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Zortress

(Everolimus) - Novartis

BOXED WARNING

Should only be prescribed by physicians experienced in immunosuppressive therapy and management of organ transplant patients. Immunosuppression may lead to increased susceptibility to infection and possible development of malignancies (eg, lymphoma, skin cancer). Increased risk of kidney arterial and venous thrombosis leading to graft loss reported, mostly within the first 30 days post-transplantation. Increased nephrotoxicity may occur in combination with standard doses of cyclosporine; reduce dose of cyclosporine to reduce renal dysfunction, and monitor cyclosporine and everolimus whole blood trough concentrations. Increased mortality within the first 3 months post-transplantation in heart transplant patients on immunosuppressive regimens with or without induction therapy; not recommended in heart transplantation.

THERAPEUTIC CLASS

Macrolide immunosuppressant

DEA CLASS

RX

INDICATIONS

Prophylaxis of organ rejection in adults at low-moderate immunologic risk receiving a kidney transplant in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and with corticosteroids. Prophylaxis of allograft rejection in adults receiving a liver transplant administered no earlier than 30 days post-transplant concurrently in combination with reduced doses of tacrolimus and with corticosteroids.

ADULT DOSAGE

Adults: Initial: Kidney Transplant: 0.75mg bid with reduced dose of cyclosporine. Give as soon as possible after transplantation. Initiate PO prednisone once PO medication is tolerated. Liver Transplant: 1 mg bid with reduced dose of tacrolimus. Start at least 30 days post-transplant. Titrate: May require dose adjustment based on blood concentrations achieved, tolerability, individual response, change in concomitant medications, and clinical situation. Optimally, dose adjustments should be based on trough concentrations obtained 4 or 5 days after a previous dosing change. Steroid doses may be further tapered on an individualized basis, depending on clinical status and function of graft. Recommended Therapeutic Range: 3-8ng/mL (based on LC/MS/MS assay method). Hepatic Impairment: Mild (Child-Pugh Class A): Reduce initial daily dose by 1/3 of normal daily dose. Moderate or Severe (Child-Pugh Class B or C): Reduce initial daily dose to 1/2 of the normal daily dose. Refer to PI for further drug monitoring instructions and for cyclosporine or tacrolimus therapeutic drug monitoring parameters.

HOW SUPPLIED

Tab: 0.25mg, 0.5mg, 0.75mg

WARNINGS/PRECAUTIONS

Limit exposure to sunlight and UV light. Prophylaxis for *Pneumocystis jiroveci (carinii)* pneumonia and cytomegalovirus recommended. Increased risk of hepatic artery thrombosis (HAT), which may lead to graft loss or death; do not give earlier than 30 days after liver transplant. Consider switching to other immunosuppressive therapies if renal function does not improve after dose adjustments or if dysfunction is thought to be drug related. Angioedema, increased risk of delayed wound healing, increased occurrence of wound-related complications, and generalized fluid accumulation reported. Interstitial lung disease (ILD) reported; resolution may occur upon drug interruption with or without glucocorticoid therapy. Consider diagnosis of ILD for symptoms of infectious pneumonia that do not respond to antibiotic therapy and in whom infectious, neoplastic, and other non-drug causes have been ruled out. Increased risk of hyperlipidemia and proteinuria with higher whole blood trough concentrations; use of anti-lipid therapy may not normalize lipid levels. Polyoma virus infections including polyoma virus-associated nephropathy (PVAN) and progressive multiple leukoencephalopathy (PML) may occur; may lead to renal dysfunction and kidney graft loss; consider reductions in immunosuppression if evidence of PVAN or PML develops. Concomitant use with cyclosporine may increase risk of thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; monitor hematologic parameters. May increase risk of new-onset diabetes mellitus (DM) after transplant; monitor glucose levels. Azospermia or oligospermia may be observed. Avoid with rare hereditary problems of galactose intolerance (Lapp lactase deficiency, glucose-galactose malabsorption); diarrhea and malabsorption may occur. Safety and efficacy not established in kidney transplant patients at high immunologic risk or in recipients of transplanted organs other than kidney and liver.

ADVERSE REACTIONS

Peripheral edema, constipation, HTN, nausea, anemia, urinary tract infection, hyperlipidemia, diarrhea, pyrexia, increased blood creatinine, hyperkalemia, headache, hypercholesterolemia, insomnia, upper respiratory tract infections.

