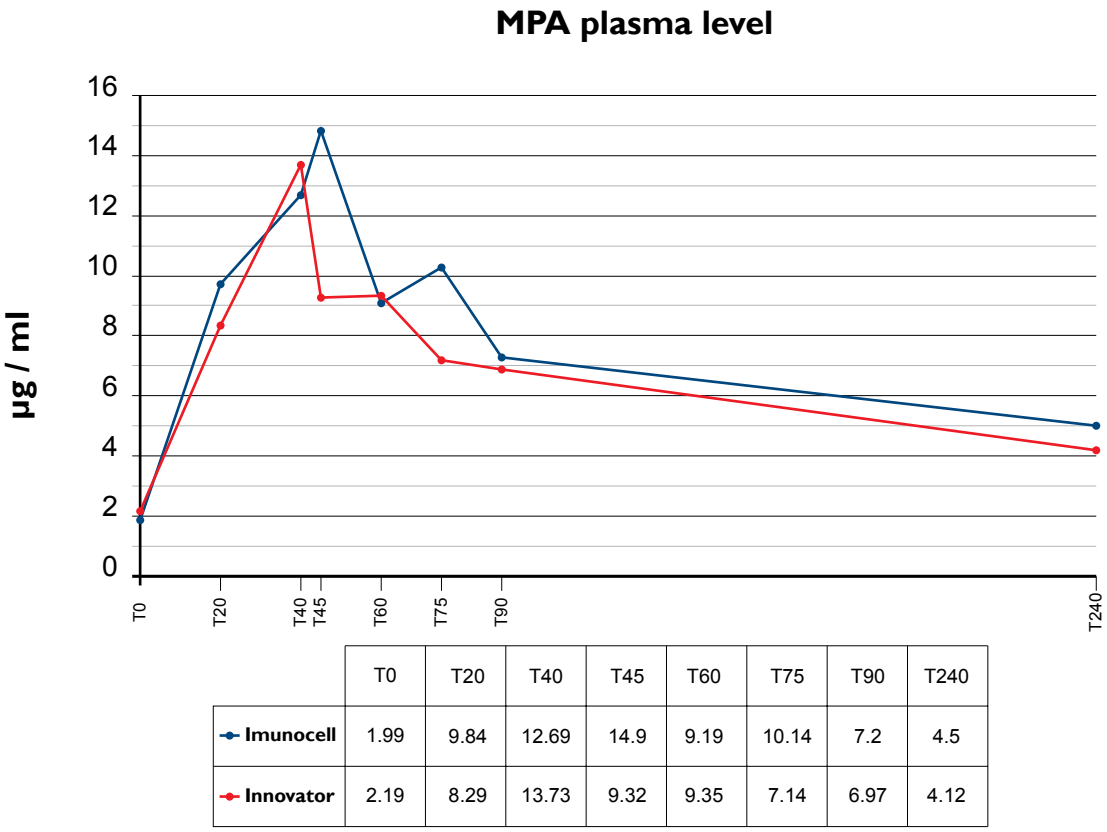
Analysis of Weight distribution of the patients

Weight	Min	55	
	1st Quartile	61.25	
	Median	72	
	Mean	71.79	
	3rd Quartile	80.5	
	Max	96	
	95 % confidence interval	67.75826	75.8132
	std. deviation	11.72434	

Statistical Analysis of the patient's Height

Height	Min	153	
	1st Quartile	162.5	
	Median	174	
	Mean	171.7	
	3rd Quartile	179.5	
	Max	190	
	95% confidence interval	167.9923	175.322
	std. deviation	10.66865	

Figure 2: The average pharmacokinetic profile of MPA plasma levels for both Innovator and Imunocell® (imcell) (concentration in µg/ml vs. time in minutes).



	T0	T20	T40	T45	T60	T75	T90	T240
Imunocell	1.99	9.84	12.69	14.9	9.19	10.14	7.2	4.5
Innovator	2.19	8.29	13.73	9.32	9.35	7.14	6.97	4.12

	Formulation		
Time	**Innovator**	**Imunocell®**	**P**
T0	2.19	1.99	0.58
T20	8.29	9.84	0.42
T40	13.73	12.69	0.75
T45	9.32	14.9	0.05*
T60	9.35	9.19	0.9
T1:15	7.14	10.14	0.1
T1:20	6.97	7.2	0.73
T2	4.12	4.5	0.74

*= significant

The analysis of the average of the clinical chemistry for Imunocell® vs. Innovator

Formulation				
Test	**Reference range**	**Imunocell®**	**Innovator**	**P**
S. CREATININE	0.60 – 1.30	1.25	1.20	0.6
S. BUN	7 – 18	20.71	20.26	0.86
S. URIC ACID	2.6 – 7.2	7.5	7.15	0.31
S. ALT =SGPT	30 -65	37.83	40.35	0.26
S. AST = SGOT	15 – 37	20.94	23.12	0.31
S. T. BILIRUBIN	<1	0.58	0.59	0.68
S. ALBUMIN	3.4 -5	3.91	3.9	0.87
S. GLUCOSE	70 -110	88.71	83.84	0.1
S. TRIGLYCERIDES	30 -150	170.55	175.16	0.7
S. CALCIUM	8.5 -10.1	9	9.05	0.63
S. PHOSPHOROUS	2.5 - 4.9	3.06	3.13	0.52
S. LDH	100 – 190	130.03	152.51	0.098
S. ALP	50 -136	93.88	115	0.12
S. CHOLESTEROL	< 200	180.82	180.91	0.99
LDL -CHOLESTEROL	> 40	48.92	53.81	0.36
HDL-CHOLESTEROL	< 130	99.89	97.93	0.78
S. SODIUM	136 – 145	140.89	140.93	0.94
S. POTASSIUM	3.5 - 5.1	4.28	4.42	0.12
S. CHLORIDE	98 – 107	101.71	102.63	0.09
S.MAGNESIUM	1.8-2.4	1.73	1.75	0.78

