Everolimus: Drug information

(For additional information see "Everolimus: Patient drug information" and see "Everolimus: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Immunosuppression (Zortress):

Increased susceptibility to infection and the possible development of malignancies, such as lymphoma and skin cancer, may result from immunosuppression.

Only health care providers experienced in immunosuppressive therapy and management of transplant patients should use everolimus. Manage patients receiving the drug in facilities equipped and staffed with adequate laboratory and supportive medical resources. The health care provider responsible for maintenance therapy should have complete information requisite for the follow-up.

Renal graft thrombosis (Zortress):

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, was reported, mostly within the first 30 days post-transplantation.

Nephrotoxicity (Zortress):

Increased nephrotoxicity can occur with use of standard doses of cyclosporine in combination with everolimus. Therefore, use reduced doses of cyclosporine in combination with everolimus in order to reduce renal dysfunction. It is important to monitor the cyclosporine and everolimus whole blood trough concentrations.

Mortality in heart transplant (Zortress):

Increased mortality, often associated with serious infection, within the first 3 months of post-transplantation was observed in a clinical trial of de novo heart transplant patients receiving immunosuppressive regimens with or without induction therapy. Use in heart transplantation is not recommended.

Brand Names: US

Afinitor; Afinitor Disperz; Zortress

Brand Names: Canada

Afinitor; Afinitor Disperz

Pharmacologic Category

Antineoplastic Agent, mTOR Kinase Inhibitor; Immunosuppressant Agent; mTOR Kinase Inhibitor

Dosing: Adult

Note: Tablets (Afinitor, Zortress) and tablets for oral suspension (Afinitor Disperz) are not interchangeable; Afinitor Disperz is only indicated for the treatment of subependymal giant cell astrocytoma (SEGA), in conjunction with therapeutic monitoring. Do not combine formulations to achieve total desired dose.

Breast cancer, advanced, hormone receptor-positive, HER2-negative: Oral: 10 mg once daily (in combination with exemestane), continue treatment until disease progression or unacceptable toxicity

Neuroendocrine tumors (GI, lung, or pancreatic origin), advanced: Oral: 10 mg once daily, continue treatment until disease progression or unacceptable toxicity

Renal angiomyolipoma: Oral: 10 mg once daily, continue treatment until disease progression or unacceptable toxicity

Renal cell cancer, advanced (RCC): Oral: 10 mg once daily, continue treatment until disease progression or unacceptable toxicity

Renal cell carcinoma, advanced (off-label dose/combination): Oral: 5 mg once daily (in combination with lenvatinib), continue until disease progression or unacceptable toxicity (Motzer 2015)

Liver transplantation, rejection prophylaxis (begin at least 30 days post-transplant): Oral: Initial: 1 mg twice daily; adjust maintenance dose if needed at a 4- to 5-day interval (from prior dose adjustment) based on serum concentrations, tolerability, and response; goal serum concentration is between 3 and 8 ng/mL (based on an LC/MS/MS assay method). If trough is <3 ng/mL, double total daily dose (using available tablet strengths); if trough >8 ng/mL on 2 consecutive measures, decrease dose by 0.25 mg twice daily. Administer in combination with tacrolimus (reduced dose required) and corticosteroids

Renal transplantation, rejection prophylaxis: Oral: Initial: 0.75 mg twice daily; adjust maintenance dose if needed at a 4- to 5-day interval (from prior dose adjustment) based on serum concentrations, tolerability, and response; goal serum concentration is between 3 and 8 ng/mL (based on an LC/MS/MS assay method). If trough is <3 ng/mL, double total daily dose (using available tablet strengths); if trough >8 ng/mL on 2 consecutive measures, decrease dose by 0.25 mg twice daily. Administer in combination with basiliximab induction and concurrently with cyclosporine (dose adjustment required) and corticosteroids

Subependymal giant cell astrocytoma (SEGA; dosing based on body surface area [BSA]): Oral:
Note: Continue until disease progression or unacceptable toxicity.

Initial dose: 4.5 mg/m^2 once daily; round to nearest tablet (tablet or tablet for oral suspension) size.

If trough <5 ng/mL: Increase dose by 2.5 mg daily (tablets) or 2 mg daily (tablets for oral suspension).

If trough >15 ng/mL: Reduce dose by 2.5 mg daily (tablets) or 2 mg daily (tablets for oral suspension). If dose reduction necessary in patients receiving the lowest strength available, administer every other day.

Therapeutic drug monitoring: Assess trough concentration ~2 weeks after initiation or with dosage

modifications, initiation or changes to concurrent CYP3A4/P-glycoprotein (P-gp) inhibitor/inducer therapy, changes in hepatic impairment, or when changing dosage forms between tablets and tablets for oral suspension; adjust maintenance dose if needed at 2-week intervals to achieve and maintain trough concentrations between 5 and 15 ng/mL; once stable dose is attained and if BSA is stable throughout treatment, monitor trough concentrations every 6 to 12 months (monitor every 3 to 6 months if BSA is changing).

Carcinoid tumors, advanced (off-label use): Oral: 10 mg once daily (in combination with octreotide LAR) until disease progression or toxicity (Pavel 2010)

Heart transplantation (≥3 months post-transplantation) (off-label use): Oral: 0.75 mg twice daily (in combination with reduced dose cyclosporine and a corticosteroid); adjust everolimus dose based on everolimus trough concentrations (Eisen 2003; Eisen 2013; Hollis 2015)

Waldenström macroglobulinemia, relapsed or refractory (off-label use): Oral: 10 mg once daily until disease progression or toxicity (Ghobrial 2010)

Dosage adjustment for concomitant CYP3A4 inhibitors/inducers and/or P-gp inhibitors:

Breast cancer, neuroendocrine tumors, RCC, renal angiomyolipoma:

CYP3A4/P-gp inducers: Strong inducers: Avoid coadministration with strong CYP3A4/P-gp inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort); if concomitant use cannot be avoided, consider doubling the everolimus dose, using increments of 5 mg or less, with careful monitoring. If the strong CYP3A4/P-gp enzyme inducer is discontinued, consider allowing 3 to 5 days to elapse prior to reducing the everolimus to the dose used prior to initiation of the CYP3A4/P-gp inducer.

CYP3A4/P-gp inhibitors:

Strong inhibitors: Avoid concomitant administration with strong CYP3A4/P-gp inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole).

Moderate CYP3A4/P-gp inhibitors (eg, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil): Reduce everolimus dose to 2.5 mg once daily; may consider increasing from 2.5 mg to 5 mg once daily based on patient tolerance. When the moderate inhibitor is discontinued, allow ~2 to 3 days to elapse prior to adjusting the everolimus upward to the recommended starting dose or to the dose used prior to initiation of the moderate inhibitor.

