Managing Adverse Events

in Cancer Patients Treated With Everolimus

For educational purposes only.
Does not cover all adverse events associated with everolimus therapy.

AFINITOR® (everolimus) is an oral mammalian target of rapamycin (mTOR) inhibitor that has been approved by the Food and Drug Administration for the following oncology indications[1]:

- Treatment of postmenopausal women with advanced hormone receptor–positive human epidermal growth factor receptor 2–negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole
- Treatment of adults with progressive neuroendocrine tumors of pancreatic origin (pNET) that are unresectable, locally advanced, or metastatic
- Treatment of adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03[2]

- Adverse events (AEs) were classified by severity according to the NCI common terminology criteria for AEs:

Grading (severity) scale for each AE term	
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life threatening or debilitating
Grade 5	Death related

Key Adverse Events Associated With Everolimus[1]

• Stomatitis	• Hyperlipidemia
• Rash	• Hematologic AEs
• Noninfectious pneumonitis	• Other – Hepatic impairment – Renal dysfunction
• Infection	
• Hyperglycemia	

- Awareness of and vigilant monitoring for signs and symptoms of these potential adverse events are critical.
- Management of AEs may require temporary dose reduction and/or interruption of everolimus therapy.

Components of AE Management[3]

- A thorough medical history

- Patient awareness and education
  - Inform of risks
  - Advise of signs and symptoms

- AE management guidance
  - Include everolimus dose adjustment or withdrawal as necessary

Incidence of Key Adverse Events (Any Grade) Associated With Everolimus for the Approved Oncology Indications*[1]

	mRCC	pNET	Advanced BC
Any grade adverse event, %			
Stomatitis[a]	44	70	67
Infection[b]	37	16-25	50
Noninfectious pneumonitis[c]	14	17	19
Rash	29	59	39
Metabolic AEs			
Glucose increased	57	75	69
Hyperglycemia[d]	NR	NR	14
Cholesterol increased	77	66	70
Triglycerides increased	73	39	50
Hematologic AEs			
Hemoglobin decreased	92	86	68
Platelets decreased	23	45	54
Lymphocytes decreased	51	45	54
Neutrophils decreased	14	30	31

*The information in this table does not describe all of the AEs that were experienced in the everolimus clinical trials.

[a]For advanced BC, includes the terms stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis, and lip ulceration. For pNET, includes the terms stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation. For RCC, includes the terms stomatitis, aphthous stomatitis, and mouth and tongue ulceration.

[b]For advanced BC and RCC, includes all preferred terms within the "infections and infestations" system organ class. For pNET, includes the terms urinary tract infection and nasopharyngitis/rhinitis/URI only.

[c]For advanced BC, includes the terms pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis. For pNET, includes the terms pneumonitis, interstitial lung disease, pulmonary fibrosis, and restrictive pulmonary disease. For RCC, includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

[d]For advanced BC, hyperglycemia was indicated as a preferred term within the "metabolism and nutrition disorders" system organ class.

BC, breast cancer; mRCC, metastatic renal cell carcinoma; NR, not reported; pNET, pancreatic neuroendocrine tumors; URI, upper respiratory infection.

Stomatitis[1,4-8]

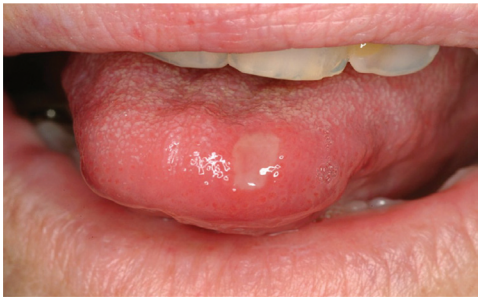


Image courtesy of Carmen Jacobs, RN, OCN; MD Anderson Cancer Center, Houston, Texas.

Medical history

- Obtain information about oral hygiene.
- Rule out other differential diagnoses.
  - Consider evaluation for herpes virus or fungal infection.

