For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

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Mycophenolic Acid Delayed-Release Tablets USP 180 mg/360 mg

RENODAPT-S® 180/360 रिनोडेप्ट - एस १८० / ३६०

COMPOSITION
RENODAPT-S® 180
Each Delayed-Release tablet contains:
Mycophenolate Sodium USP
Equivalent to Mycophenolic Acid 180 mg
Colour: Titanium Dioxide IP

RENODAPT-S® 360
Each Delayed-Release tablet contains:
Mycophenolate Sodium USP
Equivalent to Mycophenolic Acid 360 mg
Colours: Tartrazine yellow, Yellow oxide of Iron and Titanium Dioxide IP

PHARMACEUTICAL FORM
Delayed-Release Tablets

ATC Code: L04AA06

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Immunosuppressant

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 to 2 hours. Approximately 10% of all morning pharmacokinetic profiles showed a delayed T_{max}, sometimes up to several hours, without any expected impact on the 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%. The pharmacokinetics of MPA is dose proportional and linear over the dose range of 180 to 2,160 mg which has been studied.
Compared to the fasting state, administration of a single dose of MPA 720 mg with a high fat meal (55 g fat, 1,000 calories) had no effect on the systemic exposure of MPA (area under the concentration time curve, AUC), which is the most relevant pharmacokinetic parameter linked to efficacy. However there was a 33% decrease in the maximal concentration of MPA (C_{max}). Moreover, T_{up} and T_{max} were on average 3 to 5 hours delayed, with several patients having a T_{max} of more than 15 hours.
The effect of food on MPA may lead to an absorption overlap from 1 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 litres. 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 (uremia, hepatic failure, hypoalbuminemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Elimination
The half life of MPA is approximately ranges between 8 and 16 hours and the clearance is 8.6 L/h.

Metabolism
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 pharmacological activity. In stable renal transplant patients on ciclosporin based immunosuppression, approximately 28% of the oral MPA 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.

Excretion
Although negligible amounts of MPA are present in urine (<1.0%), the majority of MPA is eliminated in 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. 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 MPA. 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
The mean pharmacokinetic parameters for MPA following the administration of MPA are shown in the table below. In the early post transplant period, mean MPA AUC and mean MPA C_{max} were approximately one-half of the values measured six months post transplant.

Mean (SD) Pharmacokinetic Parameters for MPA Following Oral Administration to Renal Transplant Patients on Ciclosporin-Based Immunosuppression

Adult chronic, multiple dosing 720 mg BID **(Study ERLB 301)** n=48	Dose	T_{max}* (h)	C_{max} (g/m L)	AUC 0-12 (g ×h/mL)
14 days post-transplant	720 mg	2	13.9 (8.6)	29.1 (10.4)
3 months post-transplant	720 mg	2	24.6 (13.2)	50.7 (17.3)
6 months post-transplant	720 mg	2	23.0 (10.1)	55.7 (14.6)
Adult chronic, multiple dosing 720 mg BID	**Dose**	T_{max}* (h)	C_{max} (µg/mL)	AUC 0-12 (g ×h/mL)
18 months post-transplant **(Study ERLB 302)** n=18	720 mg	1.5	18.9 (7.9)	57.4 (15.0)
Paediatric 450 mg/m² single dose **(Study ERL 0106)** n=16	**Dose**	T_{max}* (h)	C_{max}(g/m L)	AUC o-∞ (g ×h/mL)
	450 mg/m²	2.5	31.9 (18.2)	74.5 (28.3)

*Median values
AUC: area under the concentration-time curve; BID: twice daily (*bis in die*); C_{max}: maximum concentration, T_{max}: time to maximum concentration.

Renal Impairment
The pharmacokinetics of MPA 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 hemodialysis. Free MPA may also significantly increase in renal failure. This may be due to decreased plasma protein binding of MPA in the presence of high blood urea concentration.

Hepatic Impairment
In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. 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.

Children and Adolescents
Limited data are available on the use of MPA in children and adolescents. In the table above the mean (standard deviation, SD) pharmacokinetics of MPA are shown for stable pediatric renal transplant patients (aged 5-16 years) on ciclosporin based immunosuppression. Mean MPA AUC at a dose of 450 mg/m² was similar to that measured in adults receiving 720 mg MPA. The mean apparent clearance of MPA was approximately 6.7 L/h/m².

