

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zortress (everolimus) safely and effectively. See full prescribing information for Zortress.

Zortress (everolimus) tablets for oral use.
Initial U.S. Approval: 2010

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS, KIDNEY GRAFT THROMBOSIS; NEPHROTOXICITY; AND MORTALITY IN HEART TRANSPLANTATION

See Full Prescribing Information For Complete Boxed Warning

- Only physicians experienced in immunosuppressive therapy and management of transplant patients should use everolimus. (5.1)
- Increased susceptibility to infection and the possible development of malignancies may result from immunosuppression. (5.2, 5.3)
- Increased incidence of kidney graft thrombosis. (5.4)
- Reduced doses of cyclosporine are required for use in combination with everolimus in order to reduce nephrotoxicity. (2.2, 2.3, 5.5, 12.5, 12.6)
- Increased mortality in a heart transplant clinical trial. Use in heart transplantation is not recommended. (5.6)

RECENT MAJOR CHANGES

Boxed Warning: Mortality in Heart Transplantation	04/2012
Warnings and Precautions: Heart Transplantation (5.6)	04/2012
Warnings and Precautions: Polyoma Virus Infections (5.11)	04/2012

INDICATIONS AND USAGE

- Zortress is an mTOR inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.
- Use in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids. (1.1)
- Limitations of Use (1.2)
- Use in patients at high immunologic risk is not established.
- Avoid use of standard doses of cyclosporine in order to reduce the risk of nephrotoxicity (5.5)
- Use for prophylaxis in organs other than kidney is not established. (5.6)
- Safety and efficacy in pediatric patients (<18 years) has not been established.

DOSAGE AND ADMINISTRATION

- Starting oral dose of 0.75 mg twice daily. Adjust maintenance dose to achieve everolimus trough concentrations within the 3-8 ng/mL target range (using LCMCMS or immunoassay method). (2.1, 2.2)
- Administer as soon as possible after transplantation.
- Routine everolimus and cyclosporine therapeutic drug concentration monitoring is recommended. (2.2, 2.3)
- Administer consistently with or without food (12) at the same time as cyclosporine. (2.4)
- Moderate hepatic impairment: Reduce daily dose by half and monitor blood concentrations. (2.5)

DOSAGE FORMS AND STRENGTHS

Zortress is available as 0.25 mg, 0.5 mg, and 0.75 mg tablets. (3)

CONTRAINDICATIONS

- Patients with known hypersensitivity to everolimus, sirolimus, or to components of the drug product. (4)

WARNINGS AND PRECAUTIONS

- Angioedema: Increased risk with concomitant ACE inhibitors; monitor for symptoms and treat promptly. (5.7)
- Wound Healing/Fluid Accumulation: Increased risk for delayed wound healing. Monitor symptoms; treat promptly to minimize complications. (5.8)
- Hyperlipidemia: Elevations of serum cholesterol and triglycerides are common. Monitoring is recommended; consider intervention including anti-lipid therapy. (5.9)
- Proteinuria: Increased risk with higher trough concentrations; monitor urine protein. (5.10)
- Polyoma Virus Infections: Risk of activation of latent viral infections; BK-virus associated nephropathy has been observed; consider reducing immunosuppression. (5.11)
- Interactions with Strong Inhibitors and Inducers of CYP3A4: closely monitor everolimus trough concentrations with concomitant use. (5.12)
- Non-Infectious Pneumonitis: Monitor for clinical symptoms or radiologic changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve; consider use of corticosteroids. (5.13)
- TMA/TTP/HUS: Concomitant use with cyclosporine may increase risk. Monitor for hematological changes or clinical symptoms. (5.14)
- New Onset Diabetes After Transplantation: Blood glucose elevations may occur in dose related manner. Monitor serum glucose. (5.15)
- Male Infertility: Azospermia or oligospermia may occur. (5.16, 13.1)
- Immunizations: Live vaccines should be avoided. (5.17)

ADVERSE REACTIONS

The most common (incidence $\geq 20\%$) adverse events are: peripheral edema, constipation, hypertension, nausea, anemia, UTI, and hyperlipidemia. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

CYP3A4 inhibitors and inducers: Strong-moderate inhibitors (e.g., cyclosporine, ketoconazole, erythromycin, verapamil) and inducers (e.g., rifampin) may affect everolimus concentrations. Blood concentration monitoring is recommended; consider dose adjustment of everolimus. (5.12, 7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS, KIDNEY GRAFT THROMBOSIS; NEPHROTOXICITY; AND MORTALITY IN HEART TRANSPLANTATION

1 INDICATIONS AND USAGE

- 1.1 Prophylaxis of Organ Rejection in Renal Transplantation
- 1.2 Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage in Adult Kidney Transplant Patients
- 2.2 Therapeutic Drug Monitoring - Everolimus
- 2.3 Therapeutic Drug Monitoring- Cyclosporine
- 2.4 Administration
- 2.5 Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity Reactions

5 WARNINGS AND PRECAUTIONS

- 5.1 Management of Immunosuppression
- 5.2 Lymphomas and Other Malignancies

- 5.3 Serious Infections
- 5.4 Graft Thrombosis
- 5.5 Nephrotoxicity
- 5.6 Heart Transplantation
- 5.7 Angioedema
- 5.8 Wound Healing and Fluid Accumulation
- 5.9 Hyperlipidemia
- 5.10 Proteinuria
- 5.11 Polyoma Virus Infections
- 5.12 Interaction with Strong Inhibitors and Inducers of CYP3A4
- 5.13 Non-Infectious Pneumonitis
- 5.14 Thrombotic Microangiopathy/ Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome (TMA/TTP/HUS)
- 5.15 New Onset Diabetes After Transplant
- 5.16 Male Infertility
- 5.17 Immunizations
- 5.18 Interaction with Grapefruit Juice
- 5.19 Patients with Hereditary Disorders / Other

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

6.2 Clinical Studies Experience

6.3 Post Marketing Experience

7 DRUG INTERACTIONS

7.1 Interactions with Strong Inhibitors or Inducers of CYP3A4 and P-glycoprotein

7.2 Cyclosporine (CYP3A4/P-gp inhibitor and CYP3A4 substrate)

7.3 Ketoconazole (Strong CYP3A4 Inhibitor)

7.4 Erythromycin (Moderate CYP3A4 Inhibitor)

7.5 Verapamil (CYP3A4 and P-gp Substrate)

7.6 Atorvastatin (CYP3A4 substrate) and Pravastatin (P-gp substrate)

7.7 Simvastatin and Lovastatin

7.8 Rifampin (Strong CYP3A4) Inducers

7.9 Other Possible Interactions

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

12.5 Everolimus Whole Blood Concentrations Observed in Kidney Transplant Patients

12.6 Cyclosporine Concentrations Observed in Kidney Transplant Patients

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Prevention of Organ Rejection after Renal Transplantation