Renal transplantation: Dosage adjustments may be necessary based on everolimus serum concentrations

SEGA:

CYP3A4/P-gp inducers: Strong inducers: Avoid concomitant administration with strong CYP3A4/P-gp inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St John's wort); if concomitant use cannot be avoided, an initial starting everolimus dose of 9 mg/m^2 once daily is recommended, or, double the everolimus dose and assess tolerability; assess trough concentration after ~2 weeks; adjust dose as necessary based on therapeutic drug monitoring to maintain target trough concentrations of 5 to 15 ng/mL. If the strong CYP3A4 enzyme inducer is

discontinued, reduce the everolimus dose by ~50% or to the dose used prior to initiation of the CYP3A4/P-gp inducer; reassess trough concentration after ~2 weeks.

CYP3A4/P-gp inhibitors:

Strong inhibitors: Avoid concomitant administration with strong CYP3A4/P-gp inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole).

Moderate CYP3A4/P-gp inhibitors (eg, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil):

Currently taking a moderate CYP3A4/P-gp inhibitor and starting everolimus: 2.5 mg/m^2 once daily.

Currently taking everolimus and starting a moderate CYP3A4/P-gp inhibitor: Reduce everolimus dose by ~50%; if dose reduction is required for patients receiving the lowest strength available, administer every other day.

Discontinuing a moderate CYP3A4/P-gp inhibitor after concomitant use with everolimus: Discontinue moderate inhibitor and allow 2 to 3 days to elapse prior to resuming the everolimus dose used prior to initiation of the moderate inhibitor.

Therapeutic drug monitoring: Assess trough concentration ~2 weeks after everolimus initiation or dosage modifications, or initiation or changes to concurrent CYP3A4/P-gp inhibitor therapy; adjust maintenance dose if needed at 2-week intervals to achieve and maintain trough concentrations between 5 and 15 ng/mL.

Dosing: Pediatric

(For additional information see "Everolimus: Pediatric drug information")

Note: Tablets (Afinitor, Zortress) and tablets for oral suspension (Afinitor Disperz) are not interchangeable. Do not combine formulations to achieve total desired dose.

Subependymal giant cell astrocytoma (SEGA): Children ≥1 year: Refer to adult dosing.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

No dosage adjustment is necessary.

Dosing: Hepatic Impairment

Mild impairment (Child-Pugh class A):

Breast cancer, neuroendocrine tumors, RCC, renal angiomyolipoma: Reduce dose to 7.5 mg once daily; if not tolerated, may further reduce to 5 mg once daily.

Liver or renal transplantation: Reduce initial dose by ~33%; individualize subsequent dosing based on therapeutic drug monitoring (target trough concentration: 3 to 8 ng/mL).

SEGA: Adjustment to initial dose may not be necessary; subsequent dosing is based on therapeutic drug monitoring (monitor ~2 weeks after initiation, dosage modifications, or after any change in hepatic status;

target trough concentration: 5 to 15 ng/mL).

Moderate impairment (Child-Pugh class B):

Breast cancer, neuroendocrine tumors, RCC, renal angiomyolipoma: Reduce dose to 5 mg once daily; if not tolerated, may further reduce to 2.5 mg once daily.

Liver or renal transplantation: Reduce initial dose by ~50%; individualize subsequent dosing based on therapeutic drug monitoring (target trough concentration: 3 to 8 ng/mL).

SEGA: Adjustment to initial dose may not be necessary; subsequent dosing is based on therapeutic drug monitoring (monitor ~2 weeks after initiation, dosage modifications, or after any change in hepatic status; target trough concentration: 5 to 15 ng/mL).

Severe impairment (Child-Pugh class C):

Breast cancer, neuroendocrine tumors, RCC, renal angiomyolipoma: If potential benefit outweighs risks, a maximum dose of 2.5 mg once daily may be used.

Liver or renal transplantation: Reduce initial dose by ~50%; individualize subsequent dosing based on therapeutic drug monitoring (target trough concentration: 3 to 8 ng/mL).

SEGA: Reduce initial dose to 2.5 mg/m^2 once daily (or current dose by ~50%); subsequent dosing is based on therapeutic drug monitoring (monitor ~2 weeks after initiation, dosage modifications, or after any change in hepatic status; target trough concentration: 5 to 15 ng/mL).

Dosing: Adjustment for Toxicity

Breast cancer (adjustments apply to everolimus), neuroendocrine tumors, RCC, renal angiomyolipoma, SEGA: Toxicities may require temporary dose interruption (with or without a subsequent dose reduction) or discontinuation; reduce everolimus dose by ~50% if dosage adjustment is necessary:

Noninfectious pneumonitis:

Grade 1 (asymptomatic radiological changes suggestive of pneumonitis): No dosage adjustment is necessary; monitor appropriately.

Grade 2 (symptomatic but not interfering with activities of daily living [ADL]): Consider interrupting treatment, rule out infection, and consider corticosteroids until symptoms improve to ≤grade 1; reinitiate at a lower dose. Discontinue if recovery does not occur within 4 weeks.

Grade 3 (symptomatic, interferes with ADL; oxygen indicated): Interrupt treatment until symptoms improve to ≤grade 1; rule out infection and consider corticosteroid treatment; may reinitiate at a lower dose. If grade 3 toxicity recurs, consider discontinuing.

Grade 4 (life-threatening; ventilatory support indicated): Discontinue treatment; rule out infection; consider corticosteroid treatment.

Stomatitis (avoid the use of products containing alcohol, hydrogen peroxide, iodine, or thyme derivatives):

Grade 1 (minimal symptoms, normal diet): No dosage adjustment is necessary; manage with mouth wash (nonalcoholic or isotonic salt water) several times a day

Grade 2 (symptomatic but can eat and swallow modified diet): Interrupt treatment until symptoms improve to ≤grade 1; reinitiate at same dose; if stomatitis recurs at grade 2, interrupt treatment until symptoms improve to ≤grade 1 and then reinitiate at a lower dose. Also manage with topical (oral) analgesics (eg, benzocaine, butyl aminobenzoate, tetracaine, menthol, or phenol) ± topical (oral) corticosteroids (eg, triamcinolone).

Grade 3 (symptomatic and unable to orally aliment or hydrate adequately): Interrupt treatment until symptoms improve to ≤grade 1; then reinitiate at a lower dose. Also manage with topical (oral) analgesics (eg, benzocaine, butyl aminobenzoate, tetracaine, menthol, or phenol) ± topical (oral) corticosteroids (eg, triamcinolone).

Grade 4 (life-threatening symptoms): Discontinue treatment; initiate appropriate medical intervention.

Metabolic toxicity (eg, hyperglycemia, dyslipidemia):

Grade 1: No dosage adjustment is necessary; initiate appropriate medical intervention and monitor.

Grade 2: No dosage adjustment is necessary; manage with appropriate medical intervention and monitor.

Grade 3: Temporarily interrupt treatment; reinitiate at a lower dose; manage with appropriate medical intervention and monitor.

Grade 4: Discontinue treatment; manage with appropriate medical intervention.

