Subject:	RE: Everolimus or Affinitor in the adjuvant setting
From:	Yu, Huey-Miin Mona Pharm D. (HYu@houstonmethodist.org)
To:	bpaseman@yahoo.com;
Date:	Tuesday, April 15, 2014 11:35 AM

Sent you a few articles regarding therapy. Sorry if I sent you duplicates… below please see the specific information on Everolimus. Again, this might be too much information, but it's pretty complete medication information usually for healthcare professionals.

Let me know if you need more info.

Mona

Description

Everolimus (SDZ RAD, RAD001, Afinitor, Zortress) is a macrolide immunosuppressant and analog of sirolimus classified as a 'proliferation signal inhibitor' (PSI). Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonine kinase. The mTOR pathway is dysregulated in many human cancers. Inhibition of mTOR has been shown to reduce cell proliferation, angiogenesis, and glucose uptake by the tumor. Everolimus is FDA approved for the treatment of certain patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), progressive neuroendocrine tumors of pancreatic origin (PNET), renal angiomyolipoma and TSC, advanced renal cell carcinoma (RCC), and advanced breast cancer.[49823] A phase III trial (RECORD-1) in advanced kidney cancer patients refractory to previous targeted therapy was terminated early by a data monitoring committee due to a significant increase in progression-free survival with everolimus compared to placebo (4.9 months vs. 1.9 months, $p < 0.001$). In addition to the treatment of various malignancies, everolimus is FDA-approved for kidney transplant and liver transplant rejection prophylaxis. Everolimus inhibits antigenic and interleukin (IL-2 and IL-15) stimulated activation and proliferation of T and B lymphocytes.[49598] Afinitor received initial FDA approval for the treatment of RCC in March 2009, and Zortress received initial FDA-approval for kidney transplant rejection prophylaxis in April 2010 and approval for liver transplant rejection prophylaxis in February 2013.

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Mechanism of Action: Everolimus inhibits the mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/Akt pathway. The mTOR pathway has been shown to be dysregulated in several cancers resulting in

tumor cell growth and proliferation.[35144] In normal cellular function, PI3K and Akt are activated in response to growth factor and/or mitogenic stimuli. This activity is modulated by the tumor suppressor gene, PTEN. Excess stimulation of the PI3K/Akt pathway results in an increase in mTOR activity. mTOR phosphorylates the serine-threonine kinase, S6K, which in turn phosphorylates the 40s ribosomal protein S6, resulting in mRNA translation. Additionally, active mTOR phosphorylates the eukaryotic initiation factor binding protein, 4E-BP1. Phosphorylation of 4E-BP1 decreases its affinity for eukaryotic initiation factor, which increases the amount of free eukaryotic initiation factor and results in an increase in mRNA translation. Everolimus inhibits mTOR by forming a complex with the intracellular protein FK506 binding protein-12 (FKBP-12) which then binds to the FKBP-12-rapamycin binding domain on mTOR to effectively inhibit its kinase activity. Everolimus inhibition of mTOR occurs downstream of PI3K/Akt stimulation and upstream of S6K and 4E-BP. Everolimus has been shown to decrease the activity of S6K and 4E-BP, reducing protein synthesis and causing cell arrest in the G1-phase.[35145] In addition, in clear-cell renal cell carcinoma, loss of the von-Hippel Landau tumor suppressor gene leads to an accumulation of the hypoxia-inducible factor 1 (HIF-1) and over expression of HIF-1 target gene products. HIF-1 target gene products include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and glucose transporter 1 (GLUT 1). These products cause an increase in angiogenesis, cell proliferation, and glucose metabolism. Everolimus has been shown to inhibit the expression of HIF-1 and subsequently reduce the expression of the HIF-1 target gene products.

In kidney transplant rejection prophylaxis, everolimus inhibits antigenic and interleukin (IL-2 and IL-15) stimulated activation and proliferation of T and B lymphocytes. *In vivo*, everolimus binds to the FK506 binding protein, and the complex binds to and inhibits mTOR. In the presence of everolimus phosphorylation of p70S6 ribosomal protein kinase (p70S6K), a substrate of mTOR is inhibited. As a result, phosphorylation of the ribosomal S6 protein and subsequent protein synthesis and cell proliferation are inhibited.[41241]

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Pharmacokinetics: Everolimus is administered orally. It is approximately 74% bound to plasma proteins in both healthy subjects and patients with moderate hepatic impairment. Everolimus is a substrate of cytochrome P450 3A4 (CYP3A4) and the multidrug efflux transporter P-glycoprotein (P-gp). Six predominant metabolites have been identified in blood after oral administration; however, the activity of the metabolites is estimated to be 100-fold less than everolimus. Everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. After a 10 mg dose, the steady-state Cmax was 12-fold below the Ki for *in vitro* inhibition, making it unlikely that everolimus has a clinically significant effect on the metabolism of CYP3A4 and CYP2D6 substrates. Data regarding excretion in cancer patients are not available. After the oral administration of a single dose of radiolabeled everolimus in patients also receiving cyclosporine, 80% of the radioactivity was recovered from the feces and 5% was excreted in the urine; the parent drug was not detected in urine or feces. The mean elimination half-life is approximately 30 hours.[35144]

Affected cytochrome P450 isoenzymes and drug transporters: CYP3A4, CYP2D6, P-gp
In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.[35144] Exercise caution when coadministering with CYP3A4 and CYP2D6 substrates with a narrow therapeutic

index.[49903] Additionally, it is a substrate of CYP3A4 and both a substrate and moderate inhibitor of the multidrug efflux pump, P-glycoprotein (P-gp).

•Route-Specific Pharmacokinetics

Oral Route

Peak everolimus concentrations are achieved 1—2 hours after administration and are proportionally related to the Afinitor dose within the dose range of 5—10 mg PO once daily. At steady-state after receipt of 0.5 to 2 mg twice daily of Zortress, the everolimus Cmax and AUC are dose proportional among transplant patients. Administration with high-fat meals has been shown to reduce the Cmax and AUC by 54% and 22%, respectively in healthy subjects taking everolimus 10 mg. Administration with low-fat meals reduced AUC by 32% and Cmax by 42%. Food has no apparent effect on the post- absorption phase concentration-time profile. Everolimus may be administered with or without food, but Zortress must be taken consistently with or without food to minimize variability. Steady state concentrations are achieved within two weeks of once daily dosing with Afinitor among patients with advanced solid tumors. Steady-state with Zortress is achieved by day 4 among kidney transplant patients.[35144] [41241]

•Special Populations

Hepatic Impairment

In one study, the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that of 8 subjects with normal hepatic function. The impact of severe hepatic impairment (Child-Pugh class C) on everolimus pharmacokinetics has not been established, but the effect of severe hepatic impairment on the systemic exposure of everolimus is likely to be as large or larger as compared with values from patients with moderate hepatic impairment.[49598] In another pharmacokinetic study in 34 subjects with impaired hepatic function who received a single oral dose of Afinitor, drug exposure was increased in patients with mild (1.8-fold AUC increase), moderate (3.2-fold AUC increase), or severe (3.6-fold AUC increase) hepatic impairment compared with 13 subjects who had normal hepatic function.[49595]