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Administration

17.2 Development of Lymphomas and Other Malignancies

17.3 Increased Risk of Infection

17.4 Graft Thrombosis

17.5 Nephrotoxicity

17.6 Angioedema

17.7 Wound Healing Complications and Fluid Accumulation

17.8 Hyperlipidemia

17.9 Proteinuria

17.10 Pregnancy

17.11 Medications that Interfere with Zortress

17.12 Non-Infectious Pneumonitis

17.13 New Onset Diabetes

17.14 Immunizations

17.15 Patient with Hereditary Disorders

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS, KIDNEY GRAFT THROMBOSIS; NEPHROTOXICITY; AND MORTALITY IN HEART TRANSPLANTATION

Malignancies and Serious Infections

- Only physicians experienced in immunosuppressive therapy and management of transplant patients should prescribe Zortress. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. [See *Warnings and Precautions (5.1)*]
- Increased susceptibility to infection and the possible development of malignancies such as lymphoma and skin cancer may result from immunosuppression. [See *Warnings and Precautions (5.2 and 5.3)*]

Kidney Graft Thrombosis

- An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, was reported, mostly within the first 30 days post-transplantation. [See *Warnings and Precautions (5.4)*]

Nephrotoxicity

- Increased nephrotoxicity can occur with use of standard doses of cyclosporine in combination with everolimus. Therefore reduced doses of cyclosporine should be used in combination with everolimus in order to reduce renal dysfunction. It is important to monitor the cyclosporine and everolimus whole blood trough concentrations. [See *Dosage and Administration (2.2 and 2.3)* and *Warnings and Precautions (5.5)* and *Clinical Pharmacology (12.5 and 12.6)*]

Mortality in Heart Transplantation

- Increased mortality, often associated with serious infections, within the first three months 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. [See *Warnings and Precautions (5.6)*]

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in Renal Transplantation

Zortress is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. [See *Clinical Studies (14.1)*] Zortress is to be administered in combination with basiliximab induction and concurrently with reduced doses of cyclosporine and corticosteroids. Therapeutic drug monitoring of everolimus and cyclosporine is recommended for all patients receiving these products. [See *Dosage and Administration (2.2 and 2.3)*]

1.2 Limitations of Use

- In patients at high immunologic risk, the safety and efficacy of everolimus has not been established.
- Standard doses of cyclosporine should be avoided with everolimus in order to reduce the risk of nephrotoxicity. [See *Warnings and Precautions (5.5)*, and *Adverse Reactions (6.2)*]
- Use of everolimus for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established. [See *Warnings and Precautions (5.6)*]
- The safety and efficacy of Zortress has not been established in pediatric patients (<18 years).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Kidney Transplant Patients

An initial everolimus dose of 0.75 mg orally twice daily (1.5 mg/day) is recommended for adult kidney transplant patients in combination with reduced dose cyclosporine, administered as soon as possible after transplantation. [See *Therapeutic Drug Monitoring (2.2 and 2.3)*, *Clinical Studies (14.1)*] Patients receiving everolimus may require dose adjustments based on everolimus blood concentrations achieved, tolerability, individual response, change in concomitant medications and the clinical situation. Dose adjustments can be made at 4-5 day intervals. [See *Therapeutic Drug Monitoring (2.2)*]

Oral prednisone should be initiated once oral medication is tolerated. Steroid doses may be further tapered on an individualized basis depending on the clinical status of patient and function of graft.

2.2 Therapeutic Drug Monitoring - Everolimus

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using appropriate assay methodology. The recommended everolimus therapeutic range is 3 to 8 ng/mL. [See *Clinical Pharmacology (12.5)*] Careful attention should be made to clinical signs and symptoms, tissue biopsies, and laboratory parameters.

It is important to monitor everolimus blood concentrations, in patients with hepatic impairment, during concomitant administration of CYP3A4 inducers or inhibitors, when switching cyclosporine formulations and/or when cyclosporine dosing is reduced according to recommended target concentrations. [See *Clinical Pharmacology (12.5 and 12.6)*]

Optimally, dose adjustments of everolimus should be based on trough concentrations obtained 4 or 5 days after a previous dosing change. There is an interaction of cyclosporine on everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced. [See *Drug Interactions (7.2)*]

The everolimus recommended therapeutic range of 3 to 8 ng/mL is based on an LCMSMS assay method. Currently in clinical practice, everolimus whole blood concentrations may be measured by chromatographic or immunoassay methodologies. Because the measured everolimus whole blood concentrations depend on the assay used, individual patient sample concentration values from different assays may not be interchangeable. Consideration of assay results must be made with knowledge of the specific assay used. Therefore, communication should be maintained with the laboratory performing the assay.

2.3 Therapeutic Drug Monitoring- Cyclosporine

Both cyclosporine doses and the target range for whole blood trough concentrations should be reduced, when given in a regimen with everolimus, in order to minimize the risk of nephrotoxicity. [See *Warnings and Precautions (5.6) and Drug Interactions (7.2), Clinical Pharmacology (12.6)*]

The recommended cyclosporine therapeutic ranges when administered with everolimus are 100 to 200 ng/mL through Month 1 post-transplant, 75 to 150 ng/mL at Months 2 and 3 post-transplant, 50 to 100 ng/mL at Month 4 post-transplant, and 25 to 50 ng/mL from Month 6 through Month 12 post-transplant. The median trough concentrations observed in the clinical trial ranged between 161 to 185 ng/mL through Month 1 post-transplant and between 111 to 140 ng/mL at Months 2 and 3 post-transplant. The median trough concentration was 99 ng/mL at Month 4 post-transplant and ranged between 46 to 75 ng/mL from Months 6 through Month 12 post-transplant. [See *Clinical Pharmacology (12.6) and Clinical Studies (14.1)*]

Cyclosporine, USP Modified is to be administered as oral capsules twice daily unless cyclosporine oral solution or i.v. administration of cyclosporine cannot be avoided. Cyclosporine, USP Modified should be initiated as soon as possible - and no later than 48 hours - after reperfusion of the graft and dose adjusted to target concentrations from Day 5 onwards.