Nonhematologic toxicities (excluding pneumonitis, stomatitis, or metabolic toxicity):

Grade 1: If toxicity is tolerable, no dosage adjustment is necessary; initiate appropriate medical intervention and monitor.

Grade 2: If toxicity is tolerable, no dosage adjustment is necessary; initiate appropriate medical intervention and monitor. If toxicity becomes intolerable, temporarily interrupt treatment until improvement to ≤grade 1 and reinitiate at the same dose; if toxicity recurs at grade 2, temporarily interrupt treatment until improvement to ≤ grade 1 and then reinitiate at a lower dose.

Grade 3: Temporarily interrupt treatment until improvement to ≤grade 1; initiate appropriate medical intervention and monitor. May reinitiate at a lower dose; if toxicity recurs at grade 3, consider discontinuing.

Grade 4 (life-threatening symptoms): Discontinue treatment; initiate appropriate medical intervention.

Liver or renal transplantation:

Evidence of polyoma virus infection or PML: Consider reduced immunosuppression (taking into account the allograft risks associated with decreased immunosuppression)

Pneumonitis (grade 4 symptoms) or invasive systemic fungal infection: Discontinue

SEGA: *Severe/intolerable adverse reactions:* Temporarily interrupt or permanently discontinue treatment; if dose reduction is required upon reinitiation, reduce dose by ~50%; if dose reduction is

required for patients receiving the lowest available strength, consider alternate-day dosing.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Afinitor: 2.5 mg, 5 mg, 7.5 mg, 10 mg

Zortress: 0.25 mg, 0.5 mg, 0.75 mg

Tablet Soluble, Oral:

Afinitor Disperz: 2 mg, 3 mg, 5 mg

Generic Equivalent Available (US) No

Medication Guide and/or Vaccine Information Statement (VIS) An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication;

Zortress: http://www.pharma.us.novartis.com/product/pi/pdf/zortress_pmg.pdf

Administration May be taken with or without food; to reduce variability, take consistently with regard to food. Afinitor missed doses may be taken up to 6 hours after regularly scheduled time; if >6 hours, resume at next regularly scheduled time.

Tablets: Swallow whole with a glass of water. Do not break, chew, or crush (do not administer tablets that are crushed or broken). Avoid contact with or exposure to crushed or broken tablets.

Tablets for oral suspension: Administer as a suspension only. Administer immediately after preparation; discard if not administered within 60 minutes after preparation. Prepare suspension in water only. Do not break or crush tablets.

Preparation in an oral syringe: Place dose into 10 mL oral syringe (maximum: 10 mg/syringe; use an additional syringe for doses >10 mg). Draw ~5 mL of water and ~4 mL of air into oral syringe; allow to sit (tip up) in a container until tablets are in suspension (3 minutes). Gently invert syringe 5 times immediately prior to administration; administer contents, then add ~5 mL water and ~4 mL of air to same syringe, swirl to suspend remaining particles and administer entire contents.

Preparation in a small glass: Place dose into a small glass (≤100 mL) containing ~25 mL water (maximum: 10 mg/glass; use and additional glass for doses >10 mg); allow to sit until tablets are in suspension (3 minutes). Stir gently with spoon immediately prior to administration; administer contents, then add ~25 mL water to same glass, swirl with same spoon to suspend remaining particles and administer entire contents.

Breast cancer, neuroendocrine tumors, renal cell cancer, renal angiolipoma, SEGA: Administer at the same time each day.

Liver or renal transplantation: Administer consistently ~12 hours apart; administer at the same time as tacrolimus or cyclosporine.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016).

Use

Breast cancer, advanced (Afinitor only): Treatment of advanced hormone receptor-positive, HER2-negative breast cancer in postmenopausal women (in combination with exemestane and after letrozole or anastrozole failure)

Neuroendocrine tumors (Afinitor only): Treatment of locally advanced, metastatic or unresectable progressive pancreatic neuroendocrine tumors (PNET); treatment of progressive, well-differentiated, nonfunctional GI or lung neuroendocrine tumors in patients with unresectable, locally advanced or metastatic disease

Limitations of use: Not indicated for the treatment of functional carcinoid tumors.

Renal angiomyolipoma with tuberous sclerosis complex (Afinitor only): Treatment of renal angiomyolipoma with tuberous sclerosis complex (TSC) not requiring immediate surgery

Renal cell carcinoma, advanced (Afinitor only): Treatment of advanced renal cell cancer (RCC) after sunitinib or sorafenib failure

Subependymal giant cell astrocytoma (Afinitor or Afinitor Disperz only): Treatment of subependymal giant cell astrocytoma (SEGA) associated with TSC which requires intervention, but cannot be curatively resected

Liver transplantation (Zortress only): Prophylaxis of allograft rejection in liver transplantation (in combination with corticosteroids and reduced doses of tacrolimus, everolimus should not be administered earlier than 30 days post-transplant)

Renal transplantation (Zortress only): Prophylaxis of organ rejection in renal transplant patients at low to moderate immunologic risk (in combination with basiliximab induction and concurrent with corticosteroids and reduced doses of cyclosporine)

Use: Off-Label

Carcinoid tumors (progressive, advanced); Heart transplantation (≥3 months post-transplantation); Waldenström macroglobulinemia (relapsed or refractory)

Medication Safety Issues

Sound-alike/look-alike issues:

Everolimus may be confused with sirolimus, tacrolimus, temsirolimus

Afinitor may be confused with afatinib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Administration issues:

Tablets (Afinitor, Zortress) and tablets for oral suspension (Afinitor Disperz) are not interchangeable; do not combine formulations to achieve total desired dose.

Adverse Reactions

Transplantation:

Reactions occur in kidney and liver transplantation unless otherwise specified.

>10%:

Cardiovascular: Peripheral edema (kidney transplant: 45%; liver transplant: 18%), hypertension (kidney transplant: 30%; liver transplant: 17%)

Central nervous system: Headache (18% to 19%), insomnia (kidney transplant: 17%), procedural pain (kidney transplant: 15%)

Endocrine & metabolic: Diabetes mellitus (new onset: liver transplant: 32%; kidney transplant: 9%), hypercholesterolemia (15% to 24%), hyperkalemia (renal transplant: 18%), hypomagnesemia (kidney transplant: 14%), hypophosphatemia (kidney transplant: 13%), hyperglycemia (kidney transplant: 12%), hypokalemia (kidney transplant: 12%)

Gastrointestinal: Constipation (kidney transplant: 38%), nausea (kidney transplant: 29%; liver transplant: 14%), diarrhea (19%), vomiting (kidney transplant: 15%), abdominal pain (13%)

Genitourinary: Urinary tract infection (kidney transplant: 22%), hematuria (kidney transplant: 12%), dysuria (kidney transplant: 11%)

Hematologic & oncologic: Anemia (kidney transplant: 26%), leukopenia (3% to 12%)

