# Package Insert

## ACCOCEPT 180 & 360
## (Mycophenolic Acid Gastro Resistant Tablets 180 mg and 360 mg)

**Name and strength of active ingredient**

**Accocept 180**
Mycophenolate Sodium Ph. Eur. 192.350 mg equivalent to Mycophenolic Acid 180 mg

**Accocept 360**
Mycophenolate Sodium Ph. Eur. 384.700 mg equivalent to Mycophenolic Acid 360 mg

**Product Description**

**Accocept 180**
Lime Green colored, round shaped, biconvex bevelled edged enteric-coated tablets imprinted with M1 on one side with black ink and plain on the other side.

**Accocept 360**
Peach colored, oblong shaped, biconvex, enteric-coated tablets imprinted with M2 on one side with black ink and plain on the other side.

**Pharmacological Properties**

**Pharmacodynamic Properties**

**Mechanism of action:**

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.

**Pharmacokinetic Properties**

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. Approximately 10% of all morning pharmacokinetic profiles showed a delayed $T_{max}$, sometimes up to several hours, without any expected impact on 24 hour/daily MPA exposure.
In stable renal transplant patients on ciclosporin based immunosuppression, the gastrointestinal absorption of MPA was 93% and the absolute bioavailability was 72%. Mycophenolic acid

gastro-resistant tablets pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2,160 mg.
The effect of food on Mycophenolic acid gastro-resistant tablets may lead to an absorption overlap from one dose interval to another. However, this effect was not shown to be clinically significant.

Distribution
The volume of distribution at steady state for MPA is 50 liters. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound (97% and 82%, respectively). 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. In stable renal transplant patients on ciclosporin based immunosuppression, approximately 28% of the oral mycophenolic acid dose is converted to MPAG by presystemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 16 hours, and its clearance is 0.45 l/h.

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 de-conjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed.

Approximately 6-8 hours after mycophenolic acid gastro-resistant tablets dosing a second peak of MPA concentration can be measured, consistent with re-absorption of the de-conjugated MPA. There is large variability in the MPA trough levels inherent to MPA preparations, and high morning trough levels ($C_0$ > 10 μg/ml) have been observed in approximately 2% of patients treated with mycophenolic acid gastro-resistant tablets. However, across studies, the AUC at steady state (0-12h) which is indicative of the overall exposure showed a lower variability than the one corresponding to $C_{trough}$.

Pharmacokinetics in renal transplant patients on ciclosporin based immunosuppression
In the early post-transplant period, mean MPA AUC and mean MPA Cmax were approximately one-half of the values measured six months post-transplant.

Renal impairment

MPA pharmacokinetics appeared to be unchanged over the range of normal to absent renal function. In contrast, MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8 fold higher in the setting of anuria. Clearance of either MPA or MPAG was unaffected by haemodialysis. Free MPA may also significantly increase in the setting of

renal failure. This may be due to decreased plasma protein binding of MPA in the presence of high blood urea concentration.

Hepatic impairment
Hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease in people with alcoholic cirrhosis. 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.

Paediatric population and adolescents

Limited data are available on the use of Mycophenolic acid gastro-resistant tablets in children and adolescents.

Gender

There are no clinically significant gender differences in mycophenolic acid gastro-resistant tablets pharmacokinetics.

Older people

Pharmacokinetics in the elderly has not formally been studied. MPA exposure does not appear to vary to a clinically significant degree by age.

**Therapeutic indications**

Mycophenolic Acid Gastro-Resistant Tablets is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

**Posology and method of administration**

The recommended dose is 720 mg (four 180 mg or two 360 mg tablets) administered twice daily (1,440 mg daily dose). In patients receiving Mycophenolate mofetil (MMF) 2 g, treatment can be replaced by 720 mg administered twice daily (1,440 mg daily dose) of Accocept tablets.

General target population

Treatment with Accocept should be initiated and maintained by appropriately qualified transplant specialists. Accocept should be initiated in de-novo patients within 48 hours following transplantation.

Accocept can be taken with or without food.

Special populations

Renal impairment
No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. Patients with severe chronic renal impairment (glomerular filtration rate < 25 mL • $min^{-1}$ • 1.73 $m^{-2}$) should be carefully followed up.
Hepatic impairment
No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease.

Pediatric patients
Safety and efficacy in pediatric patients have not been established. Limited pharmacokinetic data are available for pediatric renal transplant patients.

Geriatric patients
No dose adjustment is required in this patient population.

Treatment during rejection episodes
Renal transplant rejection does not lead to changes in Mycophenolic acid; dosage reduction or interruption of Accocept is not required.