If impairment of renal function is progressive the treatment regimen should be adjusted. In renal transplant patients, the cyclosporine dose should be based on cyclosporine whole blood trough concentrations. [See *Clinical Pharmacology (12.6)*]

In renal transplantation, there are limited data regarding dosing everolimus with reduced cyclosporine trough concentrations of 25 to 50 ng/mL after 12 months. Everolimus has not been evaluated in clinical trials with other formulations of cyclosporine. Prior to dose reduction of cyclosporine it should be ascertained that steady-state everolimus whole blood trough concentration is at least 3 ng/mL. There is an interaction of cyclosporine on everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced. [See *Drug Interactions (7.2)*]

2.4 Administration

Everolimus tablets should be swallowed whole with a glass of water and not crushed before use.

Administer everolimus consistently approximately 12 hours apart with or without food to minimize variability in absorption and at the same time as cyclosporine. [See *Clinical Pharmacology (12.3)*]

2.5 Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose needs to be reduced by one-half the recommended initial daily

dose and blood concentrations should be monitored to make further adjustments as necessary. There is no information on the effects of severe hepatic impairment (Child-Pugh Class C) on everolimus pharmacokinetics. [See *Clinical Pharmacology (12.3)*]

3 DOSAGE FORMS AND STRENGTHS

Zortress is available as 0.25 mg, 0.5 mg, and 0.75 mg tablets.

Description of Zortress (everolimus) Tablets

Dosage Strength	0.25 mg	0.5 mg	0.75 mg
Appearance	White to yellowish, marbled, round, flat tablets with bevelled edge		
Imprint	“C” on one side and “NVR” on the other	“CH” on one side and “NVR” on the other	“CL” on one side and “NVR” on the other

4 CONTRAINDICATIONS

4.1 Hypersensitivity Reactions

Zortress is contraindicated in patients with known hypersensitivity to everolimus, sirolimus, or to components of the drug product.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Immunosuppression

Only physicians experienced in management of systemic immunosuppressant therapy in transplantation should prescribe Zortress. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for the maintenance therapy should have complete information requisite for the follow-up of the patient.

5.2 Lymphomas and Other Malignancies

Patients receiving immunosuppressants, including everolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

5.3 Serious Infections

Patients receiving immunosuppressants, including everolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. [See *Warnings and Precautions (5.11)* and *Adverse Reactions (6.2)*] These infections may lead to serious, including fatal, outcomes. Because of the danger of over immunosuppression of the immune system which can cause increased susceptibility to infection, combination immunosuppressant therapy should be used with caution.

5.4 Graft Thrombosis

An increased risk of kidney arterial and venous thrombosis, resulting in graft loss, has been reported, usually within the first 30 days post-transplantation. [See *Boxed Warning*]

5.5 Nephrotoxicity

Everolimus with standard dose cyclosporine increases the risk of nephrotoxicity resulting in a lower glomerular filtration rate. Reduced doses of cyclosporine are required for use in combination with everolimus in order to reduce renal dysfunction. [See *Boxed Warning, Indications and Usage (1.2)*, *Clinical Pharmacology (12.6)*] Renal function should be monitored during the administration of everolimus in combination with cyclosporine. Consider switching to other immunosuppressive therapies if renal function does not improve after dose adjustments or if the dysfunction is thought to be drug related. Caution should be exercised when using other drugs which are known to impair renal function.

5.6 Heart Transplantation

In a clinical trial of *de novo* heart transplant patients, Zortress in an immunosuppressive regimen with or without induction therapy, resulted in an increased mortality often associated with serious infections within the first three months post-transplantation compared to the control regimen. Use of Zortress in heart transplantation is not recommended.

5.7 Angioedema

Zortress has been associated with the development of angioedema. The concomitant use of everolimus with other drugs known to cause angioedema, such as angiotensin converting enzyme (ACE) inhibitors may increase the risk of developing angioedema.

5.8 Wound Healing and Fluid Accumulation

Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele and seroma. These wound-related complications may require more surgical intervention. Generalized fluid accumulation, including peripheral edema (e.g., lymphoedema) and other types of localized fluid collection, such as pericardial and pleural effusions and ascites have also been reported.

5.9 Hyperlipidemia

Increased serum cholesterol and triglycerides, requiring the need for anti-lipid therapy, have been reported to occur following initiation of everolimus and the risk of hyperlipidemia is increased with higher everolimus whole blood trough concentrations. [See *Adverse Reactions (6.2)*] Use of anti-lipid therapy may not normalize lipid levels in patients receiving Zortress.

Any patient who is administered everolimus should be monitored for hyperlipidemia. If detected, interventions, such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines. The risk/benefit should be considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen containing everolimus. Similarly, the risk/benefit of continued everolimus therapy should be re-evaluated in patients with severe refractory hyperlipidemia. Everolimus has not been studied in patients with baseline cholesterol levels >350 mg/dL.

Due to an interaction with cyclosporine, clinical trials of everolimus and cyclosporine in kidney transplant patients strongly discouraged patients from receiving the HMG-CoA reductase inhibitors simvastatin and lovastatin. During everolimus therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents. [See *Drug Interactions (7.7)*]

5.10 Proteinuria

The use of everolimus with cyclosporine in transplant patients has been associated with increased proteinuria. The risk of proteinuria increased with higher everolimus whole blood trough concentrations. Patients receiving everolimus should be monitored for proteinuria. [See *Adverse Reactions (6.2)*]

5.11 Polyoma Virus Infections

Patients receiving immunosuppressants, including everolimus, are at increased risk for opportunistic infections; including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes fatal, outcomes. These include polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection, and JC virus associated progressive multiple leukoencephalopathy (PML). PVAN has been observed in patients receiving immunosuppressants, including everolimus. PVAN is associated with serious outcomes; including deteriorating renal function and kidney graft loss. [See *Adverse Reactions (6.2)*] Patient monitoring may help detect patients at risk for PVAN. Reductions in immunosuppression should be considered for patients who develop evidence of PVAN or PML. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

5.12 Interaction with Strong Inhibitors and Inducers of CYP3A4

Co-administration with strong CYP3A4-inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and strong inducers (e.g., rifampin, rifabutin) is not recommended without close monitoring of everolimus whole blood trough concentrations. [See *Drug Interactions (7)*]

5.13 Non-Infectious Pneumonitis

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with symptoms consistent with infectious pneumonia or radiologic changes in whom infectious, neoplastic and other non-drug causes have been ruled out through appropriate investigations. Fatal cases have been reported. Non-infectious pneumonitis may respond to drug interruption with or without glucocorticoid therapy. [See *Adverse Reactions (6.2)*]

5.14 Thrombotic Microangiopathy/ Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome (TMA/TTP/HUS)

The concomitant use of everolimus with cyclosporine may increase the risk of thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Monitor hematologic parameters. [See *Adverse Reactions (6.2)*]

5.15 New Onset Diabetes After Transplant

Everolimus has been shown to increase the risk of new onset diabetes mellitus after transplant. Blood glucose concentrations should be monitored closely in patients using everolimus.

