everolimus (e-ver-o-li-mus)
Afinitor, Afinitor Disperz, Zortress

Classification
Therapeutic: antineoplastics, immunosuppressants
Pharmacologic: kinase inhibitors

Pregnancy Category C (Zortress), D (Afinitor)

Indications
Afinitor: Advanced renal cell carcinoma which has failed treatment with sunitinib or sorafenib; Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in patients who are not candidates for curative surgical resection; Progressive noncurative lesions of pancreatic endocrine tumors (PNET) in patients with unresectable, locally advanced or metastatic disease; Renal angiomyolipoma with TSC in patients not requiring immediate surgery. Treatment of spontaneous subependymal lesions with advanced human type 2 neurons positive. SEGA-negative renal cancer in combination with exemestane, after failure of treatment with lenvatinib or aminoside. Zortress: Prevention of organ rejection in patients who have received a kidney transplant and are at low-to-moderate immunologic risk; Prevention of organ rejection in patients who have received a liver transplant.

Action

Pharmacokinetics
Absorption: Well absorbed following oral administration. Distribution: 20% confined to plasma. Metabolism and Excretion: Mostly metabolized by liver and other systems (CYP3A4 and P-gp); metabolites are mostly excreted in feces (80%) and urine (5%). Half-life: 30 hr.

Contraindications/Precautions
Contraindicated in: Hypersensitivity to everolimus or other rapamycins; Severe hepatic impairment (Child-Pugh class C); Concurrent use with strong CYP3A4 inhibitors (i.e. ketoconazole, erythromycin, clarithromycin, saquinavir, nefazodone, ritonavir, indinavir, voriconazole); Heart transplantation (Zortress) (? risk of mortality); OB: Avoid use during pregnancy (Afinitor), use only if benefit to mother outweighs risk to fetus (Zortress); Lactation: Avoid breast feeding.

Use Cautiously in: Mild or moderate hepatic impairment (Child-Pugh class A or B); Concurrent use of moderate CYP3A4 and/or P-glycoprotein inhibitors; Concurrent use with immunosuppressants; Exposure to sunlight/UV light (may risk of malignant skin changes); Geri: May be more sensitive to drug effects; Pedi: Safety not established for indications other than SEGA.

Adverse Reactions/Side Effects
CNS: fatigue, weakness, headache.
CV: peripheral edema.
Resp: PNEUMONITIS, cough, dyspnea, pulmonary embolism.
GI: HEPATIC ARTERY THROMBOSIS, anorexia, constipation, diarrhea, mucositis, mouth ulcers, nausea, stomatitis, vomiting, dysgeusia.
GU: acute renal failure, infertility, proteinuria.
Derm: delayed wound healing, dry skin, pruritus, rash.
Hemat: HEMOLYTIC UREMIC SYNDROME, THROMBOTIC MI
CROANGIOPATHY, THROMBOTIC THROMBOCYTOPENIC PURPURA, anemia, leukopenia, thrombocytopenia.
Metab: hyperlipidemia, hyperglycemia, hypertriglyceridemia.
MS: extremity pain.
Misc: ANGIOEDEMA, fever, hypersensitivity reactions including ANAPHYLAXIS, infection (including activation of latent viral infections such as BK virus-associated nephropathy), kidney arterial/venous thrombosis (Zortress), risk of lymphoma/skin cancer (Zortress).

Interactions
Drug-Drug: Strong CYP3A4 inhibitors, including azolamycins, clarithromycin, indinavir, ritonavir, saquinavir, telithromycin, voriconazole; Zortress; moderate CYP3A4 and/or P-gp inhibitors (e.g. erythromycin, clarithromycin, nefazodone, atazanavir, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) levels and the risk of toxicity;
avoid concurrent use. Moderate inhibitors of CYP3A4, including aperpitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil; levels and the risk of toxicity; levels of everolimus (Afinitor). Avoid concurrent use with strong CYP3A4 inducers including carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampin. A dose of everolimus may be required. CYP3A4, aminoglycosides, amphotericin B, cyclosporine, or cyclosporine: ACE inhibitors may risk of angioedema. May anti-body formation and risk of adverse reactions from live virus vaccines, avoid use of live virus vaccines during treatment.

Drug-Natural Products: St. John’s wort may levels and efficacy, avoid concurrent use.

Drug-Food: Blood levels and risk of toxicity with grapefruit juice, avoid concurrent use.

Route/Dosage

Advanced Renal Cell Carcinoma, Advanced PNET, Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, and Renal Angiomyolipoma with TSC

PO (Adults): 10 mg once daily; Concurrent use of moderate inhibitors of CYP3A4 and/or P-glycoprotein — dose to 2.5 mg daily; Concurrent use of strong inducers of CYP3A4 — dose as in 5 mg increments up to 20 mg daily.

Hepatic Impairment

PO (Adults): Mild hepatic impairment (Child–Pugh Class A) — 7.5 mg once daily; may be 3.75 mg once daily if not well tolerated. Moderate hepatic impairment (Child–Pugh Class B) — 5 mg once daily; may be 2.5 mg once daily if not well tolerated. Severe hepatic impairment (Child–Pugh Class C) — 2.5 mg once daily.

SEG A with TSC

PO (Adults and Children ≥1 y): 6 mg/m². Titrate, as needed, at 2–wk intervals to achieve recommended whole blood trough concentration. Concurrent use of moderate inhibitors of CYP3A4 and/or P-glycoprotein — 2.5 mg/m². Concurrent use of strong inducers of CYP3A4 — 0.5 mg/m².