Gender
There are no clinically significant gender differences in MPA pharmacokinetics.

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

PRECLINICAL SAFETY DATA
The hematopoetic and lymphoid system were the primary organs affected in repeated dose toxicity studies conducted with mycophenolate sodium in rats and mice. These effects occurred at systemic exposure levels which are equivalent to or less than the clinical exposure at the recommended dose of 1.44 g/day of MPA in renal transplant patients.
Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses.
The non-clinical toxicity profile of mycophenolic acid (as sodium salt) appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population.
Three genotoxicity assays (*in vitro* mouse lymphoma assay, micronucleus test in V79 Chinese hamster cells and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolic acid to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.
Mycophenolic acid (as sodium salt) was not tumorigenic in rats and mice. The highest dose tested in the animal carcinogenicity studies resulted in approximately 0.6-5 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 1.44 g/day.
Mycophenolic acid (as sodium salt) had no effect on fertility of male or female rats up to dose levels at which general toxicity and embryotoxicity were observed.
In a teratology study performed with mycophenolic acid (as sodium salt) in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day of MPA.
In a pre- and postnatal development study in rat, mycophenolic acid (as sodium salt) caused (developmental delays abnormal pupillary reflex in females and preputial separation in males) at the highest dose of 3 mg/kg that also induced malformations.
Mycophenolic acid (as sodium salt) showed a phototoxic potential in an *in vitro* 3T3 NRU phototoxicity assay.

CLINICAL PARTICULARS
Therapeutic Indications
RENODAPT-S® 180 / RENODAPT-S® 360 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
Treatment with RENODAPT-S® 180 / RENODAPT-S® 360 should be initiated and maintained by appropriately qualified transplant specialists.
The recommended dose is 720 mg administered twice daily (1,440 mg total daily dose) on an empty stomach, one hour before or two hours after food intake. This dose of mycophenolate sodium corresponds to 1 g mycophenolate mofetil administered twice daily (2 g daily dose) in terms of mycophenolic acid (MPA) content.
For additional information about the corresponding therapeutic doses of mycophenolate sodium and mycophenolate mofetil, see sections Special Warnings and Precautions for Use and Pharmacokinetic Properties.
In *de novo* patients, RENODAPT-S® 180 / RENODAPT-S® 360 should be initiated within 72 hours following transplantation.
RENODAPT-S® 180 / RENODAPT-S® 360 can be taken with or without food. Patients may select either option but must adhere to their selected option.
In order to retain the integrity of the enteric coating, RENODAPT-S® 180 / RENODAPT-S® 360 tablets should not be crushed, chewed or cut prior to ingestion and hence should be swallowed whole.
Where crushing of RENODAPT-S® 180 / RENODAPT-S® 360 tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane.

Children and Adolescents
Insufficient data are available to support the efficacy and safety of RENODAPT-S® 180 / RENODAPT-S® 360 in children and adolescents. Limited pharmacokinetic data are available for paediatric renal transplant patients.

Elderly
The maximum recommended dose in elderly patients is 720 mg administered twice daily.

Patients with Renal Impairment
In patients experiencing delayed renal graft function post operatively, no dose adjustments are needed (see section Pharmacokinetic Properties).
Patients with severe renal impairment (glomerular filtration rate <25 ml min $^{-1}$.73 m $^{-2}$) should be carefully monitored and the daily dose of RENODAPT-S® 180 / RENODAPT-S® 360 should not exceed 1,440 mg.

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

Treatment During Rejection Episodes
Renal transplant rejection does not lead to changes in pharmacokinetics of mycophenolic acid (MPA); dosage modification or interruption of RENODAPT-S® 180 / RENODAPT-S® 360 is not required.

Contraindications
Hypersensitivity to mycophenolate sodium, mycophenolic acid, or mycophenolate mofetil or to any of the excipients (see section List of Excipients).
RENODAPT-S® 180 / RENODAPT-S® 360 is contraindicated in women who are breastfeeding (see section Pregnancy and Lactation).
For information on use in pregnancy and lactation and contraceptive requirements, see section Pregnancy and Lactation.