5.16 Male Infertility

Azospemia or oligospemia may be observed. [See *Adverse Reactions (6.3) and Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)*] Everolimus is an anti-proliferative drug and affects rapidly dividing cells like the germ cells.

5.17 Immunizations

The use of live vaccines should be avoided during treatment with everolimus; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.18 Interaction with Grapefruit Juice

Grapefruit and grapefruit juice inhibit cytochrome P450 3A4 and P-gp activity and should therefore be avoided with concomitant use of everolimus and cyclosporine.

5.19 Patients with Hereditary Disorders / Other

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take everolimus as this may result in diarrhea and malabsorption.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity reactions [See *Contraindications (4.1)*]
- Lymphomas and Other Malignancies [See *Boxed Warning, Warnings and Precautions (5.2)*]
- Serious Infections [See *Warnings and Precautions (5.3)*]
- Graft Thrombosis [See *Warnings and Precautions (5.4)*]
- Nephrotoxicity [See *Warnings and Precautions (5.5)*]
- Angioedema [See *Warnings and Precautions (5.7)*]
- Wound Healing and Fluid Accumulation [See *Warnings and Precautions (5.8)*]
- Hyperlipidemia [See *Warnings and Precautions (5.9)*]
- Proteinuria [See *Warnings and Precautions (5.10)*]
- Polyoma Virus Infections [See *Warnings and Precautions (5.11)*]
- Non-infectious Pneumonitis [See *Warnings and Precautions (5.13)*]

- Thrombotic Microangiopathy/Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TMA/TTP/HUS) [*See Warnings and Precautions (5.14)*]
- New Onset Diabetes After Transplant [*See Warnings and Precautions (5.15)*]
- Male Infertility [*See Warnings and Precautions (5.16)*]

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to everolimus in an open-label, randomized trial of *de novo* kidney transplant patients of concentration-controlled everolimus at an initial starting dose of 1.5 mg per day [target trough concentrations 3 to 8 ng/mL with reduced doses of cyclosporine (n=274) compared to mycophenolic acid (n=273) with standard doses of cyclosporine]. All patients received basiliximab induction therapy and corticosteroids. The population was between 18 and 70 years; more than 43% were 50 years of age or older, 63% of all recipients were male and 64% were Caucasian. Demographic characteristics were comparable between treatment groups. The most frequent diseases leading to transplantation were balanced between groups and included hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus.

Adverse reactions were systematically collected in this trial.

In this clinical trial, significantly more patients discontinued everolimus 1.5 mg/day treatment (83/277, 30%) than discontinued the control regimen (60/277, 22%). Of those patients who prematurely discontinued treatment, most discontinuations were due to adverse reactions: 18% in the everolimus group compared to 9% in the control group (p-value = 0.004). This difference was more prominent between treatment groups among female patients. In those patients discontinuing study medication, adverse reactions were collected up to 7 days after study medication discontinuation and serious adverse reactions up to 30 days after study medication discontinuation.

Discontinuation of everolimus at a higher dose (3 mg/day) was 95/279, 34%, including 20% due to adverse reactions, and this regimen is not recommended (see below).

The overall incidences of serious adverse events were 57% (159/278) in the everolimus group and 52% (141/273) in the mycophenolic acid group. Infections and infestations reported as serious adverse reactions had the highest incidence in both groups [20% (54/274) in the everolimus group and 25% (69/273) in the control group]. The difference was mainly due to the higher incidence of viral infections in the Myfortic group, mainly CMV and BK virus infections. Injury, poisoning and procedural complications reported as serious adverse reactions had the second highest incidence in both groups [14% (39/274) in the everolimus group and 12% (32/273) in the control group] followed by renal and urinary disorders [10% (28/274) in the everolimus group and 13% (36/273) in the control group] and vascular disorders [10% (26/274) in the everolimus group and 7% (20/273) in the control group].

A total of 13 patients died during the first 12 months of study; 7 (3%) in the everolimus group and 6 (2%) in the control group. The most common causes of death across the study groups were related to cardiac conditions and infections.

There were 12 (4%) graft losses in the everolimus group and 8 (3%) in the control group over the 12 month study period. Of the graft losses, 4 were due to renal artery and two due to renal vein thrombosis in the everolimus group (2%) compared to two renal artery thromboses in the control group (1%). [*See Boxed Warning and Warnings and Precautions (5.4)*]

The most common ($\geq 20\%$) adverse reactions observed in the everolimus group were: peripheral edema, constipation, hypertension, nausea, anemia, urinary tract infection, and hyperlipidemia.

Infections

The overall incidence of bacterial, fungal and viral infections reported as adverse reactions was higher in the control group (68%) compared to the everolimus group (64%) and was primarily due to an increased number of viral infections (21% in the control group and 10% in the everolimus group). The incidence of cytomegalovirus (CMV) infections reported as adverse reactions was 8% in the control group compared to 1% in the everolimus group; and 3% of the serious CMV infections in the control group versus 0% in the everolimus group were considered serious. [*See Warnings and Precautions (5.3)*]

BK Virus

BK virus infections were lower in incidence in the everolimus group (2 patients, 1%) compared to the control group (11 patients, 4%). One of the two BK virus infections in the everolimus group and two of the 11 BK virus infections in the control group were also reported as serious adverse events. BK virus infections did not result in graft loss in any of the groups in the clinical trial.

Wound Healing and Fluid Collections

Wound healing-related reactions were identified through a retrospective search and request for additional data. The overall incidence of wound-related events, including lymphocele, seroma, hematoma, dehiscence, incisional hernia, and infections was 35% in the everolimus group compared to 26% in the control group. More patients required intraoperative repair debridement or drainage of incisional wound complications and more required drainage of lymphoceles and seromas in the everolimus group compared to control.

