Oral contraceptives: The pharmacokinetics of oral contraceptives were unaffected by co-administration of **Revograf**.
Trimethoprimlsulphamethxazole: No effect on the bioavailability of MPA was observed.

Tacrolimus:
In renal transplant patients: For patients on tacrolimus, the dose of **Revograf** should not exceed 1g twice a day. Patients should be carefully observed and managed appropriately.

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

OVERDOSAGE
MPA cannot be removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/ml), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestrymine, can remove MPA by increasing excretion of the drug.

Special Remarks
For oral use only. Keep out of the reach and sight of children.
Store below 30°C in a dry place, protect from light.
Do not crush tablet. Store in the original package.
Revograf tablets should be handled with care.
Dosage: As directed by the physician.
To be dispensed on the prescription of a registered medical practitioner only.

Stability
This medicine should not be used after expiry date (EXP) shown on the pack.
See also outer pack for storage remarks.

Presentation
Tablets 500 mg 10's, 20's, 50's Pack
Capsules 250 mg 10's, Pack

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
ریوگراف گولی کو احتیاط سے استعمال کریں۔ گولی کو ہرگز نہ توڑیں۔
بچوں کی پہنچ سے دور رکھیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔
خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone, Bin Qasim,
Karachi-75020, Pakistan.

Art No. 480/2

REVOGRAF

(Mycophenolate Mofetil)

250 mg Capsule / 500 mg Tablets

ریوگراف

(مائیکوفینولیٹ موفیٹل)

۲۵۰ ملی گرام کیپسول / ۵۰۰ ملی گرام گولیاں

Composition:

Each film coated tablet contains:	Each capsule contains:
Mycophenolate Mofetil (USP) ... 500mg	Mycophenolate Mofetil (USP) ... 250mg
Product Complies USP Specifications.	Product Complies USP Specifications.

Properties and Effects
Mycophenolate mofetil is the 2 – morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine mono-phosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. MPA has more potent cytostatic effects on lymphocytes than on other cells. **Revograf** is highly effective in the prophylaxis of organ rejection and the treatment of refractory organ rejection in patients receiving allogeneic renal transplants and in the prophylaxis of organ rejection in patients receiving allogeneic cardiac or hepatic transplants.

PHARMACOKINETICS
Absorption
Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94%. Mycophenolate mofetil after oral administration is below the limit of quantitation (0.4 µg/ml).

Distribution
Secondary increases in plasma MPA concentrations are approximately at 6-12 hours post-dose, consistent with enterohepatic recirculation. A reduction of approximately 40% in the AUC of MPA is associated with co-administration of cholestyramine (4 g t.i.d.), consistent with interruption of enterohepatic recirculation. At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

Metabolism
MPA is conjugated primarily with glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. In vivo, MPAG is converted to free MPA via enterohepatic recirculation.

Elimination
Oral administration of radiolabelled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the dose recovered in the urine and 6% recovered in the feces. Most (about 87%) of a dose is excreted in the urine as MPAG. A negligible amount of drug (<1% of dose) is excreted as MPA in the urine.

INDICATIONS
Revograf tablets are indicated for the prophylaxis of acute organ rejection and for the treatment of refractory organ rejection in patients receiving allogeneic renal transplants. **Revograf** tablets are indicated for the prophylaxis of acute organ rejection and increased graft and patient survival in patients receiving allogeneic cardiac transplants.

Revograf is indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

Revograf should be used concomitantly with cyclosporin and corticosteroids.

DOSAGE AND ADMINISTRATION
Standard dosage for prophylaxis of renal rejection
A dose of 1 g administered twice a day (daily dose of 2 g) is recommended for use in renal transplant patients.

Standard dosage for prophylaxis of cardiac rejection
A dose of 1.5 g administered twice a day (daily dose of 3 g) is recommended for use in cardiac transplant patients.

Standard dosage for prophylaxis of hepatic rejection
A dose of 1.5 g orally twice a day (daily dose of 3 g) is recommended for use in hepatic transplant patients.