Patient education

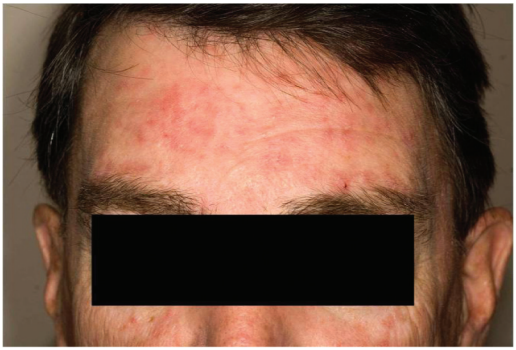
- Focus on patient awareness and early intervention.
- Inform patients of the possibility of developing mouth ulcers and oral stomatitis.
- Educate patients about good oral hygiene.
  - Rinse mouth with baking soda, salt water, or equivalent product regularly.
  - Brush and floss after each meal.
  - Use mild toothpaste (eg, children's) and a soft-bristled toothbrush.
  - Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives.
- Encourage regular dental examinations.

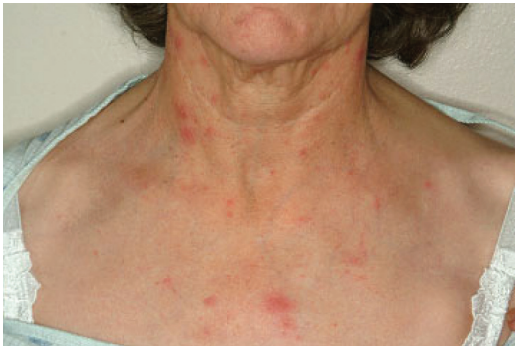
- Promptly report any signs or symptoms.
  - Symptoms tend to occur early, so encourage patients to report soon after onset to initiate early intervention.
  - Contact caregiver at first sign of mouth discomfort and/or lesions that interfere with eating and drinking.
- Warn patients to avoid foods that are spicy/acidic/salty.

AE management guidance: stomatitis

Grade	Symptoms	Management	Everolimus dose modification
1	Minimal (normal diet)	• Manage with nonalcoholic or salt water (0.9%) mouth wash several times a day	• No dose adjustment required
2	Symptomatic but can eat and swallow modified diet	• Manage with topical analgesic mouth treatments (eg, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids (ie, triamcinolone oral paste) • Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives	• Temporary dose interruption until recovery to grade ≤1 • Re-initiate everolimus at the same dose • If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1; re-initiate everolimus at a lower dose
3	Symptomatic and unable to adequately eat or hydrate orally		• Temporary dose interruption until recovery to grade ≤1; re-initiate everolimus at a lower dose
4	Severe (symptoms are life threatening)		• Discontinue everolimus and treat with appropriate medical therapy

Rash[1,7,9,10]





Images courtesy of Carmen Jacobs, RN, OCN; MD Anderson Cancer Center, Houston, Texas.

Patient education

- Focus on patient awareness and early intervention.
  - Inform patients of the possibility of developing rash.
- Promptly report any signs or symptoms.
  - Symptoms tend to occur early, so encourage patients to report soon after onset to initiate early intervention.
- Educate patients about practicing good skin care.
  - Moisturize frequently, using a thick, alcohol-free emollient cream (eg, Eucerin®, Aquaphor®, or Cetaphil®).
  - Take short, lukewarm showers, using mild, moisturizing, fragrance-free soap.
  - Bathe in lukewarm water plus 1-2 cups of baking soda or Aveeno® bath treatment.
  - Use a sunscreen of SPF 15 or higher, preferably containing zinc oxide or titanium dioxide; minimize sun exposure.

AE management guidance: rash

Grade	Management	Everolimus dose modification
1	• Mild rash may resolve spontaneously • More severe rash can be treated with topical steroids, topical antibiotics, and/or oral antihistamines • For grade 3 or intolerable grade 2 papulopustular rash, oral antibiotics are recommended	• If toxicity is tolerable, no dose adjustment required
2		• If toxicity is tolerable, no dose adjustment required • If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1; re-initiate everolimus at the same dose • If toxicity recurs at grade 2, interrupt everolimus until recovery to grade ≤1; re-initiate everolimus at a lower dose
3		• Temporary dose interruption until recovery to grade ≤1 • Consider re-initiating everolimus at a lower dose; if toxicity recurs at grade 3, consider discontinuation
4		• Discontinue everolimus

Noninfectious Pneumonitis[1,4,6,7]

Medical history

- Obtain a complete medical history about pulmonary conditions.
  - In patients with severely impaired lung function (significant pulmonary fibrosis, severe chronic obstructive pulmonary disease), consider not using everolimus.
- Perform pulmonary function testing as needed, according to patient symptoms.

