Imunocell®

Mycophenolate Mofetil

Composition:
Imunocell®: Each film coated tablet contains mycophenolate mofetil 500mg.
Excipients: Microcrystalline cellulose, magnesium stearate, povidone, croscarmellose sodium, colloidal anhydrous silica, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, red iron oxide, black iron oxide.
Pharmaceutical forms and presentations
Imunocell®: Film coated tablets, box of 50.
Pharmacological properties
Mycophenolate Mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA exerts its effects by selective reversible, non competetive inhibition of inosine monophosphate dehydrogenase which consequently leads to inhibition of de novo pathway for guanosine nucleotide synthesis without encorporation into DNA. MPA exerts a higher cytostatic effect on B and T lymphocytes that are critically dependant on de novo pathway for purine synthesis than on other cells that can use salvage pathways as an alternative.
Pharmacokinetics
Absorption: Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to MPA, the active metabolite. Mycophenolate mofetil is not detectable in plasma after oral administration. Influence of food: C_{max} reduced to 77%. The mean bioavailability of oral mycophenolate mofetil, based on the AUC of MPA, is 94% of that of IV mycophenolate mofetil.
Distribution: As a result of enterohepatic recirculation, a secondary rise in plasma MPA concentration is generally observed of approximately 6-12 hrs post-dose. The AUC of MPA is reduced by approximately 40% when mycophenolate mofetil is administered simultaneously with cholestyramine (4 g t.i.d.), indicating that there is a significant amount of enterohepatic recirculation. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at the MPAG concentration range normally seen in stable renal transplant patients; however at higher concentrations of MPAG such as those seen in patients with delayed graft function or severe renal failure, the bound fraction in vitro decreases to 62%.
Metabolism: MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.
Elimination: Enterohepatic recirculation determination of the $t_{1/2}$ of MPA is difficult. The apparent half-life is approximately 16-18 hrs. Approximately 93% of a dose is eliminated via the kidneys mostly as MPAG, while approximately 5.5% is eliminated in the feces.
Pharmacokinetics in special clinical situations: In a single-dose study (6 subjects per group), plasma MPA AUCs observed in subjects with severe chronic renal failure (glomerular filtration rate < 25 ml/min/1.73m^2) were 28-75% higher than those of healthy subjects or patients with less severe renal failure. The mean increase in MPA AUC observed in subjects with severe renal failure was comparable to the increase in MPA AUC seen when the daily dose of mycophenolate mofetil is increased from 2g to 3g. Mean MPA AUC_{0-12} in post-transplant patients with delayed graft function was comparable to that seen in post-transplant patients without delayed graft function. Liver failure has no influence on pharmacokinetics. Pharmacokinetics in elderly patients were not investigated.
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.
Contra-Indications
Imunocell® is contra-indicated in patients who are hypersensitive to mycophenolate mofetil, mycophenolic acid, or any other component in this medication.
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 < 1.3x10^3/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 AUC_{0-12} was comparable to, but MPAG AUC_{0-12} 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
There are no well controlled studies about the use of mycophenolate mofetil in pregnant women, thus it must not be used by pregnant women unless the potential benefit to the mother outweighs the potential risk to the fetus. Effective contraception must be used prior to and during mycophenolate mofetil therapy and 6 weeks after stopping therapy. Studies in rats have shown that mycophenolate mofetil is excreted in milk, however it is not known if this is applicable to humans. Considering the potential risk of severe adverse reactions, occuring in nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug while taking into account its importance to the mother.
Drug Interactions
Mycophenolate mofetil has not been administered concomitantly with azathioprine.
Acyclovir: Higher MPAG (8.6%) and acyclovir (17.4%) plasma AUCs were observed when mycophenolate mofetil was administered with acyclovir in comparison to administration of each drug alone. Because MPAG and acyclovir plasma concentrations are increased in the presence of renal failure, the potential exists for the 2 drugs to compete for tubular secretion, hence further increases in concentrations of both drugs may occur.
Antacids with magnesium and aluminum hydroxides: Absorption of mycophenolate mofetil was reduced when administered concomitantly with antacids.
Cholestyramine: There was a 40% reduction in the AUC of MPA.
Cyclosporin A: Cyclosporin A pharmacokinetics were unaffected by mycophenolate mofetil.
Ganciclovir: No pharmacokinetic interaction was observed between mycophenolate mofetil and IV ganciclovir.
Oral contraceptives: No pharmacokinetic interaction was observed between mycophenolate mofetil and 1mg norethindrone and 35µg ethinyl estradiol. This single-dose study demonstrates the absence of any gross pharmacokinetic interaction, but cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long-term dosing conditions with mycophenolate mofetil which might adversely affect theThis single-dose study demonstrates the absence of any gross pharmacokinetic interaction, but cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long-term dosing conditions with mycophenolate mofetil which might adversely affect the efficacy of the oral contraceptive.
Trimethoprim/Sulfamethoxazole: No effect on the bioavailability of MPA was observed.
Other interactions: Coadministration of probenecid and mycophenolate mofetil in monkeys causes a 3-fold increase in the plasma AUC of MPAG. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.
Side effects
It is often difficult to establish the side effect profile of immunosuppressants due to the possible effects of the basic disease and the generally extensive concomitant medication.
