



WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES, AND SERIOUS INFECTIONS

- **Use during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. Females of reproductive potential must be counseled regarding pregnancy prevention and planning (see Warnings and Precautions, Use in Specific Populations).**
- **Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression (see Warnings and Precautions).**
- **Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections (see Warnings and Precautions).**
- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Mycophenolic Acid. Patients receiving Mycophenolic acid should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient (see Warnings and Precautions).**

1. NAME OF THE MEDICINAL PRODUCT

Novofortic 180mg Enteric Coated Tablets

Novofortic 360mg Enteric Coated Tablets

2.QUALITATIVE AND QUANTITATIVE COMPOSITION:

Novofortic 180mg Enteric Coated Tablets: Each delayed release tablet contains Mycophenolic Acid (as Mycophenolate Sodium).....180mg

Novofortic 360mg Enteric Coated Tablets: Each delayed release tablet contains Mycophenolic Acid (as Mycophenolate Sodium).....360mg

3. PHARMACEUTICAL FORM

Enteric coated tablets

Novofortic Tablet 180mg: Lime green colour, bevel edge round shaped enteric coated tablet plain on both sides.

Novofortic Tablet 360mg: Pale orange-red color, ovaloid shaped enteric coated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Indications and Usage

Prophylaxis of Organ Rejection in Kidney Transplant

Mycophenolic acid is indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Mycophenolic acid is indicated for the prophylaxis of organ rejection in pediatric patients 5 years of age and older who are at least 6 months post kidney transplant. Mycophenolic acid is to be used in combination with cyclosporine and corticosteroids.

4.2 Limitations of Use

Mycophenolic Acid delayed-release tablets and mycophenolate mofetil (MMF) tablets and capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent.

4.3 Dosage and Administration

Dosage in Adult Kidney Transplant Patients

The recommended dose of Mycophenolic Acid is 720 mg administered twice daily (1440 mg total daily dose).

Dosage in Pediatric Kidney Transplant Patients

The recommended dose of Mycophenolic Acid in conversion (at least 6 months post-transplant) pediatric patients age 5 years and older is 400 mg/m² body surface area (BSA) administered twice daily (up to a maximum dose of 720 mg administered twice daily).

Administration

Mycophenolic Acid tablets should be taken on an empty stomach, 1 hour before or 2 hours after food intake. Mycophenolic Acid tablets should not be crushed, chewed, or cut prior to ingesting. The tablets should be swallowed whole in order to maintain the integrity of the enteric coating. Pediatric patients with a BSA of 1.19 to 1.58 m² may be dosed either with three Mycophenolic Acid 180 mg tablets, or one 180 mg tablet plus one 360 mg tablet twice daily (1080 mg daily dose). Patients with a BSA of >1.58 m² may be dosed either with four Mycophenolic Acid 180 mg tablets, or two Mycophenolic Acid 360 mg tablets twice daily (1440 mg daily dose). Pediatric doses for patients with BSA <1.19 m² cannot be accurately administered using currently available formulations of Mycophenolic Acid tablets.

5 CONTRAINDICATIONS

5.1 Hypersensitivity Reactions

Mycophenolic Acid is contraindicated in patients with a hypersensitivity to mycophenolic acid, mycophenolate mofetil, or to any of its excipients. Reactions like rash, pruritus, hypotension, and chest pain have been observed in clinical trials and post marketing reports.

6 WARNINGS AND PRECAUTIONS

6.1 Embryofetal Toxicity

Use of Mycophenolic Acid during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.

6.2 Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning. For recommended pregnancy testing and contraception methods.

6.3 Management of Immunosuppression

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Mycophenolic Acid. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physicians responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [see Boxed Warning].

6.4 Lymphoma and Other Malignancies

Patients receiving immunosuppressants, including Mycophenolic Acid, are at increased risk of developing lymphomas and other malignancies, particularly of the skin [see Adverse Reactions]. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Post-transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children.

6.5 Serious Infections

Patients receiving immunosuppressants, including Mycophenolic Acid, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, and new or reactivated viral infections including opportunistic infections. These infections may lead to serious, including fatal outcomes. Because of the danger of over suppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

6.6 New or Reactivated Viral Infections

Reduction in immunosuppression should be considered for patients who develop evidence of new or reactivated viral infections. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft. Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

6.7 Blood Dyscrasias Including Pure Red Cell Aplasia

Patients receiving Mycophenolic Acid should be monitored for blood dyscrasias (e.g., neutropenia or anemia). The development of neutropenia may be related to Mycophenolic Acid itself, concomitant medications, viral infections, or some combination of these reactions. Complete blood count should be performed weekly during the first month, twice monthly for the second and the third month of treatment, then monthly through the first year. If blood dyscrasias occur dosing with Mycophenolic Acid should be interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly.

