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Rapamune

(Sirolimus) - Wyeth

BOXED WARNING

Increased susceptibility to infection and possible development of lymphoma and other malignancies may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use sirolimus. Use not recommended in liver or lung transplant patients. Excess mortality and graft loss in combination with tacrolimus reported in liver transplant patients. Increased hepatic artery thrombosis with cyclosporine or tacrolimus in liver transplant patients. Cases of bronchial anastomotic dehiscence, most fatal, reported in lung transplant patients.

THERAPEUTIC CLASS

Macrocyclic lactone immunosuppressant

DEA CLASS

RX

INDICATIONS

Prophylaxis of organ rejection in patients ≥13 yrs receiving renal transplants.

ADULT DOSAGE

Adults: Give initial dose as soon as possible after transplantation. Give 4 hrs after cyclosporine. Maintain on a dose for at least 7-14 days before further dose adjustment. Refer to full PI for maintenance dose adjustments. Max: 40mg/day. If estimated dose is >40mg/day due to addition of LD, LD should be administered over 2 days. Monitor trough concentration at least 3-4 days after LD(s). Low-Moderate Immunologic Risk: Initial: Give with cyclosporine and corticosteroids. Give LD equivalent to 3X the maint dose. Progressively d/c cyclosporine over 4-8 weeks at 2-4 months following transplantation. Adjust dose to maintain blood trough concentration within target range. High-Immunologic Risk: Give with cyclosporine and corticosteroids for the first 12 months. LD: Up to 15mg on Day 1 post-transplantation. Maint: 5mg/day beginning on Day 2. Obtain trough level between Days 5 and 7 and adjust daily dose thereafter. Mild or Moderate Hepatic Impairment: Reduce maintenance dose by 1/3. Severe Hepatic Impairment: Reduce maintenance by 1/2. Low Body Weight (<40kg): Adjust initial dose based on BSA to 1mg/m^2/day with a LD of 3mg/m^2. Elderly: Start at lower end of dosing range.

PEDIATRIC DOSAGE

Pediatrics: ≥13 Yrs: Give initial dose as soon as possible after transplantation. Give 4 hrs after cyclosporine. Maintain on a dose for at least 7-14 days before further dose adjustment. Refer to full PI for maintenance dose adjustments. Max: 40mg/day. If estimated dose is >40mg/day due to addition of LD, LD should be administered over 2 days. Monitor trough concentration at least 3-4 days after LD(s). Low-Moderate Immunologic Risk: Initial: Give with cyclosporine and corticosteroids. Give LD equivalent to 3X the maint dose. Progressively d/c cyclosporine over 4-8 weeks at 2-4 months following transplantation. Adjust dose to maintain blood trough concentration within target range. Mild or Moderate Hepatic Impairment: Reduce maintenance dose by 1/3. Severe Hepatic Impairment: Reduce maintenance by 1/2. Low Body Weight (<40kg): Adjust initial dose based on BSA to 1mg/m^2/day with a LD of 3mg/m^2.

HOW SUPPLIED

Sol: 1mg/mL [60mL]; Tab: 0.5mg, 1mg, 2mg

WARNINGS/PRECAUTIONS

Safety and efficacy of use in combination with cyclosporine and corticosteroids has not been studied beyond one year. Hypersensitivity reactions reported. Associated with the development of angioedema. Impaired wound healing, lymphocele, wound dehiscence, and fluid accumulation (eg, peripheral edema, lymphedema, pleural effusion, ascites, pericardial effusions) reported. May increase serum cholesterol and TG that may require treatment. May delay recovery of renal function in patients with delayed graft function. Proteinuria commonly observed. Increased risk for opportunistic infections, including activation of latent viral infections (eg, BK virus-associated nephropathy). Progressive multifocal leukoencephalopathy (PML) reported. Consider reduction in immunosuppression if BK virus nephropathy is suspected or if PML develops. Interstitial lung disease (eg, pneumonitis, bronchiolitis obliterans organizing pneumonia, pulmonary fibrosis) reported. Safety and efficacy of de novo use without cyclosporine is not established in renal transplant patients. Provide 1 yr prophylaxis for *Pneumocystis carinii* pneumonia and 3 months for cytomegalovirus after transplant. Patient sample concentration values from different assays may not be interchangeable. Increased risk of skin cancer; limit exposure to sunlight and UV light. Caution in elderly.

