

Everolimus (Zortress[®])

FOR MANAGEMENT OF RELATED IMMUNOSUPPRESSANT DRUG THERAPY

Clinical Background

- Zortress (everolimus) is an immunosuppressant medication (mTOR inhibitor), which, like sirolimus (Rapamune[®]), is used to prevent rejection of transplanted organs.
- In April 2010, the FDA approved Zortress oral tablets for prevention of organ rejection of kidney transplants in adult patients at low-moderate immunologic risk.
- Zortress is used in combination with basiliximab (immunosuppressant), reduced doses of cyclosporine (calcineurin inhibitor), and corticosteroids to augment efficacy through synergistic mechanisms of action. Calcineurin inhibitors have been associated with injury to the kidneys; therefore, combined therapy with lower doses of cyclosporine (60 percent lower than standard therapy) can reduce the cyclosporine-related side effects and infections.
- Under the brand name Certican[®], everolimus has been used as part of the immunosuppressive regimen for kidney and heart transplant patients in over 70 countries outside of the United States since 2005.
- Everolimus has a narrow therapeutic index, variable oral bioavailability, and variable pharmacokinetics. Sources of variability in the pharmacokinetics of everolimus include inter-individual differences in p-glycoprotein and in metabolism by the cytochrome P450 (CYP) isozymes 3A4 and 3A5.
- Everolimus is extensively metabolized by CYP3A4, and steady state is achieved within four to five days. Approximately 98 percent of everolimus is excreted as metabolites in the bile and 2 percent in urine, with an elimination half-life ($t_{1/2}$) estimated between 18 and 35 hours. Pharmacological activity of the metabolites has not been described.

Indications for Ordering

- Zortress is used for prophylaxis treatment of organ rejection from kidney transplant in adult patients at low-moderate immunologic risk.
- Monitoring everolimus is used to assure appropriate dosing, assess compliance, and evaluate the pharmacokinetics of everolimus under specific clinical conditions.
- Pre-dose (trough) concentrations of everolimus in whole blood have been shown to correlate with both immunosuppressive efficacy and severity of adverse effects, such as leucopenia and thrombocytopenia.
- The recommended therapeutic range for pre-dose (trough) concentrations of Zortress is 3–8 ng/mL. Symptoms of toxicity are more likely to increase when pre-dose concentrations exceed 12 ng/mL.

Interpretive Notes

- Coadministration of cyclosporine A increases the area under the concentration curve (AUC) of everolimus, but does not affect the C_{max} or $t_{1/2}$. Consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced.
- Everolimus pharmacokinetics, in adults, are not affected by age, sex, or weight. However, drug interactions with CYP3A4 inhibitors and inducers may affect everolimus concentration.
- Everolimus AUC is increased in patients with hepatic impairment. In addition, clearance of everolimus is estimated to be 20 percent higher in patients of African descent as compared to Caucasian patients.

Methodology

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

Additional Ordering Notes

- Since more than 75 percent of everolimus is bound to erythrocytes, whole blood (EDTA anticoagulation) is required.
- The safety and efficacy of everolimus has not been established in pediatric patients (<18 years).
- Use for Zortress for prophylaxis treatment in organ transplants, other than kidney, has not been established.

References

1. Zortress[®] (everolimus) [package insert]. Stein, Switzerland: Novartis Pharma Stein AG; 2010.
2. Deters M, et al. Simultaneous quantification of sirolimus, everolimus, tacrolimus, and cyclosporine by liquid chromatography-mass spectrometry (LC-MS). *Clin Chem Lab Med* 2002;40:285–92.
3. Eisen HJ, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003;349:847–58.
4. Kirchner GI, Meier-Wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* 2004;43:83–95.
5. Kovarik JM, et al. Pharmacokinetics of an everolimus-cyclosporine immunosuppressive regimen over the first six months after kidney transplantation. *Am J Transplant* 2003;3:606–13.

Test Information

0092118 **Everolimus (Zortress®)**

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.