Standard dosage for treatment of refractory renal rejection
A dose of 1.5 g administered twice a day (daily dose of 3 g) is recommended for management of refractory rejection.

Oral administration
The initial dose of **Revograf** should be given as soon as possible following renal, cardiac or hepatic transplantation.

Special dosage instructions
Patients with neutropenia
If neutropenia develops (absolute neutrophil count <1.3x10^3/µl), dosing with Revograf should be interrupted or the dose reduced.

Patients with severe renal impairment
In renal transplant patients with severe chronic renal impairment (glomerular filtration rate <25 ml/min/1.73m^2), outside of the immediate post-transplant period or after treatment of acute or refractory rejection, doses greater than 1g administered twice a day should be avoided.

Patients with delayed renal graft function post transplant
No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively.

Patients with severe hepatic impairment
No dose adjustments are needed for renal patients with severe hepatic parenchymal disease.

Elderly (>65 years)
The recommended oral doses of 1 g b.i.d. for renal transplant patients and 1.5 g b.i.d. for cardiac or hepatic transplant patients are appropriate for elderly patients.

CONTRAINDICATIONS
Allergic reactions to **Revograf** have been observed. Therefore, **Revograf** is contraindicated in patients with hypersensitivity to mycophenolate mofetil or mycophenolic acid.

WARNINGS AND PRECAUTIONS
As in all patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving **Revograf** as part of an immunosuppressive regimen 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 immunosuppressive rather than to the use of any specific agent.

As with all patients at an increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Patients receiving **Revograf** should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

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

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

Because **Revograf** has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, **Revograf** should be administered with caution in patients with active digestive system disease.
Because **Revograf** is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, on theoretical grounds it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

It is recommended that **Revograf** should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of **Revograf** with drugs that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of **Revograf**.
Administration of doses greater than 1 g b.i.d. to renal patients with severe chronic renal impairment should be avoided.
No dose adjustment is recommended for post-transplant patients with delayed renal graft function, but patients should be carefully monitored.

Elderly patients may be at an increased risk of adverse events compared with younger individuals.

Laboratory monitoring
Patients on **Revograf** should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving **Revograf** should be monitored for neutropenia. The development of neutropenia may be related to **Revograf**, concomitant medications, viral infection or some combination of these causes. If neutropenia develops (absolute neutrophil count <1.3x10^3/µl), dosing with **Revograf** should be interrupted or the dose reduced and the patient should be carefully observed.

PREGNANCY, NURSING MOTHERS
Revograf should be avoided in pregnant women unless the potential benefit outweighs the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/ml within 1 week prior to beginning therapy. It is recommended that **Revograf** therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning **Revograf** therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

UNDESIRABLE EFFECTS
The adverse event profile associated with the use of immunosuppressive drugs is often difficult to establish owing to the presence of underlying diseases and the concurrent use of many other medications.

The principal adverse reaction associated with the administration of **Revograf** in the prevention of renal, cardiac and hepatic transplant rejection in combination with cyclosporin and corticosteroids include diarrhea, leukopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infection, e.g. opportunistic infections.

Malignancies
As in patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving **Revograf** as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.

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 **Revograf** (2 g or 3 g daily) with other immunosuppressants are candida mucocutaneous, CMV viremia/syndrome and Herpes simplex.

Elderly patients (>65 years), particularly those who are receiving **Revograf** as part of a combination immunosuppressive regimen, may be at greater risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals.

INTERACTIONS
Acyclovir: Higher MPAG and acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir than when the drugs were administered alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrugs, e.g. valacyclovir, to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids with magnesium and aluminum hydroxides: Absorption of mycophenolate mofetil was decreased when the drug was administered with antacids.

Cyclosporin A: Cyclosporin A pharmacokinetic were unaffected by mycophenolate mofetil.

Ganciclovir: Co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increase 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 mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administrated, patients should be monitored carefully.