Infection: Infection (kidney transplant: 62%; liver transplant: 50%), viral infection (liver transplant: 17%; kidney transplant: 10%), bacterial infection (liver transplant: 16%), hepatitis C (liver transplant: 11%)

Local: Incisional pain (kidney transplant: 16%)

Neuromuscular & skeletal: Limb pain (kidney transplant: 12%), back pain (kidney transplant: 11%)

Renal: Increased serum creatinine (kidney transplant: 18%)

Respiratory: Upper respiratory tract infection (kidney transplant: 16%)

Miscellaneous: Postoperative wound complication (kidney transplant: 35%; liver transplant: 11%; includes incisional hernia, lymphocele, seroma, wound dehiscence), fever (13% to 19%)

1% to 10%:

Cardiovascular: Hypertensive crisis (1%), angina pectoris, atrial fibrillation, chest discomfort, chest pain, congestive heart failure, deep vein thrombosis, edema, hypotension, palpitations, pulmonary embolism, renal artery thrombosis, syncope, tachycardia, venous thromboembolism

Central nervous system: Fatigue (9%), agitation, anxiety, chills, depression, dizziness, drowsiness, hallucination, hemiparesis, hypoesthesia, lethargy, malaise, migraine, myasthenia, neuralgia, pain, paresthesia

Dermatologic: Acneiform eruption, acne vulgaris, alopecia, cellulitis, diaphoresis, folliculitis, hypertrichosis, night sweats, onychomycosis, pruritus, skin rash, tinea pedis

Endocrine & metabolic: Acidosis, amenorrhea, cushingoid appearance, cyanocobalamin deficiency, dehydration, fluid retention, gout, hirsutism, hypercalcemia, hyperparathyroidism, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypoglycemia, hyponatremia, iron deficiency, ovarian cyst

Gastrointestinal: Stomatitis (kidney transplant: 8%), dyspepsia (kidney transplant: 4%), upper abdominal pain (kidney transplant: 3%), abdominal distention, anorexia, decreased appetite, dysphagia, epigastric distress, flatulence, gastroenteritis, gastroesophageal reflux disease, gingival hyperplasia, hematemesis, hemorrhoids, intestinal obstruction, oral candidiasis, oral herpes, oral mucosa ulcer, peritoneal effusion, peritonitis

Genitourinary: Erectile dysfunction (kidney transplant: 5%), bladder spasm, perinephric abscess, perinephric hematoma, pollakiuria, proteinuria, pyuria, scrotal edema, urethritis, urinary retention, urinary urgency

Hematologic & oncologic: Neoplasm (3% to 4%), leukocytosis, lymphadenopathy, lymphorrhea, neutropenia, pancytopenia, thrombocythemia, thrombocytopenia

Hepatic: Abnormal hepatic function tests (liver transplant: 7%), ascites (liver transplant: 4%), hepatitis (noninfections), increased liver enzymes, increased serum alkaline phosphatase, increased serum bilirubin

Hypersensitivity: Angioedema (<1%)

Infection: BK virus (kidney transplant: 1%), bacteremia, candidiasis, herpes virus infection, influenza, sepsis, wound infection

Neuromuscular & skeletal: Tremor (8% to 9%), arthralgia, joint swelling, muscle spasm, musculoskeletal pain, myalgia, osteomyelitis, osteonecrosis, osteoporosis, spondylitis, weakness

Ophthalmic: Blurred vision, cataract, conjunctivitis

Renal: Hydronephrosis, increased blood urea nitrogen, interstitial nephritis, polyuria, pyelonephritis, renal failure (acute), renal insufficiency, renal tubular necrosis

Respiratory: Cough (kidney transplant: 7%), atelectasis, bronchitis, dyspnea, epistaxis, lower respiratory tract infection, nasal congestion, nasopharyngitis, oropharyngeal pain, pleural effusion, pneumonia, pulmonary edema, rhinorrhea, sinus congestion, sinusitis, wheezing

Antineoplastic:

Antineoplastic indications include advanced hormone receptor-positive, advanced nonfunctional NET of gastrointestinal or lung origin, HER2-negative breast cancer (advanced HR + BC), pancreatic neuroendocrine tumors (PNET), renal cell carcinoma (RCC), renal angiomyolipoma and tuberous sclerosis complex (TSC), and subependymal giant cell astrocytoma (SEGA)

>10%:

Cardiovascular: Edema (PNET: ≤39%), peripheral edema (advanced nonfunctional NET of gastrointestinal or lung origin, PNET: ≤39%; advanced HR + BC, RCC, TSC: 13% to 25%), hypertension (PNET, RCC, SEGA: 4% to 13%)

Central nervous system: Malaise (PNET: ≤45%), fatigue (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC: 31% to ≤45%; SEGA: 14%), headache (PNET: ≤30%; advanced HR + BC, RCC: 19% to 21%), migraine (PNET: ≤30%), behavioral problems (SEGA: 21%; includes abnormal behavior, aggressive behavior, agitation, anxiety, obsessive compulsive symptoms, panic attack), insomnia (advanced HR + BC, PNET, RCC, SEGA: 6% to 14%), dizziness (PNET, RCC: 7% to 12%)

Dermatologic: Skin rash (PNET: 59%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, RCC, SEGA: 21% to 39%; may include allergic dermatitis, macular eruption, maculopapular rash, papular rash, urticaria), cellulitis (SEGA: 29%), acne vulgaris (TSC: 22%; SEGA: 10%), nail disease (PNET: 22%; RCC: 5%), pruritus (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC: 13% to 21%), xeroderma (PNET, RCC: 13%)

Endocrine & metabolic: Hypercholesterolemia (TSC, SEGA: 81% to 85%; advanced nonfunctional NET of gastrointestinal or lung origin: 71%), decreased serum bicarbonate (PNET: 56%), hyperglycemia (advanced nonfunctional NET of gastrointestinal or lung origin: 55%; SEGA: 25%; advanced HR + BC: 14%), hypertriglyceridemia (TSC: 52%; advanced nonfunctional NET of gastrointestinal or lung origin, SEGA: 27% to 30%), hypophosphatemia (advanced nonfunctional NET of gastrointestinal or lung origin, TSC: 43% to 49%; SEGA: 9%), decreased serum calcium (PNET: 37%), hypokalemia (advanced nonfunctional NET of gastrointestinal or lung origin: 27%), hypoalbuminemia (advanced nonfunctional NET of gastrointestinal or lung origin: 18%), amenorrhea (TSC, SEGA: 15% to 17%)

Gastrointestinal: Stomatitis (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, SEGA, TSC: 62% to 78%; advanced nonfunctional NET of gastrointestinal or lung origin grade 3: 9%; grades 3/4: ≤9%; RCC: 44%, grades 3/4: ≤4%), diarrhea (advanced nonfunctional NET of gastrointestinal or lung origin, PNET: 41% to 50%; advanced HR + BC, RCC: 30% to 33%; TSC, SEGA: 14% to 17%; may include bowel urgency, colitis, enteritis, enterocolitis, steatorrhea), abdominal pain (PNET: 36%; RCC, SEGA: 5% to 9%), decreased appetite (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET: 22% to 30%; TSC:

6%), nausea (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, RCC: 26% to 29%; SEGA: 8%), vomiting (15% to 29%), weight loss (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET: 22% to 28%; RCC: 9%; SEGA: 5%), anorexia (RCC: 25%), dysgeusia (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET: 18% to 22%; RCC: 10%; TSC: 5%), mucositis (RCC: 19%; grades 3/4: ≤1%), constipation (advanced HR + BC, PNET, SEGA: 10% to 14%), xerostomia (advanced HR + BC, PNET, RCC: 8% to 11%)

Genitourinary: Urinary tract infection (PNET: 16%; advanced HR + BC, RCC: 5% to 10%), irregular menses (TSC, PNET: 10% to 11%)

Hematologic & oncologic: Increase in fasting plasma glucose (PNET: 75%, grades 3/4: 17%; TSC: 14%), prolonged partial thromboplastin time (SEGA: 72%), anemia (advanced nonfunctional NET of gastrointestinal or lung origin: 81%; TSC: 61%; SEGA: 41%; advanced nonfunctional NET of gastrointestinal or lung origin grade 3: 5%), lymphocytopenia (advanced nonfunctional NET of gastrointestinal or lung origin: 66%, grade 3:15%, grade 4: 2%; TSC: 20%, grade 3: 1%), thrombocytopenia (advanced nonfunctional NET of gastrointestinal or lung origin: 33%; RCC, TSC: 19%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin grade 3: 2%; advanced nonfunctional NET of gastrointestinal or lung origin grade 4: 1%), leukopenia (advanced nonfunctional NET of gastrointestinal or lung origin: 49%; TSC: 37%; advanced nonfunctional NET of gastrointestinal or lung origin grade 3: 2%), neutropenia (SEGA: 46%, grade 3: 9%; advanced nonfunctional NET of gastrointestinal or lung origin: 32%)

Hepatic: Increased serum alkaline phosphatase (PNET: 74%; TSC: 32%, grade 3: 1%), increased serum AST (advanced HR + BC: 69%; advanced nonfunctional NET of gastrointestinal or lung origin, PNET: 56% to 57%; RCC, TSC, SEGA: 23% to 33%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, RCC, TSC grade 3: ≤4%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, RCC grade 4: ≤1%), increased serum ALT (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET: 46% to 51%, RCC, TSC, SEGA: 18% to 21%; advanced nonfunctional NET of gastrointestinal or lung origin grade 3: 5%; RCC, TSC grade 3: 1%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin grade 4: ≤1%)

Infection: Infection (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin: 50% to 58%; RCC: 37%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, RCC grade 3: 4% to 8%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, RCC grade 4: 1% to 3%)

Neuromuscular & skeletal: Weakness (RCC: 33%; advanced nonfunctional NET of gastrointestinal or lung origin: 23%; advanced HR + BC: 13%), arthralgia (advanced HR + BC, PNET, TSC: 13% to 20%), back pain (advanced HR + BC, PNET: 14% to 15%), limb pain (PNET, RCC, SEGA: 8% to 14%)

Renal: Increased serum creatinine (RCC: 50%; advanced HR + BC, PNET: 19% to 24%, advanced HR + BC, RCC grade 3: 1% to 2%, PNET grades 3/4: 2%)

Respiratory: Respiratory tract infection (SEGA: 31%, grade 3: 1%, grade 4: 1%; includes viral respiratory tract infection), cough (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC, TSC: 20% to 30%; includes productive cough), nasopharyngitis (PNET: ≤25%; advanced HR + BC, RCC: 6% to 10%), rhinitis (PNET: ≤25%), upper respiratory tract infection (PNET: ≤25%; TSC: 11%; advanced HR + BC: 5%), dyspnea (advanced

HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC: 20% to 24%; includes dyspnea on exertion), epistaxis (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC, TSC, SEGA: 5% to 22%), pneumonitis (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC: 14% to 19%; TSC, SEGA: 1%; advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC grade 3: 2% to 4%; advanced HR + BC, PNET grade 4: <1%; may include interstitial pulmonary disease, pulmonary alveolar hemorrhage, pulmonary alveolitis, pulmonary fibrosis, pulmonary infiltrates, pulmonary toxicity, restrictive pulmonary disease), oropharyngeal pain (PNET: 11%)

Miscellaneous: Fever (advanced HR + BC, advanced nonfunctional NET of gastrointestinal or lung origin, PNET, RCC, SEGA: 15% to 31%)

1% to 10%:

Cardiovascular: Chest pain (RCC: 5%), tachycardia (RCC: 3%), congestive heart failure (RCC: 1%), deep vein thrombosis (RCC: <1%)

Central nervous system: Depression (TSC: 5%), paresthesia (RCC: 5%), chills (RCC: 4%)

Dermatologic: Alopecia (advanced HR + BC: 10%), palmar-plantar erythrodysesthesia (RCC: 5%), erythema (RCC: 4%), onychoclasis (RCC: 4%), skin lesion (RCC: 4%), acneiform eruption (RCC: 3%)

Endocrine & metabolic: Diabetes mellitus (PNET: 10%; RCC: exacerbation of diabetes mellitus: 2%, new onset: <1%), hypermenorrhea (TSC, SEGA: 6% to 10%), menstrual disease (TSC, SEGA: 6% to 10%), decreased serum fibrinogen (SEGA: 8%), increased luteinizing hormone (TSC, SEGA: 1% to 4%), increased follicle-stimulating hormone (TSC: 3%), ovarian cyst (TSC: 3%)

Gastrointestinal: Gastroenteritis (SEGA: 10%; includes viral gastroenteritis, gastrointestinal infection), hemorrhoids (RCC: 5%), dysphagia (RCC: 4%)

Genitourinary: Vaginal hemorrhage (TSC: 8%), dysmenorrhea (SEGA: 6%), uterine hemorrhage (SEGA: 6%), cystitis (advanced HR + BC: 3%)

Hematologic & oncologic: Hemorrhage (RCC: 3%)

Hepatic: Increased serum bilirubin (RCC: 3%; grade 3: <1%, grade 4: <1%)

Hypersensitivity: Hypersensitivity reaction (TSC, SEGA: 3%; includes anaphylaxis, chest pain, dyspnea, flushing), angioedema (RCC, TSC: ≤1%)

Infection: Candidiasis (advanced HR + BC, RCC: <1%), hepatitis C (advanced HR + BC: <1%), sepsis (advanced HR + BC, RCC: <1%)

Neuromuscular & skeletal: Muscle spasm (PNET: 10%), jaw pain (RCC: 3%)

Ophthalmic: Eyelid edema (RCC: 4%), conjunctivitis (RCC: 2%)

Otic: Otitis media (TSC: 6%)

Renal: Renal failure (RCC: 3%)