Hepatic Impairment

PO (Adults and Children ≥1 y): Severe hepatic impairment (Child–Pugh Class C) — 2.5 mg/m².

Kidney Transplantation

PO (Adults): 11.5 mg twice daily (with reduced-dose cyclosporine); titrate to achieve recommended whole blood trough concentration.

Hepatic Impairment

PO (Adults): Mild hepatic impairment (Child–Pugh Class A) — daily dose by 50%. Moderate or severe hepatic impairment (Child–Pugh Class B or C) — daily dose by 50%.

Liver Transplantation

PO (Adults): 11.5 mg twice daily (with reduced-dose tacrolimus) (start at 30 days post-transplant); titrate to achieve recommended whole blood trough concentration.

Hepatic Impairment

PO (Adults): Mild hepatic impairment (Child–Pugh Class A) — daily dose by 50%. Moderate or severe hepatic impairment (Child–Pugh Class B or C) — daily dose by 50%.

NURSING IMPLICATIONS

Assessment

● Assess for symptoms of non-infectious pneumonitis (hypoxia, pleural effusion, cough, dyspnea) during therapy. If symptoms are mild, therapy may continue. Therapy should be interrupted for moderate symptoms and corticosteroids may be used. Re-initiate everolimus at a ≥50% reduced dose when symptoms resolve. If symptoms are severe, discontinuance therapy. Corticosteroids may be used until clinical symptoms resolve. Base re-initiation of therapy on individual clinical circumstances.

● Assess for mouth ulcers, stomatitis, or oral mucositis. Topical treatments may be used; avoid peroxide-containing mouthwashes and antifungals unless fungal infection has been diagnosed.

● Assess for signs and symptoms of systemic fungal infections (fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, serious systemic illness with or without concomitant shock). Consider stopping therapy until infection has been diagnosed and adequately treated.
everolimus

Lab Test Considerations:
- Monitor renal function prior to and periodically during therapy. May cause ↑BUN, serum creatinine, and proteinuria. Monitor fasting serum glucose and lipid profile prior to and periodically during therapy. May cause ↑triglycerides, cholesterol, glucose. Attempts to achieve optimal glucose and lipid control prior to therapy.
- Monitor CBC prior to and periodically during therapy; may cause ↓hemoglobin, lymphocytes, neutrophils, and platelets.
- Max causes ↑ALT, AST, phosphorus, and bilirubin.
- Monitor everolimus trough levels 2 hrs after initiation of therapy, a change in dose, a change in co-administration of CYP3A4 and/or Pgp inducers or inhibitors, change in hepatic function, or change in dose form between everolimus tablets and Disperz. Once at a stable dose, monitor trough concentrations every 3 to 6 months in patients with changing body surface area for duration of treatment. Therapeutic blood concentrations are 5–15 ng/mL (Affinitor) and 3-8 ng/mL via the LCMSMS assay (Zortress). If trough concentration is <5 ng/mL, increase daily dose by 2.5 mg in patients taking tablets and 2 mg for Disperz. If trough concentration is >15 ng/mL, decrease daily dose by 2.5 mg in patients taking tablets and 2 mg for Disperz. If dose reduction is required with lowest dose, administer every other day. Do not combine dose forms to achieve dose.

Potential Nursing Diagnoses
- Risk for infection (Adverse Reactions)

Implementation
- PO: Administer at the same time each day consistently with or without food, followed by a whole glass of water. Swallow tablets whole; do not break, crush, or chew.
- Administer Disperz, dispersible tablet, as a suspension only. Place dose in 10 mL syringe; do not exceed 10 mg/syringe. If higher dose required, use additional syringes. Do not break or crush tablets. Draw 5 mL water and 4 mL of air into syringe. Place filled syringe into container (tip up) for 3 min until tablets are in suspension. Invert syringe 5 times immediately prior to administration. Administer immediately after preparation. Following administration, draw 5 mL of water and 4 mL of air into same syringe, and swirl contents to suspend remaining particles. Administer entire contents of syringe. Can also be dispensed using same technique and 25 mL water in install glass.

Patient/Family Teaching
- Instruct patient to take everolimus at the same time each day as directed. Do not miss doses or remember to take them after time of normal dose. If more than 1 hr after normal dose, omit dose for that day and take next dose next day; do not take 2 doses to make up missed dose. Do not eat grapefruit or drink grapefruit juice during therapy. Advise patient to read Patient Information Leaflet prior to beginning therapy, and with each Rx refill in case of new information.
- Advise patient to report worsening respiratory symptoms or signs of infection (new or worsening cough, shortness of breath, chest pain, difficulty breathing or wheezing, fever, chills, skin rash, joint pain and inflammation, fatigue, loss of appetite, nausea, pale skin, dark urine, yellowing of the skin), pain in upper right side to health care professional promptly.
- Inform patient that mood swings may occur. Contact health care professional for treatment of pain, discomfort, or open sore in mouth occur. May require special mouthwash or gel.
- Instruct patient to avoid use of live vaccines and close contact with those who have received live vaccines.
- Instruct patient to notify health care professional of all Rx or OTC medications, vitamins, or herbal products being taken and to consult with health care professional before taking other medications.
- Skin may manifest oral effects and decrease male and female fertility. Advise female patients to use effective contraception during and for up to 8 wks following therapy and to notify health care professional if pregnancy is planned or suspected or if breastfeeding.
- Emphasize the importance of routine blood tests to determine effectiveness and side effects.

Evaluation/Desired Outcomes
- Decreased spread of tumor. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.
- Prevention of kidney transplant rejection.

Why was this drug prescribed for your patient?