Special Warnings and Precautions for Use
Patients receiving immunosuppressive regimens involving combinations of drugs, including mycophenolic acid, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section Undesirable Effects). 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 minimise 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 RENODAPT-S® 180 / RENODAPT-S® 360 should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.
Patients treated with immunosuppressants, including mycophenolic acid, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section Undesirable Effects). Among the opportunistic infections are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and 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.
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 derivative induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of therapy. Changes to RENODAPT-S® 180 / RENODAPT-S® 360 therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section Undesirable Effects).
Patients receiving mycophenolic acid 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 RENODAPT-S® 180 / RENODAPT-S® 360 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 × 10^3/µL or anemia) it may be appropriate to interrupt or discontinue RENODAPT-S® 180 / RENODAPT-S® 360.
Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section Drug Interactions).
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, RENODAPT-S® 180 / RENODAPT-S® 360 should be administered with caution in patients with active serious digestive system disease.

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Mycophenolic Acid Delayed-Release Tablets USP 180 mg/360 mg

RENODAPT-S® 180/360 रिनोडेप्ट - एस १८० / ३६०

It is recommended that RENODAPT-S® 180 / RENODAPT-S® 360 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 has been administered in combination with corticosteroids and ciclosporin.
There is limited experience with its concomitant use with induction therapies such as anti lymphocyte globulin or basiliximab. The efficacy and safety of the use of mycophenolic acid with other immunosuppressive agents (for example, tacrolimus) have not been studied.
RENODAPT-S® 180 / RENODAPT-S® 360 contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
The concomitant administration of MPA and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub therapeutic systemic MPA exposure and reduced efficacy.
MPA 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.
RENODAPT-S® 180 / RENODAPT-S® 360 therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning RENODAPT-S® 180 / RENODAPT-S® 360 therapy, during therapy and for 6 weeks following therapy discontinuation (see section Pregnancy and Lactation).

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 MPA 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 MPA 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-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 MPA. 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 MPA 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 MPA 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 MPA 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 MPA.

Ciclosporin
When studied in stable renal transplant patients, ciclosporin pharmacokinetics were unaffected by steady state dosing of MPA. When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with MPA, 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 MPA. In case of interruption or discontinuation of ciclosporin, MPA dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus
In a calcineurin cross-over study in stable renal transplant patients, steady state pharmacokinetics of MPA were measured during both Neoral and tacrolimus treatment. Mean MPA AUC was 19% higher (90% confidence interval, CI: -3, +47), whereas mean MPAG AUC was about 30% lower (90% CI: 16, 42) on tacrolimus compared to Neoral treatment. In addition, MPA AUC intra subject variability was doubled when switching from Neoral to tacrolimus. Clinicians should note this increase both in MPA AUC and variability, and adjustments to MPA 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.

Pregnancy and Lactation
Pregnancy
RENODAPT-S® 180 / RENODAPT-S® 360 therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning RENODAPT-S® 180 / RENODAPT-S® 360 therapy, during RENODAPT-S® 180 / RENODAPT-S® 360 therapy and for six weeks after discontinuing therapy. Patients should be instructed to consult their physician immediately should pregnancy occur.
The use of RENODAPT-S® 180 / RENODAPT-S® 360 is not recommended during pregnancy and should be reserved for cases where no alternative treatment is available.
There is limited data from the use of MPA in pregnant women. However, congenital malformations including ear malformations i.e. abnormally formed or absent external/middle ear, have been reported in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. Cases of spontaneous abortions have been reported in patients exposed to mycophenolic acid compounds. Studies in animals have shown reproductive toxicity (see section Preclinical Safety Data).

Lactation
MPA is excreted in milk in lactating rats. It is unknown whether MPA is excreted in human breast milk. Because of the potential for serious adverse reactions to MPA in breast fed infants, MPA is contra indicated in women who are breast-feeding (see section Contraindications).

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
The following undesirable effects cover adverse drug reactions from clinical trials:

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 (see section Special Warnings and Precautions for Use). Lymphoproliferative disease or lymphoma developed in 2 *de novo* (0.9%) patients and in 2 maintenance patients (1.3%) receiving MPA for up to 1 year. Non-melanoma skin carcinomas occurred in 0.9% of *de novo* and 1.8% of maintenance patients receiving MPA for up to 1 year; other types of malignancy occurred in 0.5% of *de novo* and 0.6% of maintenance patients.

Opportunistic Infections
All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section Special Warnings and Precautions for Use). The most common opportunistic infections in *de novo* renal transplant patients receiving MPA with other immunosuppressants in controlled clinical trials of renal transplant patients followed for 1 year were cytomegalovirus (CMV), candidiasis and herpes simplex. CMV infection (serology, viremia or disease) was reported in 21.6% of *de novo* and in 1.9% of maintenance renal transplant patients.