Adverse reactions due to major fluid collections such as edema and other types of fluid collections was 45% in the everolimus group and 40% in the control group. [See *Warnings and Precautions* (5.8)]

Neoplasms

Adverse events due to malignant and benign neoplasms were reported in 3% of patients in the everolimus group and 6% in the control group. The most frequently reported neoplasms in the control group were basal cell carcinoma, squamous cell carcinoma, skin papilloma and seborrheic keratosis. One patient in the everolimus group who underwent a melanoma excision prior to transplantation died due to metastatic melanoma. [See *Boxed Warning and Warnings and Precautions* (5.2)]

New Onset Diabetes Mellitus (NODM)

NODM reported based on adverse reactions and random serum glucose values, was 9% in the everolimus group compared to 7% in the control group.

Endocrine Effects in Males

In the everolimus group, serum testosterone levels significantly decreased while the FSH levels significantly increased without significant changes being observed in the control group. In both the everolimus and the control groups mean testosterone and FSH levels remained within the normal range with the mean FSH level in the everolimus group being at the upper limit of the normal range (11.1 U/L). More patients were reported with erectile dysfunction in the everolimus treatment group compared to the control group (5% compared to 2%, respectively).

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving everolimus with reduced dose cyclosporine or mycophenolic acid with standard dose cyclosporine. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 1 Incidence Rates of Frequent ($\geq 10\%$ in Any Treatment Group) Adverse Reactions by Primary System Organ Class and Preferred Term

Primary System Organ Class Preferred Term	Zortress (everolimus) 1.5 mg With reduced dose cyclosporine N=274 / n (%)	Myfortic (mycophenolic acid) 1.44 g With standard dose cyclosporine N=273 / n (%)
Any Adverse Events*	271 (99)	270 (99)
Blood lymphatic system disorders	93 (34)	111 (41)
Anemia	70 (26)	68 (25)
Leukopenia	8 (3)	33 (12)
Gastrointestinal disorders	196 (72)	207 (76)
Constipation	105 (38)	117 (43)
Nausea	79 (29)	85 (31)
Diarrhea	51 (19)	54 (20)

Vomiting	40 (15)	60 (22)
Abdominal pain	36 (13)	42 (15)
Dyspepsia	12 (4)	31 (11)
Abdominal pain upper	9 (3)	30 (11)
General disorders and administrative site conditions	181 (66)	160 (59)
Edema peripheral	123 (45)	108 (40)
Pyrexia	51 (19)	40 (15)
Fatigue	25 (9)	28 (10)
Infections and infestations	169 (62)	185 (68)
Urinary tract infection	60 (22)	63 (23)
Upper respiratory tract infection	44 (16)	49 (18)
Injury, poisoning and procedural complications	163 (60)	163 (60)
Incision site pain	45 (16)	47 (17)
Procedural pain	40 (15)	37 (14)
Investigations	137 (50)	133 (49)
Blood creatinine increased	48 (18)	59 (22)
Metabolism and nutrition disorders	222 (81)	199 (73)
Hyperlipidemia	57 (21)	43 (16)
Hyperkalemia	49 (18)	48 (18)
Hypercholesterolemia	47 (17)	34 (13)
Dyslipidemia	41 (15)	24 (9)
Hypomagnesemia	37 (14)	40 (15)
Hypophosphatemia	35 (13)	35 (13)
Hyperglycemia	34 (12)	38 (14)
Hypokalemia	32 (12)	32 (12)
Musculoskeletal and connective tissue disorders	112 (41)	105 (39)
Pain in extremity	32 (12)	29 (11)
Back pain	30 (11)	28 (10)
Nervous system disorders	92 (34)	109 (40)
Headache	49 (18)	40 (15)
Tremor	23 (8)	38 (14)
Psychiatric disorders	90 (33)	72 (26)
Insomnia	47 (17)	43 (16)

Renal and urinary disorders	112 (41)	124 (45)
Hematuria	33 (12)	33 (12)
Dysuria	29 (11)	28 (10)
Respiratory, thoracic and mediastinal disorders	86 (31)	93 (34)
Cough	20 (7)	30 (11)
Vascular disorders	122 (45)	124 (45)
Hypertension	81 (30)	82 (30)

* As reported in the safety analysis population defined as all randomized patients who received at least one dose of treatment and had at least one post-baseline safety assessment.

Adverse events that occurred with at least a 5% higher frequency in the everolimus 1.5 mg group compared to the control group were: peripheral edema (45% compared to 40%), hyperlipidemia (21% compared to 16%), dyslipidemia (15% compared to 9%), and stomatitis/mouth ulceration (8% compared to 3%).

A third treatment group of everolimus 3.0 mg per day (1.5 mg twice daily; target trough concentrations 6 to 12 ng/mL) with reduced-dose cyclosporine was included in the study described above. Although as effective as the lower dose everolimus group, the overall safety was worse and consequently higher doses of everolimus cannot be recommended. Out of 279 patients, 95 (34%) discontinued the study medication with 57 (20%) doing so because of adverse reactions. The most frequent adverse reactions leading to discontinuation of everolimus when used at this higher dose were injury, poisoning and procedural complications (everolimus 1.5 mg: 5%, everolimus 3.0 mg: 7%, and control: 2%), infections (2%, 6%, and 3%, respectively), renal and urinary disorders (4%, 7%, and 4%, respectively) and gastrointestinal disorders (1%, 3%, and 2%).

Less common adverse reactions, occurring in $\geq 1\%$ to $< 10\%$ of patients treated with everolimus include:

Blood and Lymphatic System Disorders: leukocytosis, leucopenia, lymphadenopathy, thrombocytopenia, thrombocytopenia

Cardiac and Vascular Disorders: angina pectoris, atrial fibrillation, cardiac failure congestive, palpitations, tachycardia, hypertension including hypertensive crisis, hypotension, deep vein thrombosis

Endocrine Disorders: Cushingoid, hyperparathyroidism

Eye Disorders: cataract, conjunctivitis, vision blurred

Gastrointestinal Disorders: abdominal pain, abdominal distention, dyspepsia, dysphagia, epigastric discomfort, flatulence, gastroesophageal reflux disease, gingival hypertrophy, hematemesis, hemorrhoids, ileus, mouth ulceration, peritonitis, stomatitis

General Disorders and Administrative Site Conditions: chest discomfort, chest pain, chills, fatigue, malaise, edema including generalized edema