Patient education

- Warn patients of the possibility of developing noninfectious pneumonitis.
- Advise patients to report promptly any new or worsening respiratory symptoms (eg, shortness of breath, cough, fever).

AE management guidance: noninfectious pneumonitis

Grade	Symptoms	Management	Everolimus dose modification
1	Asymptomatic (radiographic findings only)	• Initiate appropriate monitoring	• No dose adjustment required
2	Symptomatic, not interfering with ADL	• Rule out infection • Consider treatment with corticosteroids	• Consider interruption of therapy until symptoms improve to grade ≤1 • Re-initiate everolimus at a lower dose • Discontinue treatment if failure to recover within 4 wks
3	Symptomatic, interfering with ADL, oxygen required		• Hold treatment until recovery to grade ≤1 • Consider re-initiating everolimus at a lower dose; if toxicity recurs at grade 3, consider discontinuation
4	Life threatening, ventilatory support indicated		• Discontinue everolimus

ADL, activities of daily living.

Infection[1,3,4]

Medical history

- Obtain information about prior infections (including fungal, hepatitis, human immunodeficiency virus [HIV], tuberculosis, prior pneumonias, recurrent otitis media, sinusitis, or any other opportunistic infections), signs or symptoms of recurrent fever, and pulmonary conditions.
- ***Preexisting invasive antifungal infections should be treated before the start of everolimus therapy.***
- ***Patients with hepatitis B virus (HBV) need to be monitored closely while receiving everolimus because of the potential for viral reactivation.***

Patient education

- Inform patients that they may be more susceptible to infection while being treated with everolimus.
- Advise patients to be particularly vigilant about and aware of signs and symptoms of infection and to report promptly any such signs and symptoms (including temperatures greater than 101 degrees, shortness of breath, and cough).

AE management guidance: infection

- Be aware of and collect a specimen to culture for atypical infections.
- Use antibiotics appropriately.*
- If a diagnosis of invasive systemic fungal infection is made, promptly and permanently discontinue everolimus therapy, and treat with appropriate antifungal therapy.
- If HBV reactivation occurs, start antiviral treatment and interrupt everolimus administration until resolution (HBV DNA levels at or below baseline).

*Avoid co-administration of everolimus and strong cytochrome 3A4 inhibitors. See section on CYP3A4 interactions.

AE management guidance: infection

Grade	Description	Management	Everolimus dose modification
1	–	• Institute adequate treatment of infection with antibiotics, as appropriate • Perform culture and be aware of atypical infections • In patients who test positive for hepatitis B surface antigen, consider prophylaxis with entecavir or tenofovir	• If toxicity is tolerable, no dose adjustment required
2	Localized infection		• If toxicity is tolerable, no dose adjustment required • If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1; re-initiate everolimus at the same dose • If toxicity recurs at grade 2, interrupt everolimus until recovery to grade ≤1; re-initiate everolimus at a lower dose
3	Systemic infection	• Provide IV antibiotic, antifungal* or antiviral therapy; institute additional interventions, as for grade 1	• Temporary dose interruption until recovery to grade ≤1 • Consider re-initiating everolimus at a lower dose; if toxicity recurs at grade 3, consider discontinuation
4	Life threatening	• Provide appropriate standard therapy, as for grade 1	• Discontinue everolimus

*If diagnosis of invasive systemic fungal infection is made, everolimus therapy should be promptly and permanently discontinued. Avoid co-administration of everolimus with strong cytochrome 3A4 inhibitors.