Renal Impairment

After a 3 mg dose of radiolabeled everolimus, approximately 5% of total radioactivity was excreted in the urine. Among patients with advanced cancer, no significant influence of creatinine clearance (25—178 ml/min) was detected on oral clearance of everolimus. Also, the pharmacokinetic parameters of everolimus among patients after renal transplantation were not affected by the creatinine clearance (range, 11—107 ml/min). Less than 10% of everolimus is removed within 6 hours of hemodialysis.[41241] [35144]

Geriatric

A limited reduction in everolimus oral clearance of 0.33% per year was estimated in adults 16—70 years of age. There is no evidence to suggest that elderly patients will require a different dosage recommendation compared to younger adults.[41241]

Ethnic Differences

Cross-study comparisons indicate that Japanese patients have higher exposure to everolimus than non-Japanese patients receiving the same dose. In analysis of population pharmacokinetics, Black patients had a 20% higher clearance than Caucasians. The clinical significance of these effects in Japanese and Black patients has not been established.[35144]

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For the treatment of patients with advanced renal cell cancer who have failed treatment with sunitinib or sorafenib:

Oral dosage (Afinitor only):

Adults: 10 mg PO once daily. Continue treatment for as long as clinical benefit is observed or until unacceptable toxicity develops. Severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of Afinitor (see Afinitor Dosage Adjustments). Dose adjustment is necessary if Afinitor is coadministered with some CYP3A4 inhibitors or inducers (see Afinitor Dosage Guidance in Patients on Strong CYP3A4 Inducers/Inhibitors). Avoid concomitant use with strong CYP3A4 inhibitors. [49823]

For kidney transplant rejection prophylaxis in patients at low-moderate immunologic risk:

NOTE: The safety and efficacy of everolimus have not been established in patients at high immunologic risk.

Oral dosage (Zortress only):

NOTE: Everolimus is FDA-approved for use with Cyclosporine, USP Modified formulation only; everolimus has not been evaluated in clinical trials with other formulations of cyclosporine. Cyclosporine, USP Modified is to be administered as oral capsules twice daily unless cyclosporine oral solution or intravenous administration of cyclosporine cannot be avoided. Cyclosporine and everolimus interact (see Drug Interactions), so both the cyclosporine dose and the target range for whole blood trough concentrations are to be reduced when cyclosporine is given with everolimus. Avoid standard doses of cyclosporine with everolimus to reduce the risk of nephrotoxicity.

Adults: Initially, 0.75 mg PO every 12 hours (1.5 mg/day) in combination with basiliximab induction and concurrently with reduced doses of cyclosporine, USP modified and corticosteroids; administer as soon as possible after transplantation. Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients (see Therapeutic Drug Monitoring). If needed, adjust everolimus dose at 4—5 day intervals. The everolimus dose may need adjustment based on blood concentrations, tolerability,

individual response, concomitant medication change, or clinical situation. Initiate cyclosporine as soon as possible and no later than 48 hours after reperfusion of the graft, and adjust the cyclosporine dose to target whole blood trough concentrations from day 5 onwards. In a clinical trial, the mean cyclosporine starting dose was 5.2 mg/kg/day. Initiate oral prednisone once oral medication is tolerated.[41241] According to guidelines, use of everolimus in combination with cyclosporine is effective in preventing rejection but is associated with enhanced nephrotoxicity and inferior outcomes, so significant reduction in the cyclosporine dosage is advised. If everolimus is used, guidelines recommend that it should not be started until graft function is established and surgical wounds are healed.[51731][51730]
Neonates, Infants, Children, and Adolescents: Safety and efficacy have not been established.

For the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in patients who require therapeutic intervention but are not candidates for curative surgical resection:
NOTE: The effectiveness of everolimus is based on an analysis of change in subependymal giant cell astrocytoma volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.[49823]
Oral dosage (Afinitor only):

Children, Adolescents, and Adults: 4.5 mg/m^2 PO once daily initially, then titrate dose to achieve a target trough level of 5—15 ng/ml. Continue therapy until disease progression or unacceptable toxicity; the optimal duration of therapy is unknown. Round dose to nearest strength of either Afinitor tablet or Afinitor DISPERZ. Adjust dose at 2-week intervals based on trough concentrations, tolerability, clinical response, and concomitant drug changes. Severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of Afinitor (see Afinitor Dosage Adjustments). Dose adjustment is necessary if Afinitor is coadministered with some CYP3A4 or P-glycoprotein (P-gp) inhibitors or inducers (see Afinitor Dosage Guidance in Patients on CYP3A4 and/or P-gp) Inducers/Inhibitors). Avoid concomitant use with strong CYP3A4 and/or P-gp inhibitors.[49823] In a multinational, double-blind, placebo-controlled, phase III trial in 117 patients (median age, 9.5 years; range, 0.8—26.6 years) with progressive SEGA associated with TSC, treatment with everolimus (4.5 mg/m^2 PO initially then titrated to trough concentrations of 5—15 ng/ml) resulted in a significantly improved SEGA response rate (primary endpoint) compared with placebo (35% vs 0%; $p < 0.0001$); additionally, the estimated 6-month progression-free rate was significantly improved with everolimus therapy (100% and 86%; $p = 0.0002$). After 24 weeks of treatment, the median seizure frequency per 24 hours was unchanged from baseline with either everolimus or placebo.[46589] Treatment with everolimus (3 mg/m^2/day PO initially then titrated to trough concentrations of 5—15 ng/ml) led to a significant reduction in SEGA volume ($p < 0.001$) and seizure frequency ($p = 0.02$) at 6 months compared with baseline in 28 patients (median age, 11 years; range, 3-34 years) with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) in a phase I-II study. Additionally, a SEGA volume reduction of 30% or greater was

achieved in 75% of patients and of 50% or greater was achieved in 32% of patients.[46587] In a long-term analysis of 25 patients who received at least 24 months of everolimus, 30% or greater reduction in SEGA volume responses were maintained for a median duration of 23.8 months (range, 0—39.4 months).[46588]

For the treatment of progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced or metastatic disease:

NOTE: Everolimus is not indicated for the treatment of patients with functional carcinoid tumors.[49823]

Oral dosage (Afinitor only):

Adults: 10 mg PO once daily. Continue treatment for as long as clinical benefit is observed or until unacceptable toxicity develops. Severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of Afinitor (see Afinitor Dosage Adjustments). Dose adjustment is necessary if Afinitor is coadministered with some CYP3A4 inhibitors or inducers (see Afinitor Dosage Guidance in Patients on Strong CYP3A4 Inducers/Inhibitors). Avoid concomitant use with strong CYP3A4 inhibitors.[49823]

For the treatment of breast cancer:

•for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer in postmenopausal women who have failed treatment with letrozole or anastrozole, in combination with exemestane:

 **Strength of Recommendation: Strong For, Level of Evidence: High, Detailed Level of Evidence**

Oral dosage (Afinitor only):