Method of administration

Accocept tablets can be taken with or without food. Accocept tablets should not be crushed in order to remain the integrity of the enteric coating.

**Route of Administration**

Oral use

**Contraindications**

Accocept Tablets should not be used in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients.
Accocept Tablets is contraindicated during pregnancy due to its mutagenic and teratogenic potential. (see Use in Special Populations: Pregnancy)
Accocept Tablets is contraindicated in women of childbearing potential not using highly effective contraceptive methods. (see Use in Special Populations: Pregnancy)
Accocept Tablets is contraindicated in women who are breastfeeding (see Use in Special Populations: breastfeeding)

**Special Warnings & Precautions**

Patients receiving immunosuppressive regimens involving combinations of drugs, including Mycophenolic Acid Gastro-Resistant Tablets, 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 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 Mycophenolic Acid Gastro-Resistant Tablets should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.
Immunosuppressed patients are at increased 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.
Another opportunistic infection is JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and as mentioned may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Mycophenolic Acid Gastro-Resistant Tablets in combination with other immunosuppressant. In some of these cases, switching Mycophenolic Acid Gastro-Resistant Tablets to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on Mycophenolic Acid Gastro-Resistant Tablets who develop recurrent infections should have their serum immunoglobulin measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been reports of bronchiectasis in patients who received Mycophenolic Acid Gastro-Resistant Tablets in combination with other immunosuppressants. In some of these cases, switching Mycophenolic Acid Gastro-Resistant Tablets to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have been also isolated reports of interstitial lung disease and pulmonary fibrosis, some of which are fatal. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated for any evidence of underlying interstitial lung disease.
Reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including the mycophenolic acid (MPA) derivatives Mycophenolic Acid Gastro-Resistant Tablets and mycophenolate mofetil (MMF). Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Cases of Pure Red Cell Aplasia (PRCA) have been reported in patients treated with MPA derivatives (which include mycophenolate mofetil and mycophenolate sodium) in combination with other immunosuppressants. The mechanism for MPA derivatives induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of therapy. Changes to Mycophenolic Acid Gastro-Resistant Tablets therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection.

Patients receiving Mycophenolic Acid Gastro-Resistant Tablets should be monitored for blood disorders (e.g. neutropenia or anemia), which may be related to MPA itself, concomitant

medications, viral infections, or some combination of these causes. Patients taking Mycophenolic Acid Gastro-Resistant Tablets should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If blood disorders occur (e.g. neutropenia with (absolute neutrophil count $<1.5 \times 10^3/\mu l$ or anemia) it may be appropriate to interrupt or discontinue Mycophenolic Acid Gastro-Resistant Tablets.
Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of live attenuated vaccines should be avoided.
Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.
Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration and haemorrhage and perforation, Mycophenolic Acid Gastro-Resistant Tablets should be administered with caution in patients with active serious digestive system disease.
It is recommended that Mycophenolic Acid Gastro-Resistant Tablets not be administered concomitantly with azathioprine because concomitant administration of these drugs has not been evaluated.
Mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.
Mycophenolic Acid Gastro-Resistant Tablets has been administered in combination with corticosteroids and ciclosporin.
There is limited experience with its concomitant use with induction therapies such as anti-T-lymphocyte globulin or basiliximab. The efficacy and safety of the use of Mycophenolic Acid Gastro-Resistant Tablets with other immunosuppressive agents (for example, tacrolimus) have not been studied.
The concomitant administration of Mycophenolic Acid Gastro-Resistant Tablets and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub-therapeutic systemic MPA exposure and reduced efficacy.
Mycophenolic Acid Gastro-Resistant Tablets is an IMPDH (Inosine Monophosphate Dehydrogenase) inhibitor. Therefore, it should be avoided in patients with rare hereditary deficiency of Hypoxanthine-Guanine Phosphoribosyl-Transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
Mycophenolic Acid Gastro-Resistant Tablets therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolic Acid Gastro-Resistant Tablets therapy, during therapy and for six weeks following therapy discontinuation.

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45-49%) and congenital malformations (estimated rate of 23-27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore Mycophenolic Acid Gastro-Resistant Tablets is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female and male patients of reproductive potential should be made aware of the risks and follow the recommendations provided in section Fertility, pregnancy and lactation. (e.g. contraceptive methods, pregnancy testing) prior to, during, and

after therapy with Mycophenolic Acid Gastro-Resistant Tablets. Physicians should ensure that women and men taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception

Because of the genotoxic and teratogenic potential of Mycophenolic Acid Gastro-Resistant Tablets, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Mycophenolic Acid Gastro-Resistant Tablets therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception.