Hyperglycemia[1,4,6,11,12]

Medical history

- Monitor fasting serum glucose levels before initiating everolimus therapy.
- ***Optimal glycemic control should be achieved before a patient is started on everolimus.***

Patient education

- Inform patients of the benefits for glycemic control derived from lifestyle changes such as weight loss (if applicable), physical activity incorporated into their daily routine, and dietary modifications (reducing *trans* fat intake, keeping saturated fat <7% of total calories, monitoring carbohydrate intake).
- Advise patients to report excessive thirst or increased frequency of urination.

AE management guidance: hyperglycemia

- Periodically monitor fasting serum glucose levels after the start of therapy.
- Manage according to standard consensus guidelines:
  - Achievement and maintenance of normal glycemic goal (HbA1c <7%)
  - Initial therapy with lifestyle intervention and/or metformin
  - Rapid addition of medications and transition to new medications when target glycemic goals are not achieved/sustained
  - Early addition of insulin therapy in patients not meeting target glycemic goals

AE management guidance: hyperglycemia

Grade	Description	Management	Everolimus dose modification
1	Fasting glucose: >ULN-160 mg/dL	• None	• No dose adjustment required
2	Fasting glucose: >160-250 mg/dL	• Treat hyperglycemia according to American Diabetes Association standard guidelines[11,12]	
3	Fasting glucose: >250-500 mg/dL		• Temporary dose interruption • Re-initiate everolimus at a lower dose
4	Fasting glucose: >500 mg/dL		• Discontinue everolimus

ULN, upper limit of normal.

American Diabetes Association Standards of Medical Care: http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html. Consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes: http://care.diabetesjournals.org/content/32/1/193.full.pdf+html

Hyperlipidemia[1,4,13]

Medical history

- Monitor lipid and hepatic profiles before initiating everolimus therapy.
- Significant baseline lipid abnormalities should be treated and optimal lipid control should be achieved before a patient is started on everolimus.
- Monitor lipid levels periodically after start of therapy.

Patient education

- Inform patients of the potential effects of everolimus on blood lipids.
- Implement lifestyle changes aimed at weight loss and increased physical activity (eg, dietary modifications), and manage lipid levels per standard guidelines.
  - Low-density lipoproteins (LDL) should be the primary target of therapy; secondary targets include the total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio and non–HDL-C levels.
- No clinically significant pharmacokinetic interactions between everolimus and the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors atorvastatin, pravastatin, and simvastatin have been observed.

AE management guidance: hyperlipidemia

Grade	Description	Management	Everolimus dose modification
1	• Cholesterol: >ULN-300 mg/dL • Triglycerides: 150-300 mg/dL	• None	• No dose adjustment required
2	• Cholesterol: >300-400 mg/dL • Triglycerides: >300-500 mg/dL	• Treat hyperlipidemia per standard guidelines[13] • Triglycerides ≥500 mg/dL increase risk of pancreatitis; treat promptly with fibrates	
3	• Cholesterol: >400-500 mg/dL • Triglycerides: >500-1000 mg/dL		• Temporary dose interruption • Re-initiate everolimus at a lower dose
4	• Cholesterol: >500 mg/dL • Triglycerides: >1000 mg/dL		• Discontinue everolimus

ULN, upper limit of normal.
NCEP Final Report: http://circ.ahajournals.org/content/106/25/3143.full.pdf+html.

Hematologic Adverse Events[1]

Medical history

- Monitoring of complete blood count is recommended before the start of everolimus and periodically thereafter.

Patient education

- Inform patients of the potential effects of everolimus on hematologic parameters.

AE management guide: hematologic

- Dose interruption or temporary break in everolimus therapy may be required.