Postmenopausal females: 10 mg PO once daily in combination with exemestane. Continue treatment for as long as clinical benefit is observed or until unacceptable toxicity develops. Severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of Afinitor (see Afinitor Dosage Adjustments). Dose adjustment is necessary if Afinitor is coadministered with some CYP3A4 inhibitors or inducers (see Afinitor Dosage Guidance in Patients on Strong CYP3A4 Inducers/Inhibitors). Avoid concomitant use with strong CYP3A4 inhibitors.[49823] Everolimus 10 mg/day PO (median duration, 14.6 weeks) plus exemestane 25 mg/day PO (median duration, 17.4 weeks) or placebo plus exemestane was evaluated in 724 postmenopausal women with estrogen receptor-positive, human epidermal growth factor receptor 2-negative metastatic or locally advanced breast cancer refractory to letrozole or anastrozole in a randomized, double-blind, phase III trial (the BOLERO-2 trial).[47310] The primary endpoint of investigator assessed median progression-free survival (PFS) was significantly improved with everolimus plus exemestane compared with exemestane only (7.8 vs 3.2 months; hazard ratio (HR) = 0.45; 95% CI, 0.38—0.54, $p < 0.0001$); median PFS based on central assessment was 11 vs 4.1 months (HR = 0.38; 95% CI, 0.31—0.48, $p < 0.0001$). At a median follow-up time of 18 months, 25.4% and 32.2% of patients have

died in the combination therapy and exemestane only arms, respectively.[52651]

•for the treatment of hormone receptor-positive, HER2-negative metastatic breast cancer in postmenopausal women with secondary aromatase inhibitor resistance, in combination with tamoxifen†:

 **Strength of Recommendation: Strong For, Level of Evidence: Low, Detailed Level of Evidence**

Oral dosage:

Postmenopausal females: 10 mg/day PO plus tamoxifen 20 mg/day PO until disease progression or unacceptable toxicity resulted in significantly improved clinical benefit rate (primary endpoint, 61.1% vs 42.1%; p = 0.045), time to progression (TTP) (7.6 vs 4.5 months; p = 0.0021), and overall survival (OS) (16 vs 31 events; hazard ratio = 0.45; 95% CI, 0.24-0.81; p = 0.007) compared with tamoxifen alone (median follow-up, 24 months) in a randomized, phase II study in 111 postmenopausal women with estrogen receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer and primary or secondary aromatase inhibitor resistance. No crossover was permitted. Primary hormone resistance was defined as relapse during adjuvant aromatase inhibitor (AI) therapy or disease progression within 6 months of starting AI therapy for metastatic disease, and secondary hormone resistance was defined as relapse later than 6 months or a previous response and subsequent progression after starting AI therapy for metastatic disease. In exploratory analyses, a statistically significant TTP and OS benefit was observed with combination therapy in women with secondary resistance (TTP: 14.8 vs 5.5 months, p = 0.0087; OS: 4 vs 16 events, p = 0.002) but not primary resistance (TTP: 5.4 vs 3.8 months; OS: 12 vs 15 events). A higher incidence of grade 3 and 4 stomatitis and anorexia was reported in the everolimus plus tamoxifen arm; 22% of patients in the combination therapy arm and 7% of patients in the tamoxifen alone arm discontinued treatment due to adverse events.[46701]

•for the treatment of HER2-positive, trastuzumab-resistant, advanced breast cancer in patients previously treated with a taxane, in combination with vinorelbine and trastuzumab†:

 **Strength of Recommendation: Equivocal/Weak For, Level of Evidence: Low, Detailed Level of Evidence**

Oral dosage:

Adults: 5 mg/day PO plus vinorelbine 25 mg/m^2 IV weekly and trastuzumab 4 mg/kg IV once followed by 2 mg/kg IV weekly until disease progression or unacceptable toxicity.[55446]

For the treatment of renal angiomyolipoma and tuberous sclerosis complex not requiring immediate surgery:

NOTE: The effectiveness of everolimus for renal angiomyolipoma is based on durable objective responses in patients treated for a median of 8.3 months.[49823]

Oral dosage (Afinitor only):

Adults: 10 mg PO once daily. Continue treatment for as long as clinical benefit is observed or until unacceptable toxicity develops. Severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of Afinitor. Dose adjustment is necessary if Afinitor is coadministered with some CYP3A4 inhibitors or inducers. Avoid concomitant use with strong CYP3A4 inhibitors.[49823] The confirmed response rate was 42% with everolimus therapy (median treatment duration, 38 weeks) compared with 0% with placebo ($p < 0.0001$) in a randomized, double-blind, phase III trial in adult patients with renal angiomyolipoma as a feature of tuberous sclerosis complex (n = 113) or sporadic lymphangioleiomyomatosis (n = 5). Response was defined as a reduction in angiomyolipoma volume of 50% or more relative to baseline and absence of angiomyolipoma progression. The median time to response in the everolimus arm was 2.9 months; all responses lasted between 10 and 85 weeks. The median time to progression was not reached in the everolimus arm and 11.4 months in the placebo arm. Additionally, the 6-month progression-free rates were 98% and 83% in the everolimus and placebo arms, respectively; the 12-month progression-free rates were 92% and 25%, respectively.[53049]

For liver transplant rejection prophylaxis:

Oral dosage:

Adults: Initially, 1 mg PO twice daily started at least 30 days after transplantation in combination with reduced dose tacrolimus and corticosteroids. Steroid doses may be further tapered based on the patient's clinical status and graft function. Therapeutic drug monitoring of everolimus and tacrolimus is recommended. In a trial, patients received tacrolimus plus corticosteroids with or without mycophenolate mofetil for the first 30 days and then tacrolimus (target trough concentration 3—5 ng/ml) and everolimus (target trough concentration 3—8 ng/ml) plus corticosteroids.[49903]

Therapeutic Drug Monitoring:

Zortress for kidney or liver transplant rejection prophylaxis: Guidelines suggest monitoring everolimus concentrations; a trough concentration is probably adequate.[51731] According to the manufacturer, routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients who take everolimus for kidney or liver transplant rejection prophylaxis. Also, monitor everolimus blood concentrations in patients with hepatic impairment, during concomitant administration of CYP3A4 inducers or inhibitors, when switching cyclosporine formulations, and/or when cyclosporine dosing is reduced according to recommended target concentrations; everolimus concentrations may decrease if cyclosporine exposure is reduced. The recommended everolimus therapeutic range is 3 to 8 ng/ml. This recommended therapeutic range was based on the liquid chromatography mass spectrometry (LCMSMS) assay method used in clinical studies. Either the LCMSMS assay or immunoassay methods may be used to evaluate whole blood everolimus concentrations; however, these values may vary depending on the assay used and may not be interchangable. Optimally, base everolimus dose adjustments on trough concentrations obtained 4 or 5 days after a previous dosing change. In addition to drug concentrations,

carefully consider clinical signs and symptoms, tissue biopsies, and laboratory parameters. For liver transplant patients, ensure that the steady-state everolimus whole blood trough concentration is at least 3 ng/ml before reducing the tacrolimus dose. The recommended tacrolimus whole blood trough concentrations are 3—5 ng/ml by three weeks after the first everolimus dose (approximately Month 2) and through Month 12 after transplantation. Limited data exist regarding dosing everolimus with tacrolimus trough concentrations of 3—5 ng/ml after 12 months. For renal transplant patients, if impairment of renal function is progressive, adjust the treatment regimen. Ensure that the steady-state everolimus whole blood trough concentration is at least 3 ng/ml before reducing the cyclosporine dose. The recommended cyclosporine therapeutic range when administered with everolimus is 100 to 200 ng/ml through the first month after transplantation, 75 to 150 ng/ml during months 2 and 3 after transplantation, 50 to 100 ng/ml during month 4 after transplantation, and 25 to 50 ng/ml during months 6 through 12 after transplantation. Limited data exist regarding dosing everolimus with cyclosporine trough concentrations of 25 to 50 ng/ml after 12 months.[49903]