Hepatobiliary Disorders: hepatic enzyme increased, bilirubin increased

Infections and Infestations: BK virus infection [See Warnings and Precautions (5.11)], bacteremia, bronchitis, candidiasis, cellulitis, folliculitis, gastroenteritis, influenza, nasopharyngitis, onychomycosis, oral candidiasis, osteomyelitis, pneumonia, pyelonephritis, sinusitis, tinea pedis, urethritis, wound infection, herpes infections [See Boxed Warning and Warnings and Precautions (5.3)]

Injury Poisoning and Procedural Complications: incision site complications including infections, perinephric collection, seroma, wound dehiscence, incisional hernia, perinephric hematoma, localized intraabdominal fluid collection, impaired healing, lymphocele, lymphorrhea

Metabolism and Nutrition Disorders: blood urea increased, acidosis, anorexia, dehydration, diabetes mellitus [See Warnings and Precautions (5.15)], fluid retention, gout, hypercalcemia, hypercholesterolemia [See Warnings and

Precautions (5.9)], hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypoglycemia, hyponatremia, iron deficiency, vitamin B12 deficiency

Musculoskeletal and Connective Tissues Disorders: arthralgia, joint swelling, muscle spasms, muscular weakness, musculoskeletal pain, myalgia, osteonecrosis, osteopenia, osteoporosis, spondylitis

Nervous System Disorders: dizziness, hemiparesis, hypoaesthesia, paresthesia, somnolence, syncope, tremor

Psychiatric Disorders: agitation, anxiety, depression, hallucination

Renal and Urinary Disorders: bladder spasm, hydronephrosis, micturation urgency, nephritis interstitial, pollakiuria, polyuria, proteinuria [*See Warnings and Precautions (5.10)*], pyuria, renal artery thrombosis [*See Boxed Warning and Warnings and Precautions (5.4)*], acute renal failure, renal impairment [*See Warnings and Precautions (5.5)*], urinary retention

Reproductive System and Breast Disorders: erectile dysfunction, ovarian cyst, scrotal edema

Respiratory, Thoracic, Mediastinal Disorders: atelectasis, cough, dyspnea, epistaxis, nasal congestion, pleural effusions, pulmonary edema, rhinorrhea, sinus congestion, wheezing

Skin and Subcutaneous Tissue Disorders: alopecia, dermatitis acneiform, hirsutism, hyperhidrosis, hypertrichosis, night sweats, pruritus, rash

Less common, serious adverse reactions include:

- Non-infectious Pneumonitis [*See Warnings and Precautions (5.13) and Adverse Reactions (6.2)*]
- Thrombotic Microangiopathy (TMA), Thrombotic Thrombocytopenic Purpura (TTP), and Hemolytic Uremic Syndrome (HUS) [*See Warnings and Precautions (5.14)*]

The combination of fixed dose everolimus and standard doses cyclosporine in previous clinical trials resulted in frequent elevations of serum creatinine with higher mean and median serum creatinine values was observed than in the current study with reduced doses of cyclosporine. These results indicate that everolimus increases the cyclosporine-induced nephrotoxicity; and therefore should only be used in a concentration-controlled regimen with reduced doses of cyclosporine. [*See Boxed Warnings, Indications and Usage (1.2) and Warnings and Precautions (5.5)*]

6.3 Post Marketing Experience

Adverse reactions identified from the post-marketing use of the combination regimen of everolimus and cyclosporine that are not specific to any one transplant indication include angioedema [*See Warnings and Precautions (5.4)*], pancreatitis and pulmonary embolism. There have also been reports of male infertility with mTOR inhibitors including everolimus. [*See Warnings and Precautions (5.16)*].

7 DRUG INTERACTIONS

7.1 Interactions with Strong Inhibitors or Inducers of CYP3A4 and P-glycoprotein

Everolimus is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall and is a substrate for the multidrug efflux pump, P-glycoprotein. Therefore, absorption and subsequent elimination of systemically absorbed everolimus may be influenced by medicinal products that affect CYP3A4 and/or P-glycoprotein. Concurrent treatment with strong inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (e.g., rifampin, rifabutin) of CYP3A4 is not recommended. Inhibitors of P-glycoprotein (e.g., digoxin, cyclosporine) may decrease the efflux of everolimus from intestinal cells and increase everolimus blood concentrations. *In vitro*, everolimus was a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of medicinal products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. [*See Therapeutic Drug Monitoring (2.2)*]

All *in vivo* interaction studies were conducted without concomitant cyclosporine. Pharmacokinetic interactions between everolimus and concomitantly administered drugs are discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

7.2 Cyclosporine (CYP3A4/P-gp inhibitor and CYP3A4 substrate)

The steady-state C_{max} and AUC estimates of everolimus were significantly increased by co-administration of single dose cyclosporine. [*See Clinical Pharmacology (12.3)*] Dose adjustment of everolimus might be needed if the cyclosporine

dose is altered. [See *Dosage and Administration (2.3)*] Everolimus had a clinically minor influence on cyclosporine pharmacokinetics in transplant patients receiving cyclosporine (Neoral).

7.3 Ketoconazole (Strong CYP3A4 Inhibitor)

Multiple-dose ketoconazole administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max} , AUC, and half-life. It is recommended that strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) not be co-administered with everolimus. [See *Warnings and Precautions (5.12)*, and *Clinical Pharmacology (12.3)*]

7.4 Erythromycin (Moderate CYP3A4 Inhibitor)

Multiple-dose erythromycin administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max} , AUC, and half-life. If erythromycin is co-administered, everolimus blood concentrations should be monitored and a dose adjustment made as necessary. [See *Clinical Pharmacology (12.3)*]

7.5 Verapamil (CYP3A4 and P-gp Substrate)

Multiple-dose verapamil administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max} and AUC. Everolimus half-life was not changed. If verapamil is co-administered, everolimus blood concentrations should be monitored and a dose adjustment made as necessary. [See *Clinical Pharmacology (12.3)*]

7.6 Atorvastatin (CYP3A4 substrate) and Pravastatin (P-gp substrate)

Single-dose administration of everolimus with either atorvastatin or pravastatin to healthy subjects did not influence the pharmacokinetics of atorvastatin, pravastatin and everolimus, as well as total HMG-CoA reductase bioreactivity in plasma to a clinically relevant extent. However, these results cannot be extrapolated to other HMG-CoA reductase inhibitors. Patients should be monitored for the development of rhabdomyolysis and other adverse events as described in the respective labeling for these products.