Respiratory: Streptococcal pharyngitis (SEGA: 10%), pleural effusion (RCC: 7%), pneumonia

(advanced HR + BC, RCC, SEGA: 4% to 6%), bronchitis (advanced HR + BC, RCC: 4%), pharyngolaryngeal pain (RCC: 4%), rhinorrhea (RCC: 3%), sinusitis (advanced HR + BC, RCC: 3%)

Miscellaneous: Postoperative wound complication (RC: <1%; wound healing impairment)

<1%, postmarketing, and/or case reports: Arterial thrombosis, aspergillosis, azoospermia, cholecystitis, cholelithiasis, complex regional pain syndrome, decreased plasma testosterone, hemolytic uremic syndrome, hypersensitivity angiitis, male infertility, nephrotoxicity, oligospermia, pancreatitis (including acute pancreatitis), pericardial effusion, pneumonia (*Pneumocystis jiroveci)*, polyoma virus infection, progressive multifocal leukoencephalopathy, reactivation of HBV, respiratory distress, thrombosis of vascular graft (kidney), thrombotic thrombocytopenic purpura

Contraindications Hypersensitivity to everolimus, sirolimus, other rapamycin derivatives, or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Angioedema: Everolimus is associated with the development of angioedema; concomitant use with other agents known to cause angioedema (eg, ACE inhibitors) may increase the risk.

• Bone marrow suppression: Decreases in hemoglobin, neutrophils, platelets, and lymphocytes have been reported. Monitor blood counts at baseline and periodically.

• Edema: Generalized edema (including peripheral edema and lymphedema) and local fluid accumulation (eg, pericardial effusion, pleural effusion, ascites) may occur.

• Fertility effects: May cause infertility. In females, menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone and follicle-stimulating hormone have occurred. Azoospermia and oligospermia have been observed in males.

• Graft thrombosis: **[US Boxed Warning]: An increased risk of renal arterial and venous thrombosis has been reported with use in renal transplantation, generally within the first 30 days after transplant; may result in graft loss.**

• Hepatic artery thrombosis: MTOR inhibitors are associated with an increase in hepatic artery thrombosis, most cases have been reported within 30 days after transplant and usually proceeded to graft loss or death. Do not use everolimus prior to 30 days post liver transplant.

• Infections: **[US Boxed Warning]: Everolimus has immunosuppressant properties which may result in infection;** the risk of developing bacterial (including mycobacterial), viral, fungal, and protozoal infections and for local, opportunistic (including polyomavirus infection), and/or systemic infections is increased; may lead to sepsis, respiratory failure, hepatic failure, or fatality. Polyoma virus infection in transplant patients may be serious and/or fatal. Polyoma virus-associated nephropathy (due to BK virus), which may result in serious cases of deteriorating renal function and renal graft loss, has been observed with use in renal transplantation. JC virus-associated progressive multiple leukoencephalopathy (PML) may also be associated with everolimus use in transplantation. Reduced immunosuppression (taking into account the risks of rejection) should be considered with evidence of polyoma virus infection or PML. Reactivation of hepatitis B has been observed in patients receiving everolimus. Resolve preexisting invasive fungal infections prior to treatment initiation. Cases (some fatal) of *Pneumocystis jiroveci* pneumonia (PCP) have been

reported with everolimus use. Consider PCP prophylaxis in patients receiving concomitant corticosteroid or other immunosuppressant therapy. In addition, transplant recipient patients should receive prophylactic therapy for PCP and for cytomegalovirus (CMV). Monitor for signs and symptoms of infection during treatment. Discontinue if invasive systemic fungal infection is diagnosed (and manage with appropriate antifungal therapy).

• Malignancy: **[US Boxed Warning]: Immunosuppressant use may result in the development of malignancy, including lymphoma and skin cancer.** The risk is associated with treatment intensity and the duration of therapy. To minimize the risk for skin cancer, limit exposure to sunlight and ultraviolet light; wear protective clothing, and use effective sunscreen.

• Metabolic effects: Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported. Higher serum everolimus concentrations are associated with an increased risk for hyperlipidemia. Use has not been studied in patients with baseline cholesterol >350 mg/dL. Monitor fasting glucose and lipid profile prior to treatment initiation and periodically thereafter. Monitor more frequently in patients with concomitant medications affecting glucose. Increases in serum glucose are common; may alter insulin and/or oral hypoglycemic therapy requirements in patients with diabetes. The risk for new-onset diabetes is increased with everolimus use after transplantation. Manage with appropriate medical therapy (if possible, optimize glucose control and lipids prior to treatment initiation). Antihyperlipidemic therapy may not normalize levels.

• Mucositis/stomatitis: Use is associated with mouth ulcers, mucositis, and stomatitis; manage with topical therapy; avoid the use of alcohol-, hydrogen peroxide–, iodine-, or thyme-based mouthwashes. Due to the high potential for drug interactions, avoid the use of systemic antifungals unless fungal infection has been diagnosed.

• Nephrotoxicity: Elevations in serum creatinine (generally mild), renal failure, and proteinuria have been observed with everolimus use; monitor renal function (BUN, creatinine, and/or urinary protein). Risk of nephrotoxicity may be increased when administered with calcineurin inhibitors (eg, cyclosporine, tacrolimus); dosage adjustment of calcineurin inhibitor is necessary. Monitor for proteinuria; the risk of proteinuria is increased when everolimus is used in combination with cyclosporine, and with higher serum everolimus concentrations.

• Pulmonary toxicity: Noninfectious pneumonitis, interstitial lung disease (ILD), and/or noninfectious fibrosis have been observed with mTOR inhibitors, including everolimus; some cases were fatal. Symptoms include dyspnea, cough, hypoxia and/or pleural effusion; promptly evaluate worsening respiratory symptoms. Cases of ILD have been reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. Consider opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PCP) when evaluating clinical symptoms. May require treatment interruption followed by dose reduction (pneumonitis has developed even with reduced doses) and/or corticosteroid therapy; discontinue for grade 4 pneumonitis. Consider discontinuation for recurrence of grade 3 toxicity after dosage reduction. In patients who require steroid therapy for symptom management, consider PCP prophylaxis. Imaging may overestimate the incidence of clinical pneumonitis.

• Wound healing complication: Everolimus use may delay wound healing and increase the occurrence of wound-related complications (eg, wound dehiscence, infection, incisional hernia, lymphocele, seroma); may require surgical intervention. Use everolimus with caution in the peri-surgical period.

Disease-related concerns:

• Heart transplantation: **[US Boxed Warning]: Increased mortality (usually associated with infections) within the first 3 months after transplant was noted in a study of patients with *de novo* heart transplant receiving immunosuppressive regimens containing everolimus (with or without induction therapy). Use in heart transplantation is not recommended.** The boxed warning in the labeling (Zortress) is based on severe infectious complications, rather than efficacy (reduction in the incidence of cardiac allograft vasculopathy). Despite labeled warnings for this off-label indication, some centers continue to use everolimus (with reduced calcineurin inhibitor exposure). However, everolimus initiation in heart transplantation is delayed until 3 to 6 months post-transplantation due to impaired wound healing and pericardial effusions early on in the postoperative period (Andreassen 2014; Andreassen 2016; Costanza 2010; Hirt 2013; Hollis 2015).