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.

**Interaction with other medicinal products and other forms of interaction**

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 gastro-resistant tablets 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 gastro-resistant tablets 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.

Gastro protective agents

Magnesium and aluminium containing antacids:
MPA AUC and $C_{max}$ have been shown to decrease by approximately 37% and 25%, respectively, when a single dose of magnesium-aluminium containing antacids is given concomitantly with mycophenolic acid gastro-resistant tablets. Magnesium aluminium-containing antacids may be used intermittently for the treatment of occasional dyspepsia. However the chronic, daily use of magnesium-aluminium containing antacids with mycophenolic acid gastro-resistant tablets is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.

Proton pump inhibitors:
In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of mycophenolic acid gastro-resistant tablets and pantoprazole given at 40 mg twice daily during the four previous days. No data are available with other proton pump inhibitors given at high doses.

Oral contraceptives

Interaction studies between MMF and oral contraceptives indicate no interaction. Given the metabolic profile of MPA, no interactions would be expected for Mycophenolic Acid Gastro-Resistant Tablets and oral contraceptives.

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 mycophenolic acid gastro-resistant tablets.

Ciclosporin

When studied in stable renal transplant patients, ciclosporin pharmacokinetics were unaffected by steady state dosing of mycophenolic acid gastro-resistant tablets. When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with mycophenolic acid gastro-resistant tablets, ciclosporin may decrease the concentration of MPA as well (by approximately 20%, extrapolated from mycophenolate mofetil data), but the exact extent of this decrease is unknown because such an interaction has not been studied. However, as efficacy studies were conducted in combination with ciclosporin, this interaction does not modify the recommended posology of mycophenolic acid gastro-resistant tablets. In case of interruption or discontinuation of ciclosporin, mycophenolic acid gastro-resistant tablets dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus

Clinicians should note the increase both in MPA AUC and variability, and adjustments to mycophenolic acid gastro-resistant tablets 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.

**Fertility, Pregnancy and Lactation**

Pregnancy

Accocept tablets is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods (see Contraindications).

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 counseled regarding pregnancy prevention, and planning.

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

Due to the mutagenic and teratogenic potential of mycophenolate, **women of child bearing potential should use two reliable forms of contraception** simultaneously, including at least one 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 recommended 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 risks associated with the transfer of seminal fluid also apply to men who have had a 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 Accocept.

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. coloboma, 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 2% of live births in the overall population and 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 in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Studies in animals have shown reproductive toxicity.

Breastfeeding

Accocept 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.

Fertility

No specific studies with Accocept in humans have been conducted to evaluate effects on fertility.

**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 mechanism of action and pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

**Undesirable effects**

Malignancies

Patients receiving immunosuppressive regimens involving combinations of drugs, including MPA, 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 *de novo* renal transplant patients receiving mycophenolic acid gastro-resistant tablets with other immunosuppressants in controlled clinical trials of renal transplant patients followed for 1 year were cytomegalovirus (CMV), candidiasis and herpes simplex.

Older people

Elderly patients may generally be at increased risk of adverse drug reactions due to immunosuppression.

Other adverse drug reactions

The table below contains adverse drug reactions possibly or probably related to mycophenolic acid gastro-resistant tablets compiled according to MedDRA system organ class.

Adverse reactions are listed according to the following categories:
Very common, Common, Uncommon, Rare, Very rare

| | |
|---|---|
| **Infections and infestations** | |
| Very common | Viral, bacterial and fungal infections |
| Common | Upper respiratory tract infections, pneumonia |
| Uncommon | Wound infection, sepsis, osteomyelitis |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | |
| Uncommon | Skin papilloma, basal cell carcinoma, Kaposi´s sarcoma, lymphoproliferative disorder, squamous cell carcinoma |
| **Blood and lymphatic system disorders** | |
| Very common | Leukopenia |
| Common: | Anaemia, thrombocytopenia |
| Uncommon: | Lymphopenia, neutropenia, lymphadenopathy |
| **Metabolism and nutrition disorders** | |
| Very common | Hypocalcemia, hypokalemia, hyperuricemia |
| Common: | Hyperkalemia, hypomagnesemia |
| Uncommon: | Anorexia, hyperlipidaemia, diabetes mellitus, hypercholesterolaemia, hypophosphataemia |
| **Psychiatric disorders** | |
| Very common | Anxiety |
| Uncommon | Abnormal dreams, delusional perception, insomnia |
| **Nervous system disorders** | |
| Common | Dizziness, headache |
| Uncommon: | Tremor |
| **Eye disorders** | |
| Uncommon: | Conjunctivitis, vision blurred |
| **Cardiac disorders** | |
| Uncommon: | Tachycardia, ventricular extrasystoles |
| **Vascular disorders:** | |
| Very common | Hypertension |
| Common: | Hypotension |

