

# Everolimus (Afinitor) Drug Monitoring

## Indications for Ordering

Optimize drug therapy and monitor patient adherence

## Test Description

Quantitative liquid chromatography-tandem mass spectrometry

## Tests to Consider

### [Everolimus by Tandem Mass Spectrometry 0092118](#)

- Trough concentrations should be assessed ~2 weeks after commencing treatment

## Disease Overview

### Clinical issues

- Everolimus is used in
  - Prophylaxis of organ rejection in adult individuals receiving a kidney or liver transplant
    - Dose is titrated to achieve a whole-blood predose (trough) concentration of 3-8 ng/mL
    - Adverse effects may occur when predose (trough) whole-blood concentrations >15 ng/mL
  - Advanced renal-cell carcinoma treatment after treatment failure with sunitinib or sorafenib
  - Subependymal giant-cell astrocytoma (SEGA) associated with tuberous sclerosis treatment when individual is not a candidate for surgical resection
- SEGA population
  - Dose is individualized to individual's body surface area
  - Routine therapeutic drug concentration monitoring is recommended for all individuals
  - Dose is titrated to achieve a whole-blood trough concentration of 5-15 ng/mL

### Physiology

- Everolimus is an inhibitor of mTOR
  - mTOR is a serine-threonine kinase downstream from the PI3K-AKT pathway
  - Inhibition of mTOR reduces cell proliferation, angiogenesis and glucose uptake

### Drug profile

- Substrate of the CYP3A4 and Pgp
  - If moderate inhibitors of either system are required, 50% dose reduction of everolimus is recommended
- Everolimus is the main circulating component in human blood
  - >75% bound to erythrocytes

- Six main metabolites
  - 3 monohydroxylated metabolites
  - 2 hydrolytic ring-opened products
  - Phosphatidylcholine conjugate
- Blood-to-plasma ratio
  - 17/73%
  - Concentration – dependent over a range of 5-5,000 ng/mL
- Plasma protein binding is ~74% in both healthy individuals and individuals with moderate hepatic impairment
- Clearance of everolimus
  - AUC of everolimus in 8 subjects with Child-Pugh Class B was twice that in 8 subjects with normal hepatic function
  - ~20% higher in individuals of African descent compared to Caucasian descent
- Cancer individuals
  - 20% of everolimus is confined to the plasma when individuals are given 10 mg doses
  - No apparent relationship between oral clearance and individual age or gender
- SEGA individuals
  - Higher trough concentrations are associated with larger reductions in SEGA volume
    - Responses have been observed at trough concentrations as low as 3 ng/mL, so increased dose may not be necessary if efficacy is achieved

## Test Interpretation

**Analytical sensitivity** – limit of detection is 2.0 ng/mL

- Interferences from commonly used drugs and associated metabolites have not been observed

### Results

Concentration is reported

### Limitations

- Results from different methodologies (mass spectrometry versus immunoassay) cannot be used interchangeably
- Generally, immunoassay methods have been reported to have a positive bias in results when compared to mass spectrometry due to antibody cross-reactivity