ADVERSE REACTIONS

Infection, lymphoma, malignancy, graft loss, peripheral edema, hypertriglyceridemia, HTN, constipation, hypercholesterolemia, increased creatinine, abdominal pain, diarrhea, headache.

DRUG INTERACTIONS

See Boxed Warning. CYP3A4 and P-glycoprotein (P-gp) inducers may decrease concentrations. CYP3A4 and P-gp inhibitors may increase concentrations. Avoid with strong inhibitors (eg, ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, clarithromycin) and strong inducers (eg, rifampin, rifabutin) of CYP3A4 and P-gp. May increase levels with cyclosporine, bromocriptine, cimetidine, cisapride, clotrimazole,

danazol, diltiazem, fluconazole, protease inhibitors (eg, HIV and hepatitis C that include drugs such as ritonavir, indinavir, bocepravir, telaprevir) metoclopramide, nicardipine, troleandomycin, and verapamil. May decrease levels with carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's wort. May increase verapamil concentration. Vaccines may be less effective; avoid live vaccines. Increases risk of angioedema with ACE inhibitors. Increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiography with calcineurin inhibitor. Do not dilute or take with grapefruit juice. Caution with other nephrotoxic drugs (eg, aminoglycosides, amphotericin B). Monitor for possible development of rhabdomyolysis with HMG-CoA inhibitors and/or fibrates.

PREGNANCY

Category C, not for use in nursing.

MECHANISM OF ACTION

Immunosuppressant; inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism distinct from that of other immunosuppressants. Also inhibits antibody production.

PHARMACOKINETICS

Absorption: (Sol) AUC=194ng•hr/mL, C_{max}=14.4ng/mL, T_{max}=2.1 hrs. (Tab) AUC=230ng•hr/mL, C_{max}=15ng/mL, T_{max}=3.5 hrs. Different pharmacokinetic data resulted from concentration-controlled trials of pediatric renal transplants. **Distribution:** V_d=12L/kg; plasma protein binding (92%). **Metabolism:** Intestinal wall and liver (extensive) via O-demethylation and/or hydroxylation; hydroxy, demethyl, and hydroxydemethyl (major metabolites). **Elimination:** Feces (91%), urine (2.2%); $T_{1/2}$=62 hrs.

ASSESSMENT

Assess for drug hypersensitivity, immunologic risk, hepatic impairment, body weight/body mass index, hyperlipidemia, infections, pregnancy/nursing status, and possible drug interactions.

MONITORING

Monitor for infections including opportunistic infections and activation of latent infections, development of PML, lymphoma/lymphoproliferative disease, other malignancies particularly of the skin, signs and symptoms of graft loss, hypersensitivity reactions, interstitial lung disease, and hyperlipidemia. Monitor trough concentrations, especially in patients with altered drug metabolism, who weigh <40kg, and with hepatic impairment, and when a change is made during concurrent administration of strong CYP3A4 inducers or inhibitors. Monitor urinary protein excretion, renal/hepatic functions, cholesterol, TG, and BP.

PATIENT COUNSELING

Instruct patients to limit sunlight and UV light exposure by wearing protective clothing and using a sunscreen with a high protection. Inform patients about the potential risks during pregnancy and instruct to use effective contraception prior to, during therapy, and 12 weeks after therapy has been stopped.

ADMINISTRATION/STORAGE

Administration: Oral route. Give consistently with or without food. (Tab) Do not crush, chew, or split. (Sol) Refer to PI for proper dilution and administration. **Storage:** (Sol) 2-8°C (36-46°F), should be used within 1 month once opened. May store up to 25°C (77°F) for a short period (eg, not >15 days). (Tab) 20-25°C (68-77°F). Protect from light.