Afinitor for subependymal giant cell astrocytoma (SEGA) with tuberous sclerosis complex (TSC): Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients; use the same assay and laboratory whenever possible. Determine everolimus trough concentrations approximately 2 weeks after starting treatment. Titrate the dose to obtain trough concentrations of 5—15 ng/ml. Reduce the daily dose by 2.5 mg (Afinitor tablets) or 2 mg (Afinitor DISPERZ) if trough concentrations > 15 ng/ml. If dose reduction is required for patients receiving the lowest available strength, use alternate day dosing. If the trough concentration is < 5 ng/ml, increase the daily dose by 2.5 mg (Afinitor tablets) or 2 mg (Afinitor DISPERZ). Assess trough concentrations approximately 2 weeks after any change in dose, after an initiation or change in coadministration of CYP3A4 and/or P-glycoprotein inducers or inhibitors, after any hepatic status change, or after a change in dosage form (e.g., Afinitor tablets to Afinitor DISPERZ). After a stable dose is obtained, monitor trough concentrations every 6—12 months in patients with stable body surface area (BSA) or every 3—6 months in patients with changing BSA.[49823].

Afinitor Dosage Adjustments due to Treatment-Related Toxicity:

NOTE: Reduce dose to approximately 50% of the previous dose if a dose reduction is required due to severe or intolerable adverse reactions. In patients with SEGA with TSC, consider alternate day dosing if a dose reduction is needed in a patient receiving the lowest available strength.

•Non-infectious Pneumonitis

Grade 1, asymptomatic with radiographic findings only: No dose adjustment required.

Grade 2, symptomatic but no interference with activities of daily living (ADL): Consider withholding therapy. Resume Afinitor at a lower dose when symptoms improve to <= grade 1; discontinue Afinitor if symptoms do not improve within 4 weeks.

Grade 3, symptomatic and interfering with ADL and oxygen therapy indicated: Hold therapy. Consider resuming

Afinitor at a lower dose when symptoms improve to <= grade 1. Consider discontinuing Afinitor if grade 3 toxicity recurs.

Grade 4, life-threatening and ventilator support indicated: Discontinue Afinitor therapy.

•Stomatitis

Grade 1, minimum symptoms and normal diet: No dose adjustment required.

Grade 2, symptomatic but can eat and swallow modified diet: Hold therapy until symptoms improve to <= grade 1 and resume Afinitor at the same dose. If grade 2 toxicity recurs, hold therapy and resume Afinitor at a lower dose when symptoms improve to <= grade 1.

Grade 3, symptomatic and unable to adequately eat or hydrate orally: Hold therapy. Resume Afinitor at a lower dose when symptoms improve to <= grade 1.

Grade 4, symptomatic and life-threatening: Discontinue Afinitor therapy.

•Other Non-hematologic Toxicity (excluding metabolic events)

Grade 1: No dose adjustment required if toxicity is tolerable.

Grade 2: No dose adjustment required if toxicity is tolerable. If toxicity is intolerable, hold therapy until symptoms improve to <= grade 1 and resume Afinitor at the same dose. If grade 2 toxicity recurs, hold therapy and resume Afinitor at a lower dose when symptoms improve to <= grade 1.

Grade 3: Hold therapy. Consider resuming Afinitor at a lower dose when symptoms improve to <= grade 1. If grade 3 toxicity recurs, consider discontinuing therapy.

Grade 4: Discontinue Afinitor therapy.

•Metabolic Events (e.g., hyperglycemia, dyslipidemia)

Grade 1 or 2: No dose adjustment required.

Grade 3: Temporarily withhold therapy. Resume Afinitor at a lower dose.

Grade 4: Discontinue Afinitor therapy.[49823]

Maximum Dosage Limits

•Adults

The maximum dosage is dependent on indication for therapy.

•Geriatric

The maximum dosage is dependent on indication for therapy.

•Adolescents

Safety and efficacy for Zortress have not been established. For Afinitor, maximum dosage is based on indication and plasma concentrations.

•Children

>= 3 years: Safety and efficacy for Zortress have not been established. For Afinitor, maximum dosage is based on indication and plasma concentrations.

< 3 years: Safety and efficacy have not been established.

•Infants

Safety and efficacy have not been established.

•Neonates

Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Advanced hormone receptor-positive, HER2-negative breast cancer, advanced renal cell cancer, pancreatic neuroendocrine tumors, or renal angiomyolipoma with tuberous sclerosis complex

Mild hepatic impairment (Child-Pugh class A): Afinitor 7.5 mg PO once daily; decrease dose to 5 mg PO once daily if not well tolerated.

Moderate hepatic impairment (Child-Pugh class B): Afinitor 5 mg PO once daily; decrease dose to 2.5 mg PO once daily if not well tolerated.

Severe hepatic impairment (Child-Pugh class C): Afinitor 2.5 mg PO once daily may be initiated if the benefits of therapy out weigh the risk of toxicity from increased drug exposure; do not increase dose above 2.5 mg/day.[49823]

Subependymal giant cell astrocytoma with tuberous sclerosis complex

Mild or moderate hepatic impairment (Child-Pugh class A or B): no initial Afinitor dose adjustment is necessary; however individualize subsequent dosing based on therapeutic drug monitoring; assess Afinitor levels after 2 weeks of a hepatic status change; titrate dose to achieve trough levels of 5 to 15 ng/ml.

Severe hepatic impairment (Child-Pugh class C): initiate Afinitor at 2.5 mg/m^2 PO once daily (round dose to nearest strength of either Afinitor tablet or Afinitor DISPERZ); individualize subsequent dosing based on therapeutic drug monitoring; assess Afinitor levels after 2 weeks and titrate dose to achieve/maintain trough levels of 5 to 15 ng/ml.[49823]

Renal and liver transplant rejection prophylaxis

Mild hepatic impairment (Child-Pugh class A): reduce the initial Zortress daily dosage by approximately one-third; monitor whole blood trough concentrations and adjust dose as necessary. Dose titration is needed if a patient's whole blood trough concentration as measured by an LC/MS/MS assay is not within the target trough concentration of 3—8 ng/ml.

Moderate hepatic impairment (Child-Pugh class B): reduce the initial Zortress daily dosage by approximately one-half; monitor whole blood trough concentrations and adjust dose as necessary. Dose titration is needed if a patient's whole blood trough concentration as measured by an LC/MS/MS assay is not within the target trough concentration of 3—8 ng/ml.