DRUG INTERACTIONS

Caution with drugs known to impair renal function. May increase risk of angioedema with drugs known to cause angioedema (eg, ACE inhibitors). Monitor for development of rhabdomyolysis with HMG-CoA reductase inhibitors (eg, atorvastatin, pravastatin) and/or fibrates; use of simvastatin and lovastatin are strongly discouraged in patients receiving everolimus and cyclosporine. Coadministration with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir, boceprevir, telaprevir) and strong CYP3A4 inducers (eg, rifampin, rifabutin) is not recommended without close monitoring of everolimus whole blood trough concentrations. Avoid with live vaccines, grapefruit, and grapefruit juice. Inhibitors of P-glycoprotein (P-gp) (eg, digoxin, cyclosporine), moderate inhibitors of CYP3A4 and P-gp (eg, fluconazole, macrolide

antibiotics, nicardipine, diltiazem, nelfinavir, indinavir, amprenavir, erythromycin), and verapamil may increase levels. Caution with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Increased levels with cyclosporine; dose adjustment may be needed if cyclosporine dose is altered. CYP3A4 inducers (eg, St. John's wort, carbamazepine, phenobarbital, phenytoin, efavirenz, nevirapine) may decrease levels. Combination immunosuppressant therapy should be used with caution.

PREGNANCY

Category C, not for use in nursing.

MECHANISM OF ACTION

Macrolide immunosuppressant; inhibits antigenic and interleukin (IL-2 and IL-15) stimulated activation and proliferation of T and B lymphocytes. Binds to a cytoplasmic protein, the FK506 binding protein-12 (FKBP-12), to form an immunosuppressive complex (everolimus: FKBP-12) that binds to and inhibits the mammalian target of rapamycin, a key regulatory kinase in cells.

PHARMACOKINETICS

Absorption: (0.75mg bid) AUC=75ng•h/mL, C_{max} =11.1ng/mL, T_{max}=1-2 hrs. **Distribution:** Plasma protein binding (74%); (0.75mg bid) V_d=110L. **Metabolism:** Via CYP3A4 and P-gp (monohydroxylations and O-dealkylations). **Elimination:** Feces (80%), urine (5%). (0.75mg bid) $T_{1/2}$=30 hrs.

ASSESSMENT

Assess for hereditary problems of galactose intolerance, hepatic impairment, hypersensitivity to the drug or to sirolimus, pregnancy/nursing status, and possible drug interactions. Assess that kidney transplant patients are not at high immunologic risk. Obtain baseline lipid and glucose levels.

MONITORING

Monitor for infections, angioedema, thrombosis, wound-related complications, fluid accumulation, lymphomas and other malignancies, hyperlipidemia, hepatic impairment, proteinuria, PVAN, HAT, ILD, pneumonitis, and other adverse reactions. Monitor everolimus and cyclosporine or tacrolimus whole blood trough concentrations, lipid profile, blood glucose concentrations, renal function, and hematologic parameters.

PATIENT COUNSELING

Counsel to avoid grapefruit and grapefruit juice. Inform of risk of developing lymphomas and other malignancies, particularly of the skin; instruct to limit exposure to sunlight and UV light by wearing protective clothing and using sunscreen with a high protection factor. Advise that therapy has been associated with an increased risk of kidney arterial and venous thrombosis, resulting in graft loss, usually occurring within the first 30 days post-transplantation. Inform of the risks of impaired kidney function with the combination of everolimus with cyclosporine as well as the need for routine blood concentration monitoring for both drugs and advise of the importance of SrCr monitoring. Inform of risk of hyperlipidemia and the importance of lipid profile monitoring. Advise women to avoid pregnancy throughout treatment and for 8 weeks after d/c. Instruct to notify physician of all medications and herbal/dietary supplements being taken. Inform that therapy has been associated with impaired or delayed wound healing, and fluid accumulation. Inform of increased risk of proteinuria, DM, infections, noninfectious pneumonitis, and angioedema; advise to contact physician if symptoms develop. Instruct to avoid receiving live vaccines.

ADMINISTRATION/STORAGE

Administration: Oral route. Do not crush; swallow whole with water. Administer consistently approximately 12 hrs apart with or without food and at the same time as cyclosporine or tacrolimus. **Storage:** 25^{o}C (77^{o}F); excursions permitted to 15-30^{o}C (59-86^{o}F). Protect from light and moisture.