The analysis of the average of the Urinalysis for Imunocell® vs. Innovator

Formulation		
URINALYSIS	**Innovator**	**Imunocell®**
U PROTEIN	56.92	49.09
U GLUCOSE	Neg	Neg
U BLOOD	Neg	Neg
U LEUK	Neg	Neg
U PH	5.15	5.45
U SG	1019.37	1019.37

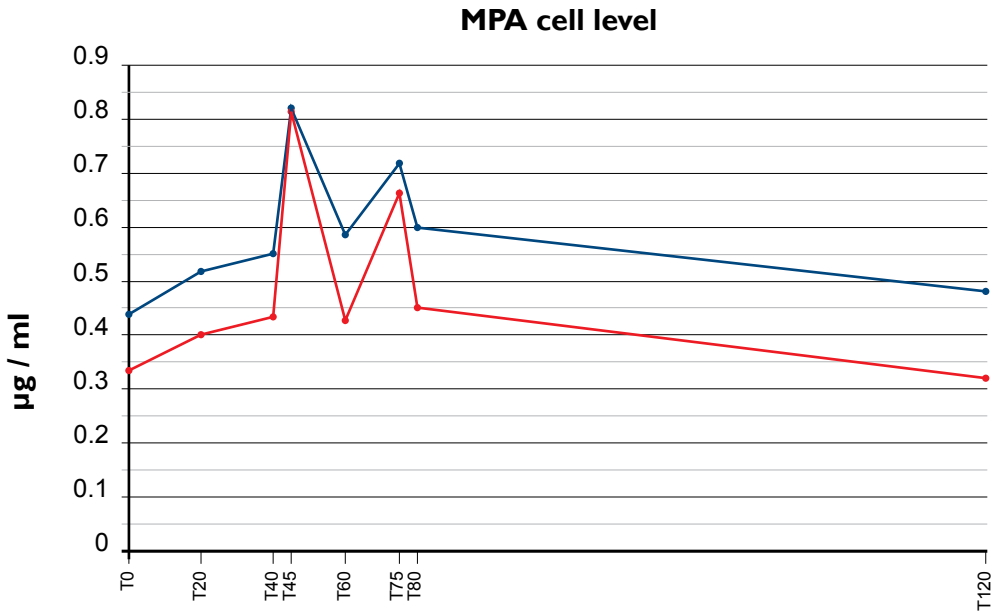
The analysis of the average of Hematology parameters for Imunocell® vs. Innovator

Formulation				
TEST	**Reference Range**	**Innovator**	**Imunocell®**	**P value**
HEMATOCRIT	37 -51	37.28	37.51	0.57
HEMOGLOBIN	12.0 -18	13.08	13.12	0.91
RBC	4.2 -6.3	4.58	4.76	0.37
WBC	4.1 -10.9	7.25	7.67	0.58
GRANULOCYTES	37 – 92	63.5	64.4	0.79
LYMPHOCYTES	0.1 – 24	28.69	28.75	0.91
PLATELETS	10 – 58.5	235	256	0.76

In the clinical study, there was no significant difference in the blood trough levels for Innovator and **Imunocell®**: Results were 1.68 µg/ml and 1.99 µg/ml respectively (P =0.58).
There was no significant difference between Innovator and **Imunocell®** at any other time except T45 with **Imunocell®** exhibiting a higher value (P =0.05)
The T_{max} was 46.21 minutes for Innovator and 41 minutes for **Imunocell®** respectively with no significant difference (p= 0.198).
The C_{max} was 16.89 µg/ml for Innovator and 17.82 µg/ml for **Imunocell®** with no significant difference (P = 0.40).
There were no significant differences in the measured laboratory parameters.

The pharmacodynamic studies[27]:

Figure 3: The average pharmacokinetic profile of MPA cell levels for both Innovator and Imunocell® (concentration in ng/ml vs. time in minutes).



	T0	T20	T40	T45	T60	T75	T80	T120
Imunocell	0.44	0.52	0.55	0.82	0.59	0.72	0.6	0.48
Innovator	0.34	0.4	0.43	0.81	0.42	0.67	0.45	0.32

Discussion

In healthy volunteers, the ratios of LSM and 90% confidence intervals for the in-transformed parameters (AUC_{0-t}, C_{max}, and T_{max}) of **Imunocell®** versus Innovator 500 mg tablets under fasting conditions were within the 80% to 125% FDA acceptance range for generic drugs and within the 90% to 111% FDA range for immunosuppressive drugs.

The results from the clinical study in stable adult renal transplant patients, indicated that patients can be safely and effectively switched from Innovator's MMF to **Imunocell®** 500 mg tablets at 1:1 ratio.

These results indicated that **Imunocell®** and Innovator's MMF 500 mg tablets are switchable in accordance with international rules and regulations.

The pharmacodynamic (cellular level) study indicates that both drugs given to the same patient will achieve similar lymphocyte cell level (**Imunocell®** site of action) and thus will have the same immunosuppressive effect.

The results from the FDA required studies for interchangeability (Bioavailability- Bioequivalence, Clinical Studies) indicates that dose for dose **Imunocell®** and Innovator's MMF 500 mg tablets are switchable. The use of generics in transplantation should be restricted to those drugs that comply with the EU and FDA rules and regulations[24-26].

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27. Data on file

Before prescribing please consult physicians' circular.

® Registered trade name

Imunocell® manufactured by BPI

- State of the art manufacturing facility
- Certified European GMP
- ISO Certified

CE GMP

Benta Pharma Industries - Dbayeh, Lebanon