Severe hepatic impairment (Child-Pugh class C): reduce the initial Zortress daily dosage by approximately one-half; monitor whole blood trough concentrations and adjust dose as necessary. Dose titration is needed if a patient's whole blood trough concentration as measured by an LC/MS/MS assay is not within the target

trough concentration of 3—8 ng/ml.

Patients with Renal Impairment Dosing

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Afinitor Dosage Guidance in Patients on CYP3A4 and/or P-glycoprotein (P-gp) Inducers/Inhibitors

Advanced hormone receptor-positive, HER2-negative breast cancer, advanced renal cell cancer, pancreatic neuroendocrine tumors, or renal angiomyolipoma with tuberous sclerosis complex

-Strong CYP3A4 and/or P-gp inducers: Avoid coadministration if possible. If a strong CYP3A4 is required, 10 mg PO once daily initially then consider increasing the dose by 5 mg increments up to 20 mg PO once daily. If the strong 3A4 inducer is discontinued, consider a washout period of 3—5 days and then resume the everolimus dose used prior to the initiation of the strong 3A4 inducer. NOTE: Dosage adjustment is based on pharmacokinetic data; no clinical data are available with this dosage adjustment.

-Strong CYP3A4 and/or P-gp inhibitors: Avoid concomitant use.

-Moderate CYP3A4 and/or P-gp inhibitors: Reduce the dose to 2.5 mg PO daily. A dose increase to 5 mg PO daily may be considered based on patient tolerance. If the moderate inhibitor is discontinued, allow a 2—3 day washout period before increasing the Afinitor dose; restart the Afinitor dose used before the initiation of the moderate CYP3A4 and/or P-gp inhibitor.[49823]

Subependymal giant cell astrocytoma with tuberous sclerosis complex

-Strong CYP3A4 and/or P-gp inducers: Avoid concomitant use if alternative therapy is available. If a concomitant strong CYP3A4 inducer is required, double the Afinitor dose or initiate Afinitor at 9 mg/m^2 PO once daily (round dose to nearest strength of either Afinitor tablet or Afinitor DISPERZ). Individualize subsequent dosing based on therapeutic drug monitoring. Assess trough concentrations approximately 2 weeks after an initiation or change in coadministration with a CYP3A4 inducer and titrate dose to achieve/maintain trough levels of 5 to 15 ng/ml. If the strong CYP3A4 inducer is discontinued, adjust the everolimus dose to the one used before initiation of the CYP3A4 inducer and assess the everolimus trough concentration approximately 2 weeks later.

-Strong CYP3A4 and/or P-gp inhibitors: Avoid concomitant use.

-Moderate CYP3A4 and/or P-gp inhibitors: Reduce the Afinitor dose by 50% or initiate Afinitor at 2.5 mg/m^2 PO once daily (round dose to nearest strength of either Afinitor tablet or Afinitor DISPERZ). Individualize subsequent dosing based on therapeutic drug monitoring. Assess trough concentrations approximately 2 weeks after an initiation or change in coadministration with a CYP3A4 inhibitor and titrate dose to achieve/maintain trough levels of 5 to 15 ng/ml. If the moderate inhibitor is discontinued, adjust the everolimus dose in 2—3 days to the one used before initiation of the moderate CYP3A4 and/or P-gp inhibitor and assess the everolimus trough concentration approximately 2 weeks later.[49823]

†

General Administration Information

For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Oral Administration

- Everolimus should be taken at the same time each day.
- Take consistently either with food or without food.[49823][49903]
- Do not combine everolimus tablets with everolimus tablets for oral suspension (Afinitor Disperz) to achieve the desired dose. Use one dosage form or the other. Afinitor Disperz should only be administered as a suspension.[49823]
- Follow procedures for proper handling of anticancer drugs. Wear gloves to avoid exposure to crushed tablets when preparing the Afinitor Disperz suspension; wash skin thoroughly if contact occurs.

Oral Solid Formulations

- Swallow Afinitor and Zortress tablets whole with a full glass of water; do not break or crush tablets.
- For Zortress, administer every 12 hours and at the same time as cyclosporine.[49823][49903]
- If an Afinitor dose is missed, take within 6 hours of missing the dose. If more than 6 hours have passed, skip the dose of the day and take the Afinitor dose the next day at the scheduled time. [49823]

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Adverse reactions

Incision site pain (16%) and procedural pain (15%) were reported in de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial.[49903]

Oral ulceration (including mucositis and stomatitis) has been reported with everolimus (Zortress, Afinitor) in clinical trials. Stomatitis/oral ulceration was reported in 8% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial.[49903] All grade oral ulceration has been reported in 44—78% of patients treated with everolimus (Afinitor) in clinical trials; grade 3 and 4 stomatitis was reported in 4—9% of patients. In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range,

0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, stomatitis (including aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation) was reported in 67% of breast cancer patients (grade 3, 8%), 70% of PNET patients (grade 3, 7%), 44% of RCC patients (grade 3, 4%; grade 4, < 1%), 78% of RA/TSC patients (grade 3, 6%), and 62% of SEGA patients (grade 3, 9%). Mucosal inflammation was reported in 19% of RCC patients (grade 3, 1%). Grade 2 and 3 oral ulcers or stomatitis may be managed with analgesic mouthwashes (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e., triamcinolone oral paste); avoid alcohol- or peroxide-containing (e.g., hydrogen peroxide) solutions and iodine or thyme derivatives. Do not use antifungal agents unless a fungal infection is present.[49823]

Everolimus (Zortress, Afinitor) may cause immunosuppression and increase the risk of bacterial, fungal, viral, or protozoal infection including opportunistic infections. Severe infections, some cases leading to respiratory or hepatic failure or death, have been reported. Infection (bacterial, fungal, and viral etiologies) was reported in 64% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. The incidence of viral infection was 10% and cytomegalovirus was 1% in patients who received everolimus (Zortress) in this study. Other infections commonly reported with everolimus (Zortress) use include urinary tract infection (22%) and upper respiratory tract infection (16%). Infections occurring in 1% to < 10% of Zortress-treated patients include bacteremia, bronchitis, candidiasis, cellulitis, folliculitis, gastroenteritis, influenza, nasopharyngitis, onychomycosis, oral candidiasis, osteomyelitis, pneumonia, pyelonephritis, sinusitis, tinea pedis, urethritis, wound infection, and herpes infection. Use everolimus cautiously with other immunosuppressant agents, as combination therapy may cause additive immunosuppression and increase the risk of infection.[49903] In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). Infection (all grade) was reported in 50% of breast cancer patients (grade 3, 4%; grade 4, 1%) and in 37% of RCC patients (grade 3, 7%; grade 4, 3%). Specific infections with everolimus (Afinitor) use included urinary tract infection (breast cancer, 10%; PNET, 16%; RCC, 5%), upper respiratory tract infection (URI) (breast cancer, 5%; RA/TSC, 11%; SEGA, 31%), nasopharyngitis (breast cancer, 10%; RCC, 6%), nasopharyngitis/rhinitis/URI (PNET, 25%), bronchitis (breast cancer, 4%; RCC, 4%), sinusitis (breast cancer, 3%; RCC, 3%), aspergillosis (RCC, < 1%), candidiasis (breast cancer, < 1%; RCC, < 1%), sepsis (breast cancer, < 1%; RCC, < 1%), otitis media (RA/TSC, 6%), gastroenteritis (SEGA, 10%), and streptococcal pharyngitis (SEGA, 11%), pneumonia (breast cancer, 4%; RCC, 6%; SEGA, 6%), cystitis (breast cancer, 3%), and hepatitis C infection (breast cancer, < 1%). Severe respiratory tract infection (grade 3, 1%; grade 4, 1%) and gastroenteritis (grade 3, 4%; grade 4, 1%) were reported in SEGA

patients. Additionally, cellulitis occurred in 29% of SEGA patients who received everolimus (Afinitor) in an open-label trial (n = 28). Monitor for signs and symptoms of infection in patients receiving everolimus. If an infection develops, start appropriate antibiotic therapy promptly and consider withholding or discontinuing everolimus. If an invasive systemic fungal infection develops, start appropriate antifungal therapy promptly and discontinue everolimus.[49823]