6.8 Serious GI Tract Complications

Gastrointestinal bleeding (requiring hospitalization), intestinal perforations, gastric ulcers, and duodenal ulcers have been reported in patients treated with Mycophenolic Acid. It should be administered with caution in patients with active serious digestive system disease.

6.9 Rare Hereditary Deficiencies

Mycophenolic should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease including renal failure.

7. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Embryofetal Toxicity
- Lymphomas and Other Malignancies
- Serious Infections
- New or Reactivated Viral Infections
- Blood Dyscrasias Including Pure Red Cell Aplasia
- Serious GI Tract Complications
- Rare Hereditary Deficiencies

7.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described below derived from two randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in de novo and converted stable kidney transplant patients.

Table 1: Adverse Reactions (%) Reported in ≥10% of de novo Kidney Transplant Patients in Either Treatment Group

System Organ Class Adverse drug reactions	Mycophenolic Acid 1.44 grams per day (n = 213)(%)	Mycophenolate Mofetil (MMF) 2 grams per day (n = 210) (%)
Blood and Lymphatic System Disorders		
Anemia	22	22
Leukopenia	19	21
Gastrointestinal System Disorders		
Constipation	38	40
Nausea	29	27
Diarrhea	24	25
Vomiting	23	20
Dyspepsia	23	19
Abdominal pain upper	14	14
Flatulence	10	13
General and Administrative Site Disorders		
Edema	17	18
Edema lower limb	16	17
Pyrexia	13	19
Investigations		
Increased blood creatinine	15	10
Infections and Infestations		
Urinary tract infection	29	33
CMV infection	20	18
Metabolism and Nutrition Disorders		
Hypocalcemia	11	15
Hyperuricemia	13	13
Hyperlipidemia	12	10
Hypokalemia	13	09
Hypophosphatemia	11	09
Musculoskeletal, Connective Tissue and Bone Disorders		
Back pain	12	06
Arthralgia	07	00

Nervous System Disorder		
Insomnia	24	24
Tremor	12	14
Headache	13	11
Vascular Disorders		
Hypertension	18	18

The trial was not designed to support comparative claims for Mycophenolic Acid for the adverse reactions reported in this table.

Table 2: Viral and Fungal Infections (%) Reported Over 0 to 12 Months

<i>de novo</i> Renal Trial		
	Mycophenolic Acid 1.44 grams per day (n = 213) (%)	Mycophenolate Mofetil 2 grams per day (n = 213) (%)
Any Cytomegalovirus	22	21
- Cytomegalovirus Disease	05	04
Herpes Simplex	08	06
Herpes Zoster	05	04
Any Fungal Infection	11	12
- Candida NOS	06	06
- Candida albicans	02	04

Table 3: Adverse Reactions Reported in <10% of Patients Treated with Mycophenolic Acid in Combination with Cyclosporine and Corticosteroid.

Eye Disorder	Vision blurred
Gastrointestinal Disorders	Abdominal pain, abdominal distension, gastroesophageal reflux disease, gingival hyperplasia
General Disorders and Administration Site Conditions	Fatigue, peripheral edema
Infections and Infestations	Nasopharyngitis, herpes simplex, upper respiratory infection, oral candidiasis, herpes zoster, sinusitis, influenza, wound infection, implant infection, pneumonia, sepsis
Investigations	Hemoglobin decrease, liver function tests abnormal
Metabolism and Nutrition Disorders	Hypercholesterolemia, hyperkalemia, hypomagnesemia, diabetes mellitus, hyperglycemia
Musculoskeletal and Connective Tissue Disorders	Arthralgia, pain in limb, peripheral swelling, muscle cramps, myalgia
Nervous System Disorders	Dizziness (excluding vertigo)
Psychiatric Disorders	Anxiety
Renal and Urinary Disorders	Renal tubular necrosis, renal impairment, hematuria, urinary retention
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, dyspnea exertional
Skin and Subcutaneous Tissue Disorders	Acne, pruritus, rash
Vascular Disorders	Hypertension aggravated, hypotension
Cardiac Disorder	Tachycardia
Blood and Lymphatic Disorders	Lymphocele, thrombocytopenia

The following additional adverse reactions have been associated with the exposure to mycophenolic acid (MPA) when administered as a sodium salt or as mofetil ester:

Gastrointestinal:

Intestinal perforation, gastrointestinal hemorrhage, gastric ulcers, duodenal ulcers, colitis (including CMV colitis), pancreatitis, esophagitis, and ileus.

Infections:

Serious life-threatening infections such as meningitis and infectious endocarditis, tuberculosis, and atypical mycobacterial infection.