7.7 Simvastatin and Lovastatin

Due to an interaction with cyclosporine, clinical studies of everolimus with cyclosporine conducted in kidney transplant patients strongly discouraged patients with receiving HMG-CoA reductase inhibitors such as simvastatin and lovastatin. [See *Warnings and Precautions (5.12)*]

7.8 Rifampin (Strong CYP3A4) Inducers

Pre-treatment of healthy subjects with multiple-dose rifampin followed by a single dose of everolimus increased everolimus clearance and decreased the everolimus C_{max} and AUC estimates. Combination with rifampin is not recommended. [See *Warnings and Precautions (5.12)* and *Clinical Pharmacology (12.3)*]

7.9 Other Possible Interactions

Moderate inhibitors of CYP3A4 and P-gp may increase everolimus blood concentrations (e.g., fluconazole; macrolide antibiotics; nifedipine, diltiazem; nelfinavir, indinavir, amprenavir). Inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood concentrations (e.g., St. John's Wort [*Hypericum perforatum*]; anticonvulsants: carbamazepine, phenobarbital, phenytoin; efavirenz, nevirapine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of everolimus in pregnant women. In rats and rabbits, everolimus crossed the placenta and was toxic to the conceptus. The potential risk for humans is unknown. Everolimus should be given to pregnant women only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should be advised to use effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

Everolimus administered daily to pregnant rats by oral gavage at 0.1 mg/kg from before mating through organogenesis resulted in increased preimplantation loss and early resorptions of fetal implants. AUCs in rats at this dose were approximately one-third those in humans administered the starting dose (0.75 mg twice daily). Everolimus administered daily by oral gavage at 0.8 mg/kg to pregnant rabbits during organogenesis resulted in increased late resorptions of fetal

implants. At this dose, AUCs in rabbits were slightly less than the AUCs in humans administered the starting clinical dose.

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites readily transferred into milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, women should avoid breast-feeding during treatment with Zortress.

8.4 Pediatric Use

The safe and effective use of Zortress in kidney transplant patients younger than 18 years of age has not been established. [See *Clinical Pharmacology* (12.3)]

8.5 Geriatric Use

There is limited clinical experience on the use of Zortress in patients of age 65 or older. There is no evidence to suggest that elderly patients will require a different dosage recommendation from younger adult patients. [See *Clinical Pharmacology* (12.3)]

8.6 Hepatic Impairment

No dosage adjustment is needed for patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose needs to be reduced by one-half recommended initial daily dose. There is no information on the effects of severe hepatic impairment (Child-Pugh Class C) on everolimus pharmacokinetics. [See *Clinical Pharmacology* (12.3)]

8.7 Renal Impairment

No dose adjustment is needed in patients with renal impairment. [See *Clinical Pharmacology* (12.3)]

10 OVERDOSAGE

Reported experience with overdose in humans is very limited. There is a single case of an accidental ingestion of 1.5 mg everolimus in a two-year-old child where no adverse reactions were observed. Single doses up to 25 mg have been administered to transplant patients with acceptable acute tolerability. Single doses up to 70 mg (without cyclosporine) have been given with acceptable acute tolerability. General supportive measures should be followed in all cases of overdose. Everolimus is not considered dialyzable to any relevant degree (<10% of everolimus removed within 6 hours of hemodialysis). In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg (limit test) in either mice or rats.

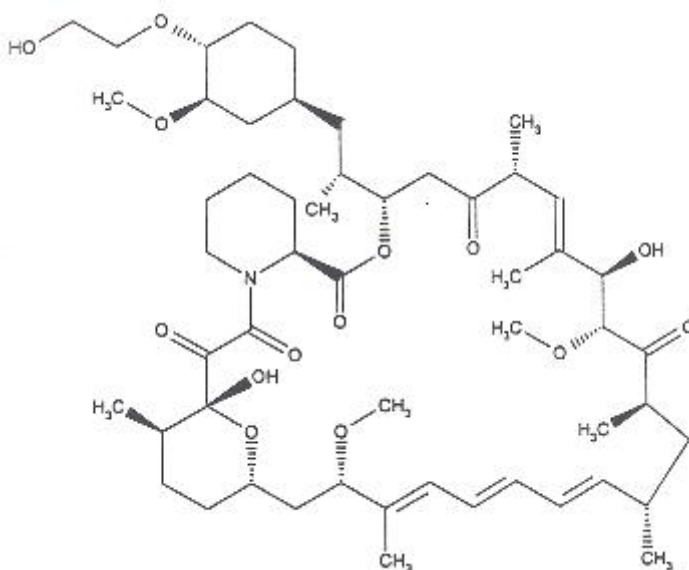
11 DESCRIPTION

Zortress (everolimus) is a macrolide immunosuppressant.

The chemical name of everolimus is

(1R, 9S, 12S, 15R, 16E, 18R, 19R, 21R, 23S, 24E, 26E, 28E, 30S, 32S, 35R)-1, 18-dihydroxy-12 -{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15, 17, 21, 23, 29, 35-hexamethyl-11, 36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}] hexatriaconta-16,24,26,28-tetraene-2, 3,10,14,20-pentaone.

The molecular formula is C₅₃H₈₃NO₁₄ and the molecular weight is 958.25. The structural formula is



Everolimus is supplied as tablets for oral administration containing 0.25 mg, 0.5 mg and 0.75 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, croscopvidone and lactose anhydrous as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Everolimus inhibits antigenic and interleukin (IL-2 and IL-15) stimulated activation and proliferation of T and B lymphocytes.

In cells, everolimus binds to a cytoplasmic protein, the FK506 Binding Protein-12 (FKBP-12), to form an immunosuppressive complex (everolimus: FKBP-12) that binds to and inhibits the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. In the presence of everolimus phosphorylation of p70 S6 ribosomal protein kinase (p70S6K), a substrate of mTOR, is inhibited. Consequently, phosphorylation of the ribosomal S6 protein and subsequent protein synthesis and cell proliferation are inhibited. The everolimus: FKBP-12 complex has no effect on calcineurin activity.

In rats and non-human primate models, everolimus effectively reduces kidney allograft rejection resulting in prolonged graft survival.

12.3 Pharmacokinetics

Everolimus pharmacokinetics have been characterized after oral administration of single and multiple doses to adult kidney transplant patients, hepatically-impaired patients, and healthy subjects.

Absorption

After oral dosing, peak everolimus concentrations occur 1 to 2 h post dose. Over the dose range of 0.5 mg to 2 mg twice daily, everolimus C_{max} and AUC are dose proportional in transplant patients at steady-state.