Non-infectious pneumonitis has been reported with everolimus (Zortress, Afinitor) in clinical trials; some cases resulted in death. Non-infectious pneumonitis was reported in < 1% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Non-infectious pneumonitis may respond to dose reductions or therapy interruption with or without the use of glucocorticoids. Monitor patients receiving everolimus for clinical symptoms or radiologic changes consistent with non-infectious pneumonitis.[49903] All grade non-infectious pneumonitis has been reported in up to 19% of patients treated with everolimus (Afinitor) in clinical trials; grade 3 and 4 non-infectious pneumonitis have been reported in up to 4% and up to 0.2% of patients, respectively. In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, pneumonitis (including interstitial lung disease, pulmonary fibrosis, restrictive pulmonary disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis) was reported with everolimus (Afinitor) use in 19% of breast cancer patients (grade 3, 4%; grade 4, 0.2%), 17% of PNET patients (grade 3, 3%; grade 4, 0.5%), 14% of RCC patients (grade 3, 4%), 1% of RA/TSC patients, and 1% of SEGA patients. Monitor patients receiving everolimus for clinical symptoms or radiologic changes consistent with non-infectious pneumonitis. Patients who develop radiological changes suggestive of pneumonitis without accompanying symptomatology may continue to receive everolimus without dose modification; initiate appropriate monitoring in these patients. Everolimus therapy may need to be withheld and/or dose reduced in patients who develop moderate to severe noninfectious pneumonitis. In patients with life-threatening pneumonitis (ventilatory support indicated), discontinue everolimus treatment. Steroids may be indicated in patients with moderate to severe noninfectious pneumonitis. [49823]

Respiratory system adverse events have been reported with everolimus (Zortress, Afinitor) use in clinical trials. Cough was reported in 7% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Atelectasis, dyspnea, epistaxis, rhinorrhea, sinus and nasal congestion, and wheezing were reported in 1% to < 10% of everolimus (Zortress)-treated patients.[49903] In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with

exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, respiratory adverse effects (all grades) reported include cough/productive cough (PNET, 25%), cough (breast cancer, 24%; RCC, 30%; RA/TSC, 20%), epistaxis (breast cancer, 17%; PNET, 22%; RCC, 18%; RA/TSC, 9%; SEGA, 5%), dyspnea (breast cancer, 21%; PNET, 20%; RCC, 24%), oropharyngeal pain (PNET, 11%), pharyngolaryngeal pain (RCC, 4%), and rhinorrhea (RCC, 3%). Grade 3 or 4 dyspnea was reported in 4.2% of breast cancer patients, 2.5% of PNET patients, and 7% of RCC patients. Grade 3 cough occurred in 0.6% of breast cancer patients, in 0.5% of PNET patients, and in less than 1% of RCC patients.[49823]

Cardiovascular adverse effects have been reported with everolimus (Zortress, Afinitor) use in clinical trials. Hypertension was reported in 30% of de novo kidney transplant patients who received Zortress with reduced dose cyclosporine (n = 274) in a randomized trial. Angina pectoris, atrial fibrillation, congestive heart failure (CHF), palpitations, sinus tachycardia, hypertensive crisis, hypotension, and chest pain (unspecified) occurred in 1% to < 10% of Zortress-treated patients.[49903] In clinical studies, Afinitor has been evaluated in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, cardiovascular adverse effects (all grades) reported with Afinitor use include hypertension (PNET, 13%; RCC, 4%), chest pain (RCC, 5%), tachycardia (RCC, 3%), and CHF (RCC, 1%). Grade 3 or 4 hypertension was reported in 1% of patients with PNET.[49823]

Allergic reaction, including angioedema and anaphylactoid reactions, have been reported with everolimus (Zortress, Afinitor) use. Other symptoms of hypersensitivity reactions were dyspnea, flushing, and chest pain. Concomitant use with other drugs known to cause angioedema (e.g., angiotensin converting enzyme inhibitors) may increase the risk of a serious reaction. Patients who have experienced a hypersensitivity reaction to everolimus, sirolimus, or another rapamycin derivative (e.g., temsirolimus) should not receive Afinitor or Zortress.[49823][49903] Monitor patients receiving everolimus for symptoms of angioedema and treat the condition promptly.[49903] Hypersensitivity was reported with everolimus (Afinitor) use in 3% of patients with renal angiomyolipoma and tuberous sclerosis complex (n = 79) and in 3% of patients with subependymal giant cell astrocytoma (n = 78) in a randomized, placebo-controlled trials.[49823]

Dermatological adverse events have been reported with everolimus (Zortress, Afinitor) use in clinical trials. Alopecia, dermatitis acneiform (acneiform rash), hirsutism, hyperhidrosis, hypertrichosis, night sweats, pruritus, or rash (unspecified) were reported in 1% to < 10% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial.

[49903] In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, dermatological adverse effects (all grades) reported include rash (breast cancer, 39%; PNET, 59%; RCC, 29%; SEGA, 21%), onycholysis (PNET, 22%; RCC, 5%), pruritus (breast cancer, 13%; PNET, 21%; RCC, 14%), xerosis (PNET, 13%; RCC, 13%), alopecia (breast cancer, 10%), palmar-plantar erythrodysesthesia (hand and foot syndrome) (RCC, 5%), erythema (RCC, 4%), onychoclasis (RCC, 4%), skin lesion (RCC, 4%), dermatitis acneiform (RCC, 3%), and acne vulgaris (RA/TSC, 22%; SEGA, 10%). Grade 3 or 4 rash was reported in 1% of breast cancer patients, 0.5% of PNET patients, and 1% of RCC patients. Additionally, grade 3 pruritus occurred in 0.2% of breast cancer patients and in less than 1% of RCC patients; grade 3 onycholysis occurred in 0.5% of PNET patients. [49823]