Respiratory:

Interstitial lung disorders, including fatal pulmonary fibrosis.

8 DRUG INTERACTIONS

8.1 Antacids with Magnesium and Aluminum Hydroxides

Concomitant use of Mycophenolic Acid and antacids decreased plasma concentrations of mycophenolic acid (MPA). It is recommended that Mycophenolic Acid and antacids not be administered simultaneously.

8.2 Azathioprine

Given that azathioprine and MMF inhibit purine metabolism, it is recommended that Mycophenolic Acid not be administered concomitantly with azathioprine or MMF.

8.3 Cholestyramine, Bile Acid Sequestrates, Oral Activated Charcoal and Other Drugs that Interfere with Enterohepatic Recirculation

Drugs that interrupt enterohepatic recirculation may decrease MPA plasma concentrations when co administered with MMF.

Therefore, do not administer Mycophenolic Acid with cholestyramine or other agents that may interfere with enterohepatic recirculation or drugs that may bind bile acids, e.g., bile acid sequestrates or oral activated charcoal, because of the potential to reduce the efficacy of Mycophenolic Acid.

8.4 Sevelamer

Concomitant administration of sevelamer and MMF may decrease MPA plasma concentrations. Sevelamer and other calcium free phosphate binders should not be administered simultaneously with Mycophenolic Acid.

8.5 Cyclosporine

Cyclosporine inhibits the enterohepatic recirculation of MPA, and therefore, MPA plasma concentrations may be decreased when Mycophenolic Acid is co-administered with cyclosporine. Clinicians should be aware that there is also a potential change of MPA plasma concentrations after switching from cyclosporine to other immunosuppressive drugs or from other immunosuppressive drugs to cyclosporine in patients concomitantly receiving Mycophenolic Acid.

8.6 Norfloxacin and Metronidazole

MPA plasma concentrations may be decreased when MMF is administered with norfloxacin and metronidazole. Therefore, Mycophenolic Acid is not recommended to be given with the combination of norfloxacin and metronidazole. Although there will be no effect on MPA plasma concentrations when Mycophenolic Acid is concomitantly administered with norfloxacin or metronidazole when given separately.

8.7 Rifampin

The concomitant administration of MMF and rifampin may decrease MPA plasma concentrations. Therefore, Mycophenolic Acid is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

8.8 Hormonal Contraceptives

Although Mycophenolic Acid may not have any influence on the ovulation-suppressing action of oral contraceptives, it is recommended to co-administer Mycophenolic Acid with hormonal contraceptives (e.g., birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution, and additional barrier contraceptive methods must be used.

8.9 Acyclovir (Valacyclovir), Ganciclovir (Valganciclovir), and Other Drugs that Undergo Renal Tubular Secretion

Acyclovir/valacyclovir/ganciclovir/ valganciclovir may be taken with Mycophenolic Acid; however, during the period of treatment, physicians should monitor blood cell counts.

8.10 Ciprofloxacin, Amoxicillin plus Clavulanic Acid and Other Drugs that Alter the Gastrointestinal Flora

No dose adjustment of Mycophenolic Acid is needed when co-administered with these drugs

8.11 Pantoprazole

Administration of a pantoprazole at a dose of 40 mg twice daily for 4 days to healthy volunteers did not alter the pharmacokinetics of a single dose of Mycophenolic Acid.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Use of Mycophenolic Acid during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. Risks and benefits of Mycophenolic Acid should be discussed with the patient. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

9.2 Contraception

Patients must use acceptable birth control during entire Mycophenolic Acid therapy, and for 6 weeks after stopping it. Females of reproductive potential taking Mycophenolic Acid must receive contraceptive counseling.

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity.

9.3 Nursing Mothers

It is not known whether MPA is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Mycophenolic Acid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

9.4 Pediatric Use

The safety and effectiveness of Mycophenolic Acid have been established in pediatric kidney transplant patients 5 to 16 years of age who were initiated on Mycophenolic Acid at least 6 months post-transplant. Pediatric doses for patients with BSA <1.19 m² cannot be accurately administered using currently available formulations of Mycophenolic Acid tablets. The safety and effectiveness of Mycophenolic Acid in de novo pediatric kidney transplant patients and in pediatric kidney transplant patients below the age of 5 years have not been established.

9.5 Geriatric Use

Clinical studies of Mycophenolic Acid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

An overdose of Mycophenolic Acid could possibly result in over suppression of the immune system and may increase the susceptibility to infection including opportunistic infections, fatal infections and sepsis. If blood dyscrasias occur (e.g., neutropenia with absolute neutrophil count <1.5 x 10³/mcl. or anemia), it may be appropriate to interrupt or discontinue Mycophenolic Acid. Possible signs and symptoms of acute overdose could include the following: hematological abnormalities such as leukopenia and neutropenia, and gastrointestinal symptoms such as abdominal pain, diarrhea, nausea and vomiting, and dyspepsia.