• Hepatic impairment: Everolimus exposure is increased in patients with hepatic impairment. For patients with breast cancer, neuroendocrine tumors, RCC, or renal angiomyolipoma with mild and moderate hepatic impairment, reduced doses are recommended; in patients with severe hepatic impairment, use is recommended (at reduced doses) if the potential benefit outweighs risks. Reduced doses are recommended in transplant patients with hepatic impairment (Child-Pugh class A, B, or C); monitor whole blood trough levels closely. For patients with SEGA, reduced doses may be needed (based on therapeutic drug monitoring) for mild and moderate hepatic impairment, and are recommended in severe hepatic impairment; monitor whole blood trough levels.

• Hereditary galactose intolerance: Avoid use in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; may result in diarrhea and malabsorption.

• Renal impairment: An increased incidence of rash, infection and dose interruptions have been reported in patients with renal insufficiency (CrCl ≤60 mL/minute) who received mTOR inhibitors for the treatment of renal cell cancer (Gupta 2011). Serum creatinine elevations and proteinuria have been reported. Monitor renal function (BUN, serum creatinine, urinary protein) at baseline and periodically, especially if risk factors for further impairment exist. Pharmacokinetic studies have not been conducted; dosage adjustments are not required based on renal impairment.

• Transplantation (solid organ): The safety and efficacy of everolimus in renal transplantation patients with high-immunologic risk or in solid organ transplant other than renal or liver have not been established. In liver transplant, tacrolimus has minimal or no pharmacokinetic impact on everolimus concentrations.

Concurrent drug therapy issues:

• Calcineurin inhibitor combination therapy: **[US Boxed Warning]: Due to the increased risk for nephrotoxicity in renal transplantation, avoid standard doses of cyclosporine in combination with everolimus; reduced cyclosporine doses are recommended when everolimus is used in combination with cyclosporine. Therapeutic monitoring of cyclosporine and everolimus concentrations is recommended.** Everolimus and cyclosporine combination therapy may result in increased proteinuria and may increase the risk for thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TMA/TTP/HUS); monitor blood counts. In liver transplantation, the tacrolimus dose and target range should be reduced to minimize the risk of nephrotoxicity. Eliminating calcineurin inhibitors from the immunosuppressive regimen may result in acute rejection.

• Drug-drug/drug-food interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

• HMG-CoA reductase inhibitors: In transplant patients, avoid the use of certain HMG-CoA reductase inhibitors (eg, simvastatin, lovastatin); may increase the risk for rhabdomyolysis due to the potential interaction with cyclosporine (which may be given in combination with everolimus for transplantation).

Dosage form specific issues:

• Tablet formulations: Tablets (Afinitor, Zortress) and tablets for oral suspension (Afinitor Disperz) are not interchangeable; Afinitor Disperz is only indicated in conjunction with therapeutic monitoring for the treatment of SEGA. Do not combine formulations to achieve total desired dose.

Other warnings/precautions:

• Appropriate use: Continue treatment with everolimus for renal cell cancer as long as clinical benefit is demonstrated or until occurrence of unacceptable toxicity.

• Assay method: For indications requiring whole blood trough concentrations to determine dosage adjustments, a consistent method should be used; concentration values from different assay methods may not be interchangeable.

• Experienced physician: **[US Boxed Warning]: In transplantation, everolimus should only be used by physicians experienced in immunosuppressive therapy and management of transplant patients. Adequate laboratory and supportive medical resources must be readily available.**

• Immunizations: Patients should not be immunized with live viral vaccines during or shortly after treatment and should avoid close contact with recently vaccinated (live vaccine) individuals. In pediatric patients treated for SEGA, complete recommended series of live virus childhood vaccinations prior to treatment (if immediate everolimus treatment is not indicated); an accelerated vaccination schedule may be appropriate.

Metabolism/Transport Effects

Substrate of CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP3A4 (weak)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

ACE Inhibitors: Everolimus may enhance the adverse/toxic effect of ACE Inhibitors. Specifically, the risk of angioedema may be increased. *Risk C: Monitor therapy*

Antidiabetic Agents: Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Antihepaciviral Combination Products: May increase the serum concentration of Everolimus. *Risk X: Avoid combination*

ARIPiprazole: CYP3A4 Inhibitors (Weak) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole pharmacologic effects. Aripiprazole dose adjustments may or may not be required based on concomitant therapy and/or indication. Consult full interaction monograph for specific recommendations. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CycloSPORINE (Systemic): May increase the serum concentration of Everolimus. Management: When using everolimus for renal cell carcinoma, avoid concurrent cyclosporine. When using everolimus as post-transplant immunosuppression, concurrent cyclosporine should be used at lower doses and with lower target serum cyclosporine concentrations. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Everolimus. Management: Avoid concurrent use of strong CYP3A4 inducers, but if strong CYP3A4 inducers cannot be avoided, consider gradually (in 5 mg increments) increasing the everolimus dose from 10 mg/day to 20 mg/day (adult doses). *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Everolimus. Management: Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma. See prescribing information for specific dose adjustment and monitoring recommendations. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Everolimus. *Risk X: Avoid combination*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Dofetilide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Dofetilide. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Efavirenz: May decrease the serum concentration of Everolimus. Management: Closely monitor everolimus serum concentrations when starting, stopping, or changing doses of efavirenz, particularly during the first 2 weeks after any change. Dose adjustment of everolimus may be required. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Grapefruit Juice: May increase the serum concentration of Everolimus. *Risk X: Avoid combination*

HYDROcodone: CYP3A4 Inhibitors (Weak) may increase the serum concentration of HYDROcodone. *Risk C: Monitor therapy*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lomitapide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lomitapide. Management: Patients on lomitapide 5 mg/day may continue that dose. Patients taking lomitapide 10 mg/day or more should decrease the lomitapide dose by half. The lomitapide dose may then be titrated up to a max adult dose of 30 mg/day. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

NiMODipine: CYP3A4 Inhibitors (Weak) may increase the serum concentration of NiMODipine. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of Everolimus. Management:

Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma. See prescribing information for specific dose adjustment and monitoring recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Pimozide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Pimozide. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of Everolimus. Management: Concurrent use of Afinitor brand everolimus with St Johns wort (SJW) is not recommended. Zortress brand everolimus prescribing information cautions that SJW may decrease everolimus concentrations, though no specific dose adjustment is recommended. *Risk X: Avoid combination*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live).

Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Venetoclax: May increase the serum concentration of Everolimus. Management: Administer everolimus at least 6 hours before venetoclax when concomitant therapy is required. *Risk D: Consider therapy modification*

Voriconazole: May increase the serum concentration of Everolimus. *Risk X: Avoid combination*

Food Interactions Grapefruit juice may increase levels of everolimus. Absorption with food may be variable. Management: Avoid grapefruit juice. Take with or without food, but be consistent with regard to food.

Pregnancy Risk Factor C (Zortress) (show table)

Pregnancy Implications Adverse events were observed in animal reproduction studies with exposures lower than expected with human doses. Based on the mechanism of action, may cause fetal harm if administered during pregnancy. Women of reproductive potential should be advised to avoid pregnancy and use highly effective birth control during treatment and for up to 8 weeks after everolimus discontinuation.

Everolimus may cause infertility. In females, menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone and follicle-stimulating hormone have occurred. Azoospermia and oligospermia have been observed in males. Females of reproductive potential should consider family planning options prior to therapy.

The National Transplantation Pregnancy Registry (NTPR) is a registry which follows pregnancies which occur in maternal transplant recipients or those fathered by male transplant recipients. The NTPR encourages reporting of pregnancies following solid organ transplant by contacting them at 877-955-6877 or NTPR@giftoflifeinstitute.org.

Breast-Feeding Considerations It is not known if everolimus is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer during therapy (Afinitor, Zortress) and for 2 weeks following the last dose (Afinitor).

Dietary Considerations Avoid grapefruit juice.

Monitoring Parameters CBC with differential (baseline and periodic), liver function; serum creatinine, urinary protein, and BUN (baseline and periodic); fasting serum glucose and lipid profile (baseline and periodic); monitor for signs and symptoms of infection, noninfectious pneumonitis, or malignancy

Liver or renal transplantation: Monitor everolimus whole blood trough concentrations (based on an LC/MS/MS assay method), especially in patients with hepatic impairment, with concomitant CYP3A4 inhibitors and inducers, and when cyclosporine formulations or doses are changed; dosage adjustments should be made on trough concentrations obtained 4 to 5 days after a previous dosage adjustment; monitor cyclosporine concentrations; monitor for proteinuria

SEGA: Monitor everolimus whole blood trough concentrations ~2 weeks after treatment initiation or with dosage modifications, initiation or changes to concurrent CYP3A4/P-glycoprotein (P-gp) inhibitor/inducer

therapy, changes in hepatic function and when changing dosage forms between Afinitor tablets and Afinitor Disperz. Maintain trough concentrations between 5 and 15 ng/mL; once stable dose is attained and if BSA is stable throughout treatment, monitor trough concentrations every 6 to 12 months (monitor every 3 to 6 months if BSA is changing).

Heart transplantation (off-label use): Everolimus trough levels; measure at least 5 days after a dose adjustment when a new steady state is achieved (ISHLT [Costanzo 2010]).

Reference Range

Recommended range for everolimus whole blood trough concentrations:

Liver and renal transplantation: 3 to 8 ng/mL (based on an LCMSMS assay method)

Subependymal giant cell astrocytoma (SEGA): 5 to 15 ng/mL (high concentrations may be associated with larger reductions in SEGA volumes, responses have been observed at concentrations as low as 5 ng/mL)

Heart transplantation) (off-label use): 3 to 8 ng/mL with reduced dose cyclosporine (Costanzo 2010; Eisen 2013; Hollis 2015) or 6 to 10 ng/mL following cyclosporine withdrawal (Andreassen 2014)

Mechanism of Action

Everolimus is a macrolide immunosuppressant and a mechanistic target of rapamycin (mTOR) inhibitor which has antiproliferative and antiangiogenic properties, and also reduces lipoma volume in patients with angiomyolipoma. Reduces protein synthesis and cell proliferation by binding to the FK binding protein-12 (FKBP-12), an intracellular protein, to form a complex that inhibits activation of mTOR (mechanistic target of rapamycin) serine-threonine kinase activity. Also reduces angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF-1) expression. Angiomyolipomas may occur due to unregulated mTOR activity in TSC-associated renal angiomyolipoma (Budde 2012); everolimus reduces lipoma volume (Bissler 2012).

Pharmacodynamics/Kinetics

Absorption: Rapid (Kirchner 2004)

Distribution: Apparent V_d: 128 to 589 L (Zortress); volume of distribution in pediatric renal transplant patients (3 to 16 years) lower than adults (Van Damme-Lombaerts 2002)

Protein binding: ~74% (Afinitor and Zortress)

Metabolism: Extensively metabolized in the liver via CYP3A4; forms 6 weak metabolites (Afinitor and Zortress)

Bioavailability:

- Tablets: ~30% (Tabernero 2008 [Afinitor]); Systemic exposure reduced by 22% with a high-fat meal and by 32% with a light-fat meal (Afinitor); Systemic exposure reduced 16% with a high-fat meal (Zortress)
- Tablets for suspension (Afinitor): AUC equivalent to tablets although peak concentrations are 20% to 36% lower; steady state concentrations are similar; Systemic exposure reduced by 12% with a high-fat meal and by 30% with a low-fat meal

Half-life elimination: ~30 hours (Afinitor and Zortress); in pediatric renal transplant patients (3 to 16

years), half-life similar to adult data (Van Damme-Lombaerts 2002)

Time to peak, plasma: 1 to 2 hours (Afinitor and Zortress)

Excretion: Feces (80%, based on solid organ transplant studies); Urine (~5%, based on solid organ transplant studies); clearance in pediatric renal transplant patients lower than adults possibly due to distributive differences (Van Damme-Lombaerts 2002)

Pricing: US

Tablet,Dispersible (Afinitor Disperz Oral)

2 mg (1): $524.81

3 mg (1): $530.05

5 mg (1): $551.68

Tablets (Afinitor Oral)

2.5 mg (1): $527.44

5 mg (1): $551.72

7.5 mg (1): $551.69

10 mg (1): $551.65

Tablets (Zortress Oral)

0.25 mg (1): $9.58

0.5 mg (1): $19.16

0.75 mg (1): $28.73

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Advacan (IN); Afinitor (AE, AR, AU, BE, BR, CH, CL, CN, CO, CY, CZ, DE, DK, EE, ES, FR, GB, HK, HR, ID, IL, IS, JO, JP, KR, KW, LB, LK, LT, LU, LV, MT, MY, NO, NZ, PH, PL, QA, RO, SA, SE, SG, SI, SK, TH, TR, TW, UA, VN, ZW); Certican (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CU, CY, CZ, DE, DK, EC, EE, ES, FI, FR, GR, HK, HN, HR, ID, IL, IN, IS, IT, JO, JP, KR, KW, LB, LK, LT, MT, MY, NL, NO, NZ, PE, PH, PK, PL, PT, PY, QA, RO, SA, SE, SG, SI, SK, TH, TR, TW, UY, VE, VN); Sertykan (UA); Vetubia (HR, RO); Votubia (CH, CY, CZ, DE, DK, EE, ES, FR, GB, LU, LV, MT, NO, PL, SE); Xevirol (BD)

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