Electrolyte laboratory abnormalities and other metabolic adverse effects have been reported with everolimus (Zortress, Afinitor) use in clinical trials. Hyperkalemia (18%), hypomagnesemia (14%), hypophosphatemia (13%), and hypokalemia (12%) were reported in de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Hypercalcemia, hypocalcemia, hyperphosphatemia, hyperuricemia, hyponatremia, hypoglycemia, increased blood urea, gout, metabolic acidosis, and dehydration occurred in 1% to < 10% of everolimus (Zortress)-treated patients.[49903] In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, laboratory abnormalities and metabolic adverse effects (all grades) reported include decreased bicarbonate levels (PNET, 56%), decreased phosphate levels (PNET, 40%; RCC, 37%) or hypophosphatemia (RA/TSC, 49%; SEGA,9%), decreased calcium levels (PNET, 37%), decreased potassium levels (breast cancer, 29%; PNET, 23%), decreased sodium levels (PNET, 16%), and increased potassium levels (PNET, 7%). Grade 3 or 4 decreased phosphate levels (PNET, 10%; RCC, 6%) or hypophosphatemia (RA/TSC, 5%; SEGA, 1%), decreased potassium levels (breast cancer, 4.2%; PNET, 4%), decreased sodium levels (PNET, 1%), and dehydration (RCC, >= 3%) were reported.[49823

Gastrointestinal adverse effects have been reported with everolimus (Zortress, Afinitor) use in clinical trials. Constipation (38%), nausea (29%), diarrhea (19%), vomiting (15%), abdominal pain (13%), dyspepsia (4%), and upper abdominal pain (3%) were reported in de novo kidney transplant patients who

received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Abdominal distention, dysphagia, epigastric discomfort, flatulence, gastroesophageal reflux disease, gingival hyperplasia, hematemesis, hemorrhoids, ileus, peritonitis, and anorexia occurred in 1% to < 10% of everolimus (Zortress)-treated patients.[49903] In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, gastrointestinal adverse effects (all grades) reported with everolimus (Afinitor) use include diarrhea (breast cancer, 33%; PNET, 50%; RCC, 30%; RA/TSC, 14%; SEGA, 17%), abdominal pain (PNET, 36%; RCC, 9%), nausea (breast cancer, 29%; PNET, 32%; RCC, 26%; SEGA, 8%), vomiting (breast cancer, 17%; PNET, 29%; RCC, 20%; RA/TSC, 15%; SEGA, 22%), constipation (breast cancer, 14%; PNET, 14%; SEGA, 10%), xerostomia (breast cancer, 11%; PNET, 11%; RCC, 8%), anorexia (breast cancer, 30%; PNET, 30%; RCC, 25%; RA/TSC, 6%), hemorrhoids (RCC, 5%), and dysphagia (RCC, 4%). Grade 3 or 4 diarrhea (breast cancer, 2.2%; PNET, 5.5%; RCC, 1%), abdominal pain (PNET, 4%), nausea (breast cancer, 0.4%; PNET, 2%; RCC, 1%), vomiting (breast cancer, 1%; PNET, 1%; RCC, 2%; SEGA, 1%), anorexia (breast cancer, 1%; PNET, 1%; RCC, 1%), and constipation (breast cancer, 0.4%) were reported.[49823]

Renal failure (unspecified), including acute renal failure, has been reported with everolimus (Zortress, Afinitor) use; some cases have been severe or fatal. Acute renal failure was reported in 1% to < 10% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Everolimus should not be used with standard dose cyclosporine due to the increased risk of nephrotoxicity resulting in a lower glomerular filtration rate. Reduced doses of cyclosporine are required for use in combination with everolimus in order to reduce renal dysfunction. Consider switching to other immunosuppressive therapies if renal function does not improve after dose adjustments or if the dysfunction is thought to be drug related. Use caution when using other drugs that are known to impair renal function. In a randomized trial, increased blood creatinine levels (18%), hematuria (12%) and dysuria (11%) were commonly reported with everolimus (Zortress) use. Other renal and urinary disorders occurring in 1% to < 10% of everolimus (Zortress)-treated patients include bladder spasm, hydronephrosis, urinary urgency, interstitial nephritis, pollakiuria, polyuria, pyuria, renal impairment, and urinary retention.[49903] In clinical studies,everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), and in 274 patients with metastatic renal cell carcinoma (RCC). Grade 3 or 4 renal failure was reported 2.9%of patients with PNET; additionally, renal failure occurred in 3% of patients with RCC. Elevated serum creatinine (SCr) levels were reported in 24% of patients with breast cancer (grade 3 or 4, 2.2%), 19% of PNET patients (grade 3 or 4, 2%), and 50% of RCC patients (grade 3, 1%) in these studies. Additionally, elevated SCr

levels occurred in 14% of patients with subependymal giant cell astrocytoma in an open-label trial (n = 28). Monitor renal function (e.g., blood urea nitrogen (BUN), SCr) prior to starting everolimus and periodically thereafter.[49823]

Reports of male infertility have been associated with mTOR inhibitors including everolimus. Everolimus is an anti-proliferative drug that affects rapidly dividing cells like the germ cells. Azoospermia or oligospermia may be observed. In male rats, testicular morphology was affected with everolimus doses of at least 0.5 mg/kg, and sperm motility, sperm head count, and plasma testosterone concentrations were diminished with doses of 5 mg/kg. Thirteen weeks after drug receipt, evidence of reversibility of these findings was noted. The 5 mg/kg dose in male rats resulted in systemic exposures approximately 5 times the systemic exposures in humans receiving 0.75 mg twice daily. The 0.5 mg/kg dose in male rats led to systemic exposures in the range of human clinical exposures. Impotence (erectile dysfunction) was reported in 5% of male de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine in a randomized trial. Although the mean testosterone and FSH concentrations remained within the normal range, the serum testosterone concentrations in the everolimus group significantly decreased, and the FSH concentrations significantly increased; no significant changes were noted in the control group. Another reproductive organ adverse effect reported in at least 1% to < 10% of Zortress-treated patients was ovarian cyst.[49903] Everolimus may also reduce female fertility. In female rats exposed to oral everolimus doses approximately 4% of the AUC (0—24 hours) in patients receiving a 10-mg daily dose (>= 0.1 mg/kg dose), there was an increase in pre-implantation loss. In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, amenorrhea (RA/TSC, 15%; SEGA, 17%), menorrhagia (RA/TSC, 10%; SEGA, 6%), menstrual irregularity (RA/TSC, 10%; SEGA, 6%), vaginal bleeding (RA/TSC, 8%), dysmenorrhea (SEGA, 6%), metrorrhagia (SEGA, 6%), and hot flashes (hot flush) (breast cancer, 6%). Additionally, 4% of patients with renal angiomyolipoma reported increased blood luteinizing hormone (LH) levels, while 3% experienced increased blood follicle stimulating hormone (FSH) levels; one percent of patients with SEGA also reported increased levels of LH.[49823]

The risk of thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP), or hemolytic-uremic syndrome (HUS) may be increased by the concomitant use of everolimus with cyclosporine. TMA, TTP, and HUS were reported in < 1% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Monitor hematologic parameters of patients taking everolimus.[49903]

