

Everolimus (Afinitor[®])

*FOR THERAPEUTIC DRUG MONITORING (WHOLE BLOOD)
IN PATIENTS WITH SEGA ASSOCIATED WITH TUBEROUS
SCLEROSIS WHO REQUIRE THERAPEUTIC INTERVENTION BUT
ARE NOT CANDIDATES FOR CURATIVE SURGICAL RESECTION*

Clinical Background

- In March 2009, the FDA approved Afinitor (everolimus) for the treatment of patients with advanced renal-cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. In October 2010, the FDA approved Afinitor (everolimus) for the treatment of patients with subependymal giant-cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.
- Tuberous sclerosis affects one to two million people worldwide, causing benign tumors to form in many vital organs, including the brain, kidney, heart, eyes, lungs, and skin. SEGAs, benign brain tumors, occur in up to 20 percent of patients with TS and can pose a significant medical risk, including potential for swelling in the brain and hydrocephalus.^{2,3}
- Loss or inactivation of TSC1 or TSC2, the oncogene suppressor tuberin-sclerosis complexes, leads to activation of downstream signaling. In tuberous sclerosis (TS), a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.¹
- Afinitor (everolimus) is an inhibitor of mTOR, a serine-threonine kinase downstream of the PI3K-AKT pathway. The mTOR pathway is dysregulated in several human cancers. Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies.¹
- Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, Afinitor (everolimus) is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus.¹
- The dose of Afinitor (everolimus) for the SEGA population is individualized to the patient's body surface area. The dose is titrated to achieve a whole-blood trough concentration of 5–10 ng/mL.¹
- The blood-to-plasma ratio of Afinitor (everolimus), which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17 to 73 percent. The amount of Afinitor (everolimus) confined to the plasma is approximately 20 percent at blood concentrations observed in cancer patients given 10 mg of Afinitor (everolimus) per day. Plasma protein binding is approximately 74 percent in both healthy subjects and patients with moderate hepatic impairment.¹ Routine Afinitor (everolimus) whole-blood therapeutic drug concentration monitoring is recommended for all SEGA patients.¹

Indications for Ordering

- Afinitor (everolimus) is approved for the treatment of SEGA associated with tuberous sclerosis (TS) in patients who require therapeutic intervention but are not candidates for curative surgical resection.
- Routine Afinitor (everolimus) whole blood therapeutic drug concentration monitoring is recommended for all patients using a validated assay. Trough concentrations should be assessed approximately two weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL.
- Avoid concomitant use with strong CYP3A4 or PgP inhibitors. If moderate inhibitors of CYP3A4 and/or PgP are required, reduce the Afinitor (everolimus) dose by approximately 50 percent. Subsequent dosing should be based on therapeutic drug monitoring (TDM). If strong inducers of CYP3A4 are required, double the Afinitor (everolimus) dose. Subsequent dosing should be based on TDM.

Interpretation

- In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.
- The average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function. In addition, clearance of everolimus is estimated to be 20 percent higher in patients of African descent as compared to Caucasian patients.
- In patients with SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, responses have been observed at trough concentrations as low as 3 ng/mL, so additional dose increase may not be necessary once acceptable efficacy has been achieved.

Methodology

- Liquid chromatography coupled with mass spectrometry (LC/MS) is the analytical method of choice for immunosuppressant drug detection.
- Afinitor (everolimus) detection by LC/MS provides excellent sensitivity (2.0 ng/mL) and specificity. Interferences from commonly used drugs and associated metabolites have not been observed.

Additional Ordering Note

Since more than 75 percent of Afinitor (everolimus) is bound to erythrocytes, whole blood (EDTA anticoagulation) is required.

References

1. Afinitor (everolimus). Package insert. East Hanover, NJ, Novartis Pharmaceuticals Corp; 2009.

2. Tuberous Sclerosis Alliance. Subependymal giant cell tumor (SGCT) or subependymal giant cell astrocytoma (SEGA). http://www.ninds.nih.gov/disorders/tuberous_sclerosis/detail_tuberous_sclerosis.htm. (accessed on September 8, 2010).
3. Adriaensen ME, et al. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. *Eur J Neurol* 2009;16:691–6.

Test Information

0092118 Everolimus by Tandem Mass Spectrometry

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.