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

Other Adverse Drug Reactions
Adverse drug reactions are listed below which is possibly or probably related to MPA reported in the controlled clinical trials in renal transplant patients, in which MPA was administered together with ciclosporin microemulsion and corticosteroids at a dose of 1,440 mg/day for 12 months. It is compiled according to MedDRA system organ class.
Adverse reactions are listed according to the following categories:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Cardiac Disorders
Uncommon: Tachycardia, pulmonary edema, ventricular extrasystoles.
Blood and Lymphatic System Disorders
Very common : Leukopenia
Common : Anemia, thrombocytopenia
Uncommon : Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy*
Nervous System Disorders
Common : Headache
Uncommon : Tremor, insomnia*
Eye Disorders
Uncommon : Conjunctivitis*, vision blurred*
Respiratory, Thoracic and Mediastinal Disorders
Common : Cough
Uncommon : Pulmonary congestion*, wheezing*
Gastrointestinal Disorders
Very common : Diarrhea
Common : Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, loose stools, nausea, vomiting
Uncommon : Abdominal tenderness, gastrointestinal hemorrhage, eructation, halitosis*, ileus*, lip ulceration*, esophagitis*, subileus*, tongue discolouration*, dry mouth*, gastro esophageal reflux disease*, gingival hyperplasia*, pancreatitis, parotid duct obstruction*, peptic ulcer*, peritonitis*
Renal and Urinary Disorders
Common : Increased blood creatinine
Uncommon : Hematuria*, renal tubular necrosis*, urethral complications
Skin and Subcutaneous Tissue Disorders
Uncommon : Alopecia, contusion*
Musculoskeletal and Connective Tissue Disorders
Uncommon : Arthritis*, back pain*, muscle cramps
Metabolism and Nutrition Disorders
Uncommon : Anorexia, hyperlipidemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphatemia
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*
General Disorders and Administration Site Conditions
Common : Fatigue, pyrexia
Uncommon : Influenza like illness, edema lower limb*, pain, rigors*, thirst*, weakness*
Hepato-biliary Disorders
Common : Hepatic function tests abnormal
Reproductive System and Breast Disorders
Uncommon : Impotence*
Psychiatric Disorders
Uncommon : Abnormal dreams*, delusional perception*
* Event reported in a single patient (out of 372) only.
Note: renal transplant patients were treated with 1,440 mg MPA daily up to 1 year. A similar profile was seen in the *de novo* and maintenance transplant population although the incidence tended to be lower in the maintenance patients. Rash has been identified as an adverse drug reaction from post marketing experience.

The following additional adverse reactions are attributed to MPA derivatives as a class effect:
Gastrointestinal Disorders:
Colitis, CMV gastritis, intestinal perforation, gastric ulcers, duodenal ulcers.
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 MPA (see section Special Warnings and Precautions for Use).
Blood and Lymphatic System Disorders:
Neutropenia, pancytopenia.
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives (see section Special Warnings and Precautions for Use).
Isolated cases of abnormal neutrophil morphology, including acquired Pelger Huet anomaly, have been observed in patients treated with MPA derivatives. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that received MPA.

Overdose
No case of overdose has been reported. 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 mainly 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.

PHARMACEUTICAL PARTICULARS :
Incompatibilities.
Not applicable

Shelf Life : Please refer carton/blister.

Storage and Precautions :
Storage: Store at 25°C, excursion permitted between 15°C and 30°C. Protect from moisture.
Keep out of reach of children.

Special Precautions for Disposal and Other Handling
Where crushing of Renodapt-S® 180/ Renodapt-S® 360 tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane
Any unused product or waste material should be disposed off in accordance with local requirements.

Nature and Contents of Container :
RENODAPT - S® 180
3 x10 Tablets, 10 tablets are packed in an Alu/Alu blister and 3 such blisters are packed in a printed carton along with pack insert.

RENODAPT - S® 360
5 x10 Tablets, 10 tablets are packed in an Alu/Alu blister and 5 such blisters are packed in a printed carton along with pack insert.

Marketed by: **Biocon Biologics India Limited**
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

® - Registered trademark

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at "**drugsafety@biocon.com**".