Thromboembolic events have been reported with everolimus (Zortress, Afinitor) in clinical trials. Kidney and hepatic arterial thrombosis and kidney venous thrombosis, leading to graft loss, have been reported

with Zortress therapy; most cases occurred within 30 days of transplantation. Do not administer Zortress less than 30 days after liver transplant. Graft loss within a 12 month study period was reported in 4% of de novo kidney transplant patients who received Zortress with reduced dose cyclosporine (n = 274) in a randomized trial. Graft loss was due to renal artery thrombosis in 4 patients and due to renal vein thrombosis in 2 patients in this study. Deep vein thrombosis (DVT) and pulmonary embolism (PE) were reported in 1% to < 10% of Zortress-treated patients.[49903] DVT occurred in <1% of patients with metastatic renal cell carcinoma who received everolimus (Afinitor; n = 274) in a randomized, placebo-controlled trial. PE (2.5%) and thrombosis (1.5%) were reported in patients with advanced pancreatic neuroendocrine tumors who received everolimus (Afinitor; n = 204) in a randomized, placebo-controlled trial.[49823]

Impaired wound healing has been reported with everolimus (Zortress, Afinitor) use. Wound-related events, including lymphocele, seroma, hematoma, wound dehiscence, incisional hernia, and infections, were reported in 35% of de novo kidney transplant patients (n = 274) who received everolimus (Zortress) with reduced dose cyclosporine in a randomized trial. Additionally, there were more complications from intraoperative repair debridement or drainage of incisional wound and more required lymphocele or seroma drainage in patients who received everolimus (Zortress) compared with control patients. Adverse events that occurred in at least 1% but less than 10% of patients in this study included incision-site complications (including infections), perinephric collection, seroma, wound dehiscence, incisional hernia, perinephric hematoma, localized intraabdominal fluid collection, impaired healing, lymphocele, and lymphorrhea. Monitor patients for symptoms of impaired wound healing and treat the condition promptly. [49903] Impaired wound healing occurred in <1% of patients with metastatic renal cell carcinoma who received everolimus (Afinitor; n = 274) in a randomized, placebo-controlled trial.[49823]

Secondary malignancy, including lymphoma and skin cancer, has been reported with everolimus (Zortress) use. The risk of secondary malignancy may be due to the immunosuppressive effects of everolimus; the risk of developing a secondary malignancy appears to be related to the duration and dose of immunosuppression. Adverse events due to malignant or benign neoplasms occurred in 3% of de novo kidney transplant patients who received Zortress (n = 274) with reduced dose cyclosporine in a randomized trial. One patient who underwent a melanoma excision before transplantation died due to metastatic melanoma.[49903]

Cushingoid features and hyperparathyroidism were reported in 1% to < 10% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial.[49903]

Cataracts, conjunctivitis, and blurred vision occurred in 1% to < 10% of de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized

trial.[49903] Conjunctivitis (2%) and eyelid edema (4%) were reported in patients with metastatic renal cell carcinoma who received Afinitor (n = 274) in a randomized, placebo-controlled trial.[49823]

Musculoskeletal adverse effects have been reported with everolimus (Zortress, Afinitor) use in clinical trials. Extremity pain (12%) and back pain (11%) were reported in de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Arthralgia, joint swelling, muscle spasms, muscular weakness, musculoskeletal pain, myalgia, osteonecrosis, osteopenia, osteoporosis, or spondylitis occurred in 1% to < 10% of everolimus (Zortress)-treated patients. [49903] In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, musculoskeletal adverse effects (all grades) reported include arthralgia (breast cancer, 20%; PNET, 15%; RA/TSC, 13%), back pain (breast cancer, 14%; PNET, 15%), extremity pain (breast cancer, 9%; PNET, 14%; RCC, 10%; SEGA, 8%), muscle spasms (PNET, 10%), and jaw pain (RCC, 3%). Grade 3 or 4 arthralgia (breast cancer, 0.8%; PNET, 1.5%), back pain (breast cancer, 0.2%; PNET, 1%), extremity pain (breast cancer, 0.4%; PNET, 0.5% RCC, 1%) were reported.[49823]

Seizures have been reported with everolimus (Afinitor) use. In clinical studies, everolimus (Afinitor) has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). Central nervous system (CNS) effects reported in these studies include headache/migraine (PNET, 30%), dysgeusia (breast cancer, 22%; PNET, 19%; RCC, 10%; RA/TSC, 5%), headache (breast cancer, 21%; RCC, 19%), dizziness (PNET, 12%; RCC, 7%), paresthesias (RCC, 5%). Grade 3 and 4 headache/migraine (PNET, 0.5%), dysgeusia (breast cancer, 0.2%), headache (breast cancer, 0.4%; RCC, < 1%), and dizziness (PNET, 0.5%).[49823] Headache (18%) and tremor (8%) were reported in de novo kidney transplant patients who received everolimus (Zortress) with reduced dose cyclosporine (n = 274) in a randomized trial. Other CNS reported in 1% to < 10% of everolimus (Zortress)-treated patients include dizziness, (hemi) paresis, hypoesthesia, paresthesia, drowsiness, and syncope. [49903]

Hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia, requiring drug therapy has been reported with everolimus (Zortress, Afinitor) use in clinical studies; the risk may be greater with

higher everolimus trough levels. Hyperlipidemia (21%), hypercholesterolemia (17%), and dyslipidemia (15%) were commonly reported in 274 de novo kidney transplant patients who received Zortress with reduced dose cyclosporine in a randomized trial. Hypertriglyceridemia occurred in 1% to < 10% of patients in this study. Monitor lipids prior to and during Zortress therapy; start lipid lowering therapy as indicated; however, anti-lipid therapy may not normalize lipid levels in patients receiving Zortress. Reevaluate the use of Zortress in patients with severe refractory hyperlipidemia.[49903] In clinical studies, Afinitor has been evaluated in 482 patients with advanced hormone-receptor positive, HER2-negative breast cancer (in combination with exemestane), in 204 patients with advanced pancreatic neuroendocrine tumors (PNET), in 274 patients with metastatic renal cell carcinoma (RCC), in 79 patients with renal angiomyolipoma and tuberous sclerosis complex (RA/TSC), and in 78 patients (mean age, 9.5 years; range, 0.8—26 years) with subependymal giant cell astrocytoma (SEGA). In these studies, adverse effects (all grades) reported with Afinitor use include elevated cholesterol levels (breast cancer, 70%; PNET, 66%; RCC, 77%; SEGA, 68%) or hypercholesterolemia (RA/TSC, 85%; SEGA, 81%) and elevated triglyceride levels (breast cancer, 50%; PNET, 39%; RCC, 73%; SEGA, 43%) or hypertriglyceridemia (RA/TSC, 52%; SEGA, 27%). Grade 3 or 4 elevated cholesterol levels were reported in 0.8% of breast cancer patients and 4% of RCC patients. Grade 3 hypercholesterolemia was reported in 1% of RA/TSC patients. Grade 3 elevated triglyceride levels were reported in 0.8% of breast cancer patients. Monitor lipids prior to and periodically during Afinitor therapy; start lipid lowering therapy as indicated. No dosage adjustment is necessary in patients who develop grade 1 or 2 metabolic events including dyslipidemia. Hold therapy and restart at a reduced dose if a patient develops grade 3 metabolic events. Discontinue therapy in patients who develop grade 4 (life-threatening) metabolic events.