The most common side effects associated with mycophenolate mofetil administration are diarrhea, vomiting, leukopenia, sepsis, and a higher frequency of certain types of infection. Adverse reactions reported in ≥ 10%, or in ≥ 3% but < 10%, of patients treated with mycophenolate mofetil in controlled clinical trials are presented below:
General: In ≥ 10% of patients: Sepsis (19.7%), infection (20.9%), fever (23.3%), asthenia (16.1%), headache (21.1%), chest pain (13.4%), abdominal pain (27.6%), back pain (12.1%), undefined pain (33.0%). In 3-10% of patients: Cyst formation, hemorrhage, accidental injury, increased drug levels, hernia, increased abdominal size, cheek pain, influenzal syndrome, facial oedema.
Cardiovascular system: In ≥ 10% of patients: Hypertension (32.4%). In 3-10% of patients: Thrombosis, hypotension (including postural hypotension), atrial fibrillation, tachycardia, palpitations, vasodilatation.
Gastrointestinal tract: In ≥ 10% of patients: Nausea (23.6%), vomiting (13.6%), dyspepsia (17.6%), diarrhea (36.1%), constipation (17.6%), oral moniliasis (12.1%). In 3-10% of patients: Gastrointestinal hemorrhage, infections, anorexia, gingival hyperplasia, gingivitis, esophagitis, gastritis, gastroenteritis, flatulence, ileus, rectal disorders, abnormal liver function values.
Metabolic system: In ≥ 10% of patients: Hyperglycemia (12.4%), hypophosphatemia (15.8%), oedema (including peripheral oedema) (12.2%). In 3-10% of patients: Increased levels of γ-GT, SGPT, SGOT, LDH, alkaline phosphatase, calcium, cholesterol, lipids, uric acid and creatinine; reduced blood levels of potassium, calcium, glucose, and proteins, acidosis, dehydration, hypervolemia, weight increase.
Blood and lymphatic system: In ≥ 10% of patients: Leukopenia (34.5%), thrombocytopenia (10.1%), anemia (25.8%), hypochromic anemia (11.5%). In 3-10% of patients: Leukocytosis, polycythemia.
Urogenital tract: In ≥ 10% of patients: Urinary tract infection (37.2%), tubular necrosis (10.0%), hematuria (14.0%). In 3-10% of patients: Albuminuria, hydronephrosis, dysuria, pollakiuria, urinary disorders.
Respiratory tract: In ≥ 10% of patients: Infection (23.0%), dyspnea (17.3%), increased coughing (15.6%). In 3-10% of patients: pneumonia, pulmonary oedema, pulmonary disorders, bronchitis, pharyngitis, sinusitis, rhinitis.
Skin and appendages: In ≥ 10% of patients: Infection with Herpes simplex (20.0%). In 3-10% of patients: Infection with Herpes zoster, skin ulcers, skin carcinoma, ecchymoses, acne, rash, skin changes, hirsutism, transpiration.
Nervous system: In ≥ 10% of patients: Insomnia (11.8%), tremor (11.5%). In 3-10% of patients: Vertigo, paresthesia, hypertension, anxiety.
Musculoskeletal system: In 3-10% of patients: Arthralgia, myalgia, calf cramps, myasthenia.
Endocrine system: In 3-10% of patients: Diabetes mellitus, parathyroid dysfunction.
Sensory organs: In 3-10% of patients: Conjunctivitis, amblyopia.
In controlled studies on the prevention of transplant rejection, patients receiving 2g/day of mycophenolate mofetil demonstrated an overall better safety profile than did those receiving 3g/day. As compared with patients receiving azathioprine or placebo, patients receiving mycophenolate mofetil showed an increased frequency of occurrence of diarrhea and a slightly increased frequency of occurence of vomiting, sepsis (generally caused by cytomegalovirus), and urinary tract infections. Leukopenia also occured more commonly in patients taking mycophenolate mofetil than in patients in control groups; it was most common in patients receiving 3g/day mycophenolate mofetil. In the studies on prevention of transplant rejection, invasive cytomegalovirus disease occured more commonly in patients receiving 3g/day of mycophenolate mofetil than in those receiving 2g/day or control therapy. Similarly, the incidence of candidemia, tissue-invasive candidiasis, and invasive aspergillosis was slightly higher in patients receiving mycophenolate mofetil than in those receiving control therapy. In the studies on prevention of transplant rejection, similar rates of fatal infection (<1%) occured in patients receiving mycophenolate mofetil as in those receiving control therapy, in both cases in combination with other immunosuppressants. Up to 1.5% of patients receiving mycophenolate mofetil for prevention of transplant rejection developed severe neutropenia (absolute neutrophil count < 500/µl). The incidence of malignancies in patients in the controlled studies on prevention of transplant rejection was low and was similar to that for renal allograft recipients reported in the literature. The incidence of lymphoproliferative diseases and lymphomas was slightly higher in patients taking mycophenolate mofetil (approximately 1%) than in the control groups (0% and 0.3%).
Dosage and administration
- Renal transplantation: The recommended dose to be used in adult renal transplant patients is 2g daily (1g b.i.d.), In case a higher level of immunosuppression is recommended the daily dose can be increased to 3g (1.5g b.i.d.).
- Cardiac transplantation: The recommended dose to be used in adult cardiac transplant patients is 3g daily (1.5g b.i.d.)
- Hepatic transplantation: The recommended dose to be used in adult hepatic transplant patients is 3g daily (1.5g b.i.d.).
The initial dose of Imunocell® must be administered within 72hrs of the transplantation operation. Imunocell® should be administered in combination with cyclosporin and corticosteroids.
- Special dosage instructions
Doses higher than 2g of Imunocell® (1g b.i.d.) should be avoided in patients with severe chronic renal failure (glomerular filtration rate < 25ml/min/1.73m^2) outside of the immediate post transplant period. In case of delayed graft function following the transplantation operation, no dosage adjustment is required. Dose reduction or interruption is required if neutropenia develops (ANC) (absolute neutrophil count < 1.3x10^3/µl) followed by appropriate diagnostic tests and treatment.
- Handling precautions
Imunocell® tablets should not be crushed due to the demonstrated teratogenic effect in rabbits and rats.
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.

Date of Revision: July 2012.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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