| | |
|---|---|
| Uncommon | Lymphocele |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common | Cough, dyspnoea |
| Uncommon: | Interstitial lung disease, Pulmonary congestion, wheezing, pulmonary oedema |
| **Gastrointestinal disorders** | |
| Very common | Diarrhoea |
| Common: | Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, nausea, vomiting |
| Uncommon: | Abdominal tenderness, gastrointestinal haemorrhage, eructation, halitosis, ileus, lip ulceration, oesophagitis, subileus, tongue discolouration, dry mouth, gastro-oesophageal reflux disease, gingival hyperplasia, pancreatitis, parotid duct obstruction, peptic ulcer, peritonitis |
| **Hepato-biliary disorders** | |
| Common | Liver function tests abnormal |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Acne, pruritus |
| Uncommon: | Alopecia |
| **Musculoskeletal and connective tissue disorders** | |
| Very common | Arthralgia |
| Common: | Myalgia |
| Uncommon: | Arthritis, back pain, muscle cramps |
| **Renal and urinary disorders** | |
| Common | Blood creatinine increased |
| Uncommon: | Haematuria, renal tubular necrosis, urethral stricture |
| **Reproductive system and breast disorders** | |
| Uncommon | Impotence |
| **General disorders and administration site conditions** | |
| Common | Asthenia, Fatigue, oedema peripheral, pyrexia |
| Uncommon | Influenza like illness, oedema lower limb, pain, rigors, thirst, weakness |
| **Injury, poisoning and procedural complications** | |
| Uncommon: | Contusion |

The following additional adverse reactions are attributed to MPA derivatives as a class effect:

Infections and infestations:
Serious, life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in

patients treated with immunosuppressants, including Mycophenolic Acid Gastro-Resistant Tablets

Blood and lymphatic system disorders:
Neutropenia, pancytopenia. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives

Immune system disorders:
Hypogammaglobulinaemia in the patients receiving Mycophenolic Acid Gastro-Resistant Tablets in combination with other immunosuppressants

Respiratory, thoracic and mediastinal disorders:
Interstitial lung disease in patients receiving Mycophenolic Acid Gastro-Resistant Tablets in combination with other immunosuppressant

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, in patients receiving MPA derivatives. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive Mycophenolic Acid Gastro-Resistant Tablets.

Gastrointestinal disorders:
Colitis, CMV gastritis, intestinal perforation, gastric ulcers, duodenal ulcers

**Post-marketing experience:**

Pregnancy, puerperium and perinatal conditions:
Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported. (see use in pregnancy)

Congenital disorders:
Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. (see use in pregnancy)

**Overdose**

There have been reports of intentional or accidental overdoses with mycophenolic acid gastro-resistant tablets, 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, 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.

**Ingredients**

Tablet core
Microcrystalline Cellulose PH 101
Croscarmellose Sodium
Povidone K-30
Talc
Colloidal Anhydrous Silica
Magnesium Stearate

Coating 180 mg
ACRYL-EZE Green 93O510003

Coating 360 mg
ACRYL-EZE Pink 93O54222

Imprinting:
Opacode Black S-1-17823
Isopropanol

**Storage Conditions**

Do not store above 30 °C. Store in the original package in order to protect from moisture.

**Instructions for Use**

Treatment with Accocept should be initiated and maintained by appropriately qualified transplant specialists. In order to retain the integrity of the enteric coating, Accocept tablets should not be crushed. Where crushing of Accocept tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. This is due to the teratogenic effects of mycophenolate.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Dosage forms and packaging available**

Alu-Alu blister ((ALU/PVC/OPA-ALU)) pack as immediate container closure system and the blister is further packed in secondary pack (carton). The lidding material is aluminium foil (hard tempered) with HSL coating on bright side and forming material is cold formable, Alu-Alu triple laminated foil (ALU/PVC/OPA-ALU). Accocept 180 mg and 360 mg Tablets are packed in Alu-

Alu blister (ALU/PVC/OPA-ALU) pack of 10 Tablets. Each printed carton contains 5 such blisters.

**Name and address of manufacturer**

**INTAS PHARMACEUTICALS LIMITED**
Plot No. 457 & 458, Village Matoda, Bavla Road
And Plot No. 191/218P, Village: Chacharwadi,
Tal- Sanand, Dist: Ahmedabad, Gujarat 382210 INDIA

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