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Mofecon-GR 360 (Mycophenolic Acid Gastro-Resistant Tablets 360mg)

VIMOFxx-09 (MY)

DESCRIPTION
Mofecon−GR 360
(Mycophenolic Acid Gastro-Resistant Tablets 360 mg):
Pink to light pink colored, enteric coated, ovaloid biconvex tablet, debossed with “C 2” on one side and plain on other side.

COMPOSITION
Mofecon−GR 360
(Mycophenolic Acid Gastro-Resistant Tablets 360 mg):
Each enteric coated tablet contains: Mycophenolic acid 360 mg
Excipients: Microcrystalline cellulose, croscarmellose sodium, povidone, colloidal silicon dioxide, talc, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, titanium dioxide, triethyl citrate, sodium bicarbonate, iron oxide yellow, iron oxide red, sodium lauryl sulfate.

PHARMACODYNAMICS
Mycophenolic acid (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 utilize salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

PHARMACOKINETICS
Absorption
Following oral administration, mycophenolate sodium is extensively absorbed. Consistent with its enteric coated design, the time to maximal concentration (T_{max}) of MPA was approximately 1.5-2 hours.

Distribution
The volume of distribution at steady state for MPA is 50 litres. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound. The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminaemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Biotransformation
MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biological activity.

Elimination
The half life of MPA is approximately 12 hours and the clearance is 8.6 l/h. Although negligible amounts of MPA are present in the urine (<1.0%), the majority of MPA is eliminated in the urine as MPAG. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6-8 hours after MPA dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA.

INDICATIONS
Indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

CONTRAINDICATIONS
- Mofecon is contraindicated during pregnancy due to its mutagenic and teratogenic potential. (see use in Special Populations: Breastfeeding)
- Mofecon is contraindicated in women of childbearing potential not using highly effective contraceptive methods. (see use in Special Populations: Breastfeeding)
- Mofecon is contraindicated in women who are breastfeeding. (see use in Special Populations: Breastfeeding)

WARNING AND PRECAUTIONS
Patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)
Mofecon is an IMDPH (inosine monophosphate dehydrogenase) inhibitor. On theoretical grounds, it should therefore be avoided in patients with a rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelly-Seegmiller syndrome.

Pregnancy, lactation, females and males of reproductive potential
Mofecon therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mofecon therapy, during therapy and for six weeks following therapy discontinuation (see Pregnancy, Lactation, Females and Males of Reproductive Potential).

Teratogenic effects
- Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortion and congenital malformations in case of exposure during pregnancy.
- Women with childbearing potential should use two reliable forms of contraception simultaneously before starting and during therapy, and for six weeks after stopping treatment; unless abstinence is the chosen method of contraception.
- Sexually active (including vasectomized) men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Female partners of male patients treated with Mofecon are also recommended to use highly effective contraception for the same period.
- Before starting Mofecon treatment, women of child bearing potential should undergo pregnancy testing. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended; the second test should be performed 8–10 days after the first one and immediately before starting mycophenolate. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported).

Contraception
Due to high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy every effort to avoid pregnancy during treatment should be taken. Therefore women with childbearing potential must use at least one form of reliable contraception before starting mycophenolic acid therapy, during therapy and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

Educational materials
In order to assist patients in avoiding fetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation Holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need of pregnancy testing. Full patient information about teratogenic risk and pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Additional precautions
Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for at least 90 days following discontinuation of mycophenolate.

Malignancies
Patients receiving immunosuppressive regimens involving combinations of drugs, including Mofecon, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimize the risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a high protection factor sunscreen.

Infections
Patients receive Mofecon should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Oversuppression of the immune system increases susceptibility to infection including opportunistic infection, fatal infections and sepsis.

Reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including mycophenolic acid (MPA) derivatives Mofecon and MMF. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives which include mycophenolate mofetil and mycophenolate sodium. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune functions. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection, should be included in the differential diagnosis in immunosuppressed patients with deteriorating renal function. Consideration should be given to reducing the total immunosuppression in patients who develop PML or PVAN. In transplant patients, however, reduced immunosuppression may place the graft at risk.

Immunosuppressed patients are at increase risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes.

Blood dyscrasias
Patients receiving Mofecon should be monitored for blood dyscrasias (e.g. neutropenia or anemia), which may be related to MPA itself, comedication, viral infections, or some combination of these causes. Patients taking Mofecon should have complete blood cell counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly throughout the first year. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count <1.5 x 103 / micro L or anemia) it may be appropriate to interrupt or discontinue Mofecon.

Cases of pure red cells aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. However, MPA derivatives may cause blood dyscrasias (see above). In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Mofecon therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize risk of graft rejection.

Vaccinations
Patients should be advised that vaccinations may be less effective during treatment with MPA and the use of the live attenuated vaccines should be avoided. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal disorders
As MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage and perforation, Mofecon should be administered with caution in patients with active serious digestive system disease.

Combination with other agents
Mofecon has been administered in combination with the following agents: antithymocyte globulin, basiliximab, ciclosporin for microemulsion and corticosteroids. The efficacy and safety of the use of Mofecon with other immunosuppressants have not been studied.

PREGNANCY AND LACTATION
Pregnancy
Mofecon is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive method.

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counselled regarding pregnancy prevention and planning.