Food Effect

In 24 healthy subjects, a high-fat breakfast (44.5 g fat) reduced everolimus C_{max} by 60%, delayed t_{max} by a median 1.3 hours, and reduced AUC by 16% compared with a fasting administration. To minimize variability, everolimus should be taken consistently with or without food. [See *Dosage and Administration* (2.4)]

Distribution

The blood-to-plasma ratio of everolimus is concentration dependent ranging from 17% to 73% over the range of 5 ng/mL to 5000 ng/mL. Plasma protein binding is approximately 74% in healthy subjects and in patients with moderate hepatic impairment. The apparent distribution volume associated with the terminal phase (V_z/F) from a single-dose pharmacokinetic study in maintenance kidney transplant patients is 342 to 107 L (range 128 to 589 L).

Metabolism

Everolimus is a substrate of CYP3A4 and P-glycoprotein. The main metabolic pathways identified in man were monohydroxylations and O-dealkylations. Two main metabolites were formed by hydrolysis of the cyclic lactone. Everolimus was the main circulating component in blood. None of the main metabolites contribute significantly to the immunosuppressive activity of everolimus.

Excretion

After a single dose of radiolabeled everolimus was given to transplant patients receiving cyclosporine, the majority (80%) of radioactivity was recovered from the feces and only a minor amount (5%) was excreted in urine. Parent drug was not detected in urine and feces.

Pharmacokinetics in Kidney Transplant Patients

Steady-state is reached by Day 4 with an accumulation in blood levels of 2- to 3-fold compared with the exposure after the first dose.

Table 2 Pharmacokinetic Parameters (mean +/- SD) Following the Administration of 0.75 mg Twice Daily

C_{max}	T_{max}	AUC	CL/F ¹	Vc/F ¹	Half-life ($T_{1/2}$)
11.1 ± 4.6 ng/mL	1-2 h	75 ± 31 ng.h/mL	8.8 L/h	110 L	30 ± 11h

¹ population pharmacokinetic analysis

The half-life estimates from 12 maintenance renal transplant patients who received single doses of everolimus capsules at 0.75 mg or 2.5 mg with their maintenance cyclosporine regimen indicate that the pharmacokinetics of everolimus are linear over the clinically-relevant dose range. Results indicate the half-life of everolimus in maintenance renal transplant patients receiving single doses of 0.75 mg or 2.5 mg everolimus during steady-state cyclosporine treatment was 30 ± 11 hours (range 19 to 53 hours).

Drug-Drug Interactions

Everolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. The pharmacokinetic interaction between everolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below. [See *Warnings and Precautions (5.12)*, and *Drug Interactions (7)*]

Cyclosporine (CYP3A4/P-gp inhibitor and CYP3A4 substrate): Everolimus should be taken concomitantly with cyclosporine. Everolimus concentrations may decrease when doses of cyclosporine are reduced, unless the everolimus dose is increased. [See *Dosage and Administration (2.1)*, *Drug Interactions (7.2)*]

In a single-dose study in healthy subjects, cyclosporine (Neoral) administered at a dose of 175 mg increased everolimus AUC by 168% (range, 46% to 365%) and C_{max} by 82% (range, 25% to 158%) when administered with 2 mg everolimus compared with administration of everolimus alone. [See *Drug Interactions (7.2)*]

Ketoconazole (Strong CYP3A4 Inhibitor): Multiple-dose administration of 200 mg ketoconazole twice daily for 5 days to 12 healthy volunteers significantly increased everolimus C_{max} , AUC, and half-life by 3.9-fold, 15-fold, and 89%, respectively, when co-administered with 2 mg everolimus. It is recommended that strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) not be co-administered with everolimus. [See *Warnings and Precautions (5.12)* and *Drug Interactions (7.3)*]

Erythromycin (Moderate CYP3A4 Inhibitor): Multiple-dose administration of 500 mg erythromycin three times daily for 5 days to 16 healthy volunteers significantly increased everolimus C_{max} , AUC, and half-life by 2.0-fold, 4.4-fold, and 39%, respectively, when co-administered with 2 mg everolimus. If erythromycin is co-administered, everolimus blood concentrations should be monitored and a dose adjustment made as necessary. [See *Drug Interactions (7.4)*]

Verapamil (CYP3A4 Inhibitor and P-gp Substrate): Multiple-dose administration of 80 mg verapamil three times daily for 5 days to 16 healthy volunteers significantly increased everolimus C_{max} and AUC by 2.3-fold and 3.5-fold, respectively, when co-administered with 2 mg everolimus. Everolimus half-life was not changed. If verapamil is co-administered, everolimus blood concentrations should be monitored and a dose adjustment made as necessary. [See *Drug Interactions (7.5)*]

Atorvastatin (CYP3A4 Substrate) and Pravastatin (P-gp Substrate): Following administration of a single dose of 2 mg everolimus to 12 healthy subjects, the concomitant administration of a single oral dose administration of atorvastatin 20

mg or pravastatin 20 mg only slightly decreased everolimus C_{max} and AUC by 9% and 10%, respectively. There was no apparent change in the mean $T_{1/2}$ or median T_{max} . In the same study, the concomitant everolimus dose slightly increased the mean C_{max} of atorvastatin by 11% and slightly decreased the AUC by 7%. The concomitant everolimus dose decreased the mean C_{max} and AUC of pravastatin by 10% and 5%, respectively. No dosage adjustments are needed for concomitant administration of everolimus and atorvastatin and pravastatin. [See *Drug Interactions (7.6)*]

Rifampin (Strong CYP3A4/ P-gp Inducer): Pre-treatment of 12 healthy subjects with multiple-dose rifampin (600 mg once-daily for 8 days) followed by a single dose of 4 mg everolimus increased everolimus clearance nearly 3-fold, and decreased C_{max} by 58% and AUC by 63%. Combination with rifampin is not recommended. [See *Drug Interactions (7.8)*]

Special Populations

Hepatic Impairment

Everolimus AUC was increased an average 2-fold in 8 patients with moderate hepatic impairment (Child-Pugh Class B) compared with 8 healthy subjects. AUC was positively correlated with serum bilirubin concentration and with prolongation in prothrombin time and negatively correlated with serum albumin concentration. The AUC of everolimus tended to be greater than that of healthy subjects if bilirubin was $>34 \mu\text{mol/L}$, prothrombin time was $>1.3 \text{ INR}$ $>4 \text{ sec}$ prolongation, and/or albumin concentration was $<35 \text{