10.1 Treatment and Management

General supportive measures and symptomatic treatment should be followed in all cases of overdose. Although dialysis may be used to remove the inactive metabolite mycophenolic acid glucuronide (MPAG), it would not be expected to remove clinically significant amounts of the active moiety, mycophenolic acid, due to the 98% plasma protein binding of mycophenolic acid. By interfering with enterohepatic circulation of mycophenolic acid, activated charcoal or bile sequestrates, such as cholestyramine, may reduce the systemic mycophenolic acid exposure. Mycophenolic Acid delayed-release tablets are an enteric formulation of mycophenolate sodium that delivers the active moiety mycophenolic acid (MPA). Mycophenolic Acid is an immunosuppressive agent. As the sodium salt, MPA is chemically designated as (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt.

11 PHARMACOLOGICAL PROPERTIES

11.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents–Selective immunosuppressants, ATC Code: L04AA06.

11.2 Clinical Pharmacology

Mycophenolic acid (MPA), an immunosuppressant, is an uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation to DNA. 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 cytostatic effects on lymphocytes.

11.3 Pharmacokinetics

Mycophenolic Acid exhibits linear and dose-proportional pharmacokinetics over the dose-range (360 to 2160 mg) evaluated. The absolute bioavailability of Mycophenolic Acid in stable renal transplant patients on cyclosporine was 72%. MPA is highly protein bound (>98% bound to albumin). The predominant metabolite of MPA is the phenolic glucuronide (MPAG) which is pharmacologically inactive. A minor metabolite AcMPAG which is an acyl glucuronide of MPAG is also formed and has pharmacological activity comparable to MPA. MPAG undergoes renal elimination. A fraction of MPAG also undergoes biliary excretion, followed by deconjugation by gut flora and subsequent reabsorption as MPA. The mean elimination half-lives of MPA and MPAG ranged between 8 and 16 hours, and 13 and 17 hours, respectively.

Absorption

Following Mycophenolic Acid oral administration without food in several pharmacokinetic studies conducted in renal transplant patients, consistent with its enteric-coated formulation, the median delay (Tlag) in the rise of MPA concentration ranged between 0.25 and 1.25 hours and the median time to maximum concentration (Tmax) of MPA ranged between 1.5 and 2.75 hours. Mycophenolic Acid pharmacokinetics is dose proportional over the dose range of 360 to 2160 mg.

Distribution

MPA is highly protein bound to albumin, >98%. The protein binding of mycophenolic acid glucuronide (MPAG) is 82%. The free MPA concentration may increase under conditions of decreased protein binding (uremia, hepatic failure, and hypoalbuminemia).

Metabolism

MPA is metabolized principally by glucuronyl transferase to glucuronidated metabolites. The AUC ratio of MPA:MPAG:acyl glucuronide is approximately 1:24:0.28 at steady state. The mean clearance of MPA was 140 (± 30) mL/min.

Elimination

The majority of MPA dose administered is eliminated in the urine primarily as MPAG (>60%) and approximately 3% as unchanged MPA following Mycophenolic Acid administration to stable renal transplant patients. The mean renal clearance of MPAG was 15.5 (± 5.9) mL/min. MPAG is also secreted in the bile and available for deconjugation by gut flora. MPA resulting from the deconjugation may then be reabsorbed and produce a second peak of MPA approximately 6 to 8 hours after Mycophenolic Acid dosing. The mean elimination half-life of MPA and MPAG ranged between 8 and 16 hours, and 13 and 17 hours, respectively.

Food Effect

Compared to the fasting state, administration of Mycophenolic Acid 720 mg with a high-fat meal (55 g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA. To avoid the variability in MPA absorption between doses, Mycophenolic Acid should be taken on an empty stomach.

12. PHARMACEUTICALS PARTICULARS

Pack Size

For 180mg & 360mg tablets:

12 x 10's (120) tablets

Alu/Alu blisters having 10 tablets in each blister and packed in unit carton with leaflet.

Storage Conditions

Store below 30°C, Protect from sunlight and moisture.

Dosage and Instructions

As directed by Physician.

Keep out of reach of children.

خوراک : ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایت : دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

For adverse event reporting, kindly email us at pharmacovigilance@oncogenpharma.com.pk

13. MANUFACTURER

Manufactured by:

oncogen

Oncogen Pharma (Pvt.) Limited.

Plot No: WH-26 & 27-A3, Korangi Creek

Industrial Park (KCIP), Karachi 75190, Pakistan.

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