BACK

Prior to starting therapy with Mofecon, female patients of childbearing potential must have two negative serum or urine pregnancy test with a sensitivity of at least 25mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting Mofecon. Repeat pregnancy test should be performed during routine follow-up visit. Results of all pregnancy test should be discussed with patient. Patients should be instructed to consult their physician immediately should they become pregnant.

Due to the mutagenic and teratogenic potential of mycophenolate, woman of child bearing potential should use two reliable forms of contraception simultaneously, including at least oen highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Sexually active men are recommend to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risk associated with the transfer of seminal fluid also apply to men who have had vasectomy. In addition, female partners of male patients are recommended to use highly effective during treatment and for total of 90 days after the last dose of Mofecon.

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits
- Abnormalities of the ear (e.g abnormally formed or absent external/middle ear) and eye (e.g colobama, microphthalmos)
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly)
- Cardiac abnormalities such as atrial and ventricular septal defects
- Oesophageal malformations (e.g oesophageal atresia)
- Nervous system malformations (such as spina bifida)

In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 4% to 5% in solid organ transplant patients treated with immunosuppressants other than mycophenolate.

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a report rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Studies in animals have shown reproductive toxicity.

Breast-feeding
Mofecon is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications).

Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk.

DRUG INTERACTIONS
The following interactions have been reported between MPA and other medicinal products:

Aciclovir and ganciclovir
The potential for myelosuppression in patients receiving both mycophenolic acid and aciclovir or ganciclovir has not been studied. Increased levels of mycophenolic acid glucuronide (MPAG) and aciclovir/ganciclovir may be expected when aciclovir/ganciclovir and mycophenolic acid are administered concomitantly, possibly as a result of competition for the tubular secretion pathway.

The changes in MPAG pharmacokinetics are unlikely to be of clinical significance in patients with adequate renal function. In the presence of renal impairment, the potential exists for increases in plasma MPAG and aciclovir/ganciclovir concentrations; dose recommendations for aciclovir/ganciclovir should be followed and patients carefully observed.

Gastroprotective agents
Magnesium and aluminium containing antacids:
Chronic, daily use of magnesium-aluminium containing antacids with Mofecon is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.

Cholestyramine and drugs that bind bile acids:
Caution should be used when co-administering drugs or therapies that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to decrease MPA exposure and thus reduce the efficacy of Mofecon.

Ciclosporin:
When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with Mofecon, ciclosporin may decrease the concentration of MPA. In case of interruption or discontinuation of ciclosporin, Mofecon dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus
When co-administered with tacrolimus, tacrolimus may increase concentration of Mycophenolic Acid. Clinicians should note this increase both in MPA AUC and variability, and adjustments to Mofecon dosing should be dictated by the clinical situation. Close clinical monitoring should be performed when a switch from one calcineurin inhibitor to another is planned.

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

SIDE EFFECTS/ ADVERSE EFFECTS
General disorders and administration site conditions: (uncommon) de novo purine synthesis inhibitors-associated acute inflammatory syndrome.

General disorder and administration site conditions
De novo purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain, and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

Side effects
Tell your doctor or pharmacist if you notice any of the following: fever, joint pain and muscle pain.

Post-Marketing experience
Congenital Disorders: Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy).

Pregnancy, Pueperium and Perinatal Conditions: Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy).

OVERDOSE
There have been reports of intentional or accidental overdoses with mycophenolic acid, whereas not all patients experienced related adverse events.

In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class, mainly blood dyscrasias and sepsis.

Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the very high plasma protein binding of MPA, 97%. By interfering with enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.

RECOMMENDED DOSE
Dosage
The recommended dose is 720 mg (two 360 mg Mofecon gastro-resistant tablets) twice daily (1440 mg daily dose). In patients receiving 2 g mycophenolate mofetil (MMF), treatment can be replaced by 720 mg twice daily (1440mg daily dose) of Mofecon.

General target population
Treatment with Mofecon should be initiated and maintained by appropriately qualified transplant specialists.

Mofecon should be initiated in *de-novo* patients within 48 hours following transplantation.

Mofecon can be taken with or without food.

Special population
Renal impairment
No dose adjustments are needed in patients experiencing delayed post-operative renal graft function (see section Pharmacokinetics). Patients with severe chronic renal impairment (glomerular filtration rate <25 ml . min^{-1} . 1.73 m^{-2}) should be carefully monitored.

Hepatic impairment
No dose adjustments are needed for renal transplant patients with severe hepatic impairment.

Paediatric patients (below 18 years)
Safety and efficacy in paediatric patients have not been established. Limited pharmacokinetic data are available for paediatric renal transplant patients.

Geriatic patients (65 years of age or above)
No dose adjustment is required in this patient population.

Treatment during rejection episodes
Renal transplant rejection does not affect mycophenolic acid pharmacokinetics; dosage reduction or interruption of Mofecon is not required.

Method of administration
Mofecon tablets should not be crushed in order to maintain the integrity of the enteric coating (see section Instruction for Use).

INSTRUCTIONS FOR USE
Mofecon tablets should not be crushed in order to remain the integrity of the enteric coating (see section Dosage and Administration).

Mycophenolate sodium has demonstrated teratogenic effects (see section Pregnancy and Lactation). If for any reasons the Mofecon tablets is crushed, avoid inhalation or direct contact with skin or mucous membrane of the powder.

Storage : Store below 30°C.
Protect from light and moisture.

Presentation/ Packing : Blister pack of 6x10's.

Product Registration Holder (Malaysia) / Product Owner /
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