Renal Failure[1]

- Serum creatinine elevations, proteinuria, and renal failure (including acute renal failure) have been observed in patients treated with everolimus:
  - Incidence of all-grade renal failure in RCC: 3%
  - Incidence of grade 3/4 renal failure in pNET: 2.9%
  - Some cases of renal failure have been fatal:
    - pNET 0.005%, RCC 0.4%
- Recommendations:
  - Patients should be advised of the risk of renal failure.
  - Monitor renal function at baseline and periodically thereafter, including measurements of:
    - Blood urea nitrogen
    - Urinary protein
    - Serum creatinine

Hepatic Impairment[1]

- Recommended dose modifications for patients with hepatic impairment are as follows:
  - Child-Pugh class A: 7.5 mg/day
  - Child-Pugh class B: 5 mg/day
  - Child-Pugh class C: 2.5 mg/day maximum, only if the desired benefit outweighs the risk

Cardiac Toxicity[1]

- Everolimus has not been associated with significant cardiac toxicity.
  - Low incidence of hypertension (4%) and congestive heart failure (1%)
  - No indication of QT/QTc interval prolongation in single doses up to 50 mg
- Routine monitoring of ejection fraction while receiving everolimus therapy is not required.

Geriatric Use[1]

- No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended.

Renal Impairment[1]

- Renal impairment is not expected to influence drug exposure, and no dosage adjustment of everolimus is recommended in patients with renal impairment.

Dose Modifications for CYP3A4 Interactions[1]

- Everolimus is a substrate of cytochrome P450 (CYP) 3A4 and P-glycoprotein (PgP).
- ***Patients should be encouraged to consult with their pharmacist or health care provider before initiating any new drug or herbal medication because of the potential for drug-drug interactions.***

Strong CYP3A4/PgP inhibitors*	Dose modifications
• Ketoconazole, itraconazole, voriconazole • Telithromycin, clarithromycin • Nefazodone • Ritonavir, atazanavir, saquinavir, indinavir, nelfinavir	• Avoid the use of strong inhibitors

*For a current listing of drug interactions, visit www.medicine.iupui.edu/flockhart/.

Moderate CYP3A4/PgP inhibitors*	Dose modifications
• Erythromycin • Verapamil • Fluconazole • Diltiazem • Amprenavir, fosamprenavir • Aprepitant	• Use caution when co-administered with a moderate CYP3A4 inhibitor, or when administration of PgP inhibitors cannot be avoided; if patients require co-administration, reduce the everolimus dose to 2.5 mg daily • An everolimus dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance; if the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the everolimus dose is increased, then treatment should return to the dose used before initiation of the moderate inhibitor
• Grapefruit, grapefruit juice, and other foods affecting CYP3A4/ PgP such as Seville oranges and star fruit	• Avoid during treatment with everolimus
Strong CYP3A4 inducers*	**Dose modifications**
• Rifampin, rifabutin, rifapentine • Carbamazepine, phenobarbital, phenytoin • St. John's wort (*Hypericum perforatum*)	• Avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration, consider increasing the everolimus dose from 10 mg daily to 20 mg daily, using 5 mg increments. However, no clinical data are available on this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the everolimus dose should be returned to the dose used before initiation of the strong CYP3A4 inducer • Avoid the use of St. John's wort during treatment with everolimus

*For a current listing of drug interactions, visit www.medicine.iupui.edu/flockhart/.

References

1. AFINITOR® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2012.
2. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 4.03. DCTD, NCI, NIH, DHHS. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf . Published May 28, 2009 (v4.03: June 14, 2010). Accessed May 30, 2012.
3. Agricola K et al. Presented at: American Association of Neuroscience Nurses (AANN) 43rd Annual Meeting; March 19-22, 2011; Kansas City, MO.
4. Porta C et al. *Eur J Cancer.* 2011;47:1287-1298.
5. Pilotte AP et al. *Clin J Oncol Nurs.* 2011;15:E83-E89.
6. Eisen T et al. *J Natl Cancer Inst.* 2012;104:93-113.
7. Moldawer NP et al. *Kidney Cancer J.* 2010;8:51-59.
8. de Oliveira F et al. *Oral Oncol.* 2011;47:998-1003.
9. Balagula Y et al. *Cancer.* March 2012. doi: 10.1002/cncr.27505.
10. Fleishman SB et al. http://media.cancercare.org/publications/original/8-ccc_rash.pdf Accessed July 27, 2012
11. American Diabetes Association. *Diabetes Care.* 2011;34:S11-S61.
12. Nathan DM et al. *Diabetes Care.* 2009;32:193-203.
13. National Cholesterol Education Program (NCEP). Final Report, *Circulation.* 2002;106:3143.