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Mycophenolic Acid Tablets

RENODAPT™ S - 540 रिनोडेप्ट एस – ५४०

Composition:
Each enteric coated tablet contains
Mycophenolic Acid 540 mg
(as sodium salt)

Warning:
Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should use Renodapt S (mycophenolic acid). Patients receiving Renodapt S 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.

Female users of childbearing potential must use contraception. Use of Renodapt S during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

Description
Renodapt S (Mycophenolic acid) is an enteric formulation of Mycophenolate sodium that delivers the active moiety mycophenolic acid(MPA). Renodapt S is an immunosuppressant agent.

Enteric coated Mycophenolate sodium has the chemical formula $C_{17}H_{19}NaO_6$ and is a sodium 4(E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,2-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate with a molecular weight of 342.32.

Clinical Pharmacolgy
Mechanism of Action
The active compound of Enteric Coated Mycophenolate sodium is MPA, a noncompetitive reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in *de novo* purine synthesis. Its inhibiting properties block lymphocyte proliferation in the S-phase. There are two isoforms of IMPDH: IMPDH type I is mainly located in non-proliferating in lymphocytes, and nearly 5-fold more sensitive to inhibition by MPA than type I. Other cell types that use the IMPDH-independent salvage pathway are not considerably affected by MPA.
The depletion of guanosine nucleotides by MPA influences DNA synthesis and also glycosylation of adhesion molecules. Thereby, MPA blocks proliferation and clonal expansion in T and B lymphocytes, inhibits antibody production and prevents the generation of cytotoxic T cells.

Pharmacokinetics
MPA is almost completely absorbed (93%), and had an absolute bioavailability of 72% when mycophenolate sodium delayed release was administered in combination with cyclosporine micro emulsion in stable renal transplant patients. The pharmacokinetics of a single oral dose of mycophenolate sodium delayed release was dose proportional and linear over 180-2160mg in stable renal transplant patients. Mean systemic MPA exposure (area under the time curve; AUC) was similar with mycophenolate sodium delayed release 720mg and Mycophenolate sodium 1000mg after a single dose and with twice-daily administration at steady state in stable renal transplant patients. Respective mean maximal plasma MPA concentrations (Cmax) were also similar after a single dose and with twice-daily administration at steady state.

Consistent with the release of MPA from the enteric-coated formulation in the intestine rather than the stomach, the median time to MPA Cmax was longer with mycophenolate sodium delayed release than with Mycophenolate sodium after a single dose (2.0 vs 0.8 hours) or with twice daily administration at steady state (2.3 vs 0.9 hours; $p < 0.01$) in stable renal transplant recipients. Coadministration of mycophenolate sodium delayed release 720mg with a high fat meal had no effect on systemic exposure to MPA, but reduced Cmax by 33% and delayed tmax by 5 hours. MPA is highly protein bound (>98%). Its mean volume of distribution at steady state is 54L and at elimination phase is 112L. MPA is primarily metabolised in the liver by glucuronyl transferase to an inactive metabolite, mycophenolic acid glucuronide (MPAG), the major urinary excretion product. Urinary excretion of MPA is negligible (≈3%). MPAG is also excreted in the bile, but glucuronidases from gut bacteria convert it back to MPA, which is reabsorbed and recirculated. The mean elimination half-life of MPA is 8-16 hours, with a mean renal clearance of 140 mL/min in stable renal transplant patients. Respective values for MPAG were 13-17 hours and 15.5 mL/min.

Indications
Renodapt S delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic organ transplants, administered in combination with other immunosuppressants.

Contraindications
Renoadapt S is contraindicated in patients with a hypersensitivity to Mycophenolate sodium, mycophenolic acid or any component of the drug product.

Warnings
Patients receiving immunosuppressive regimens including Mycophenolate sodium, 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 usual for patients with 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. Over suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. It is recommended that Mycophenolate sodium 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 Mycophenolate sodium therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil (MMF). Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in Renodapt S and the active form of the drug. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune functions.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (MMF) in combination with other immunosuppressive agents. MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Renodapt S and the active form of the drug. The mechanism for MMF induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen are also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Renodapt S therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection.

Severe neutropenia developed in up to 2.0% of renal patients receiving Mycophenolate sodium 3 g daily. Patients receiving Mycophenolate sodium should be monitored for neutropenia. The development of neutropenia may be related to Mycophenolate sodium itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops , dosing with Mycophenolate sodium should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately. Neutropenia has been observed most frequently in the period from 31 to 180 days posttransplant in patients treated for prevention of renal, cardiac, and hepatic rejection. Patients receiving Mycophenolate sodium should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Precautions
General
Mycophenolate sodium should be administered with caution in

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patients with active serious digestive system disease. On theoretical grounds, because Mycophenolate sodium is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Laboratory Tests
Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 104-week oral carcinogenicity study in mice, mycophenolate sodium in daily doses up to 180 mg/kg was not tumorigenic. The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium was genotoxic in the mouse lymphoma/thymidine kinase assay and the in vivo mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay.

Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients when corrected for BSA.

Pregnancy –Category D
Use of Renodapt S 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. 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. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus.

Nursing Mothers
It is not known whether this drug 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 Mycophenolate sodium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use
Reported clinical experience has not identified differences in responses between the elderly and younger patients.

Drug drug interactions
It is recommended that Mycophenolate sodium not be administered concomitantly with azathioprine or other immunosuppressant because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically. Antivirals like acyclovir/ Ganciclovir compete for tubular secretion, further increasing the concentrations of both drugs. In view of potential to reduce the efficacy of Mycophenolate sodium drugs that interfere with enterohepatic recirculation like cholestyramine/ colestipol, caution should be used in the concomitant administration of these drugs with Mycophenolate sodium. During treatment with Mycophenolate sodium, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Antacids, or iron salts (eg, ferrous sulfate) because they may decrease Mycophenolate sodium effectiveness. Oral contraceptives because their effectiveness may be decreased by Mycophenolate sodium.

Side Effects
All medicines may cause side effects, but many people have no, or minor, side effects The principal adverse reactions associated with the administration of Mycophenolate sodium include diarrhoea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection.

Most Frequent:
Abdominal pain with cramps, anemia, chest pain, constipation, cough, diarrhoea, dyspepsia, dyspnea, general weakness, headache,, hematuria, hypertension, infection, leukopenia, nausea, neutropenia, peripheral edema, vomiting.

Less Frequent:
Acne vulgaris, arthralgia, colitis, conduction disorder of the heart, dizziness, drowsiness, fever, gastrointestinal hemorrhage, gingival hyperplasia, insomnia, pharyngitis, skin rash, upper respiratory infection.

Rare:
Acute gingivitis, acute pancreatitis, bacterial septicemia, myalgia, oral candidiasis, stomatitis, thrombocytopenic disorder, tremors.

Overdosage
The experience with overdose of Mycophenolate sodium in humans is very limited. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhoea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations , small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine.

Dosage and administration
Renal Transplantation
Adults
The recommended dose of Mycophenolate sodium is 720 mg administered twice daily (1440 mg total daily dose) on an empty stomach, one hour before or two hours after food intake.

Note:Mycophenolate sodium delayed-release tablets and Mycophenolate mofetil tablets or capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent. Patients are to be instructed that Mycophenolate sodium 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:
Based on a pharmacokinetic study conducted in stable renal pediatric transplant patients, the recommended dose of Mycophenolate sodium in stable pediatric patients is 400 mg/m^2 body surface area (BSA) administered twice daily (up to a maximum dose of 720 mg administered twice daily). Patients with a BSA of 1.19 to 1.58 m^2 may be dosed either with three Mycophenolate sodium 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 m^2 may be dosed either with four Mycophenolate sodium 180 mg tablets or two Mycophenolate sodium 360 mg tablets twice daily (1440 mg daily dose). Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of Mycophenolate sodium tablets.

Geriatrics:
The maximum recommended dose is 720 mg administered twice daily.

Storage
Store in a cool, dry place.

Presentation
Alu-Alu blister pack of 10 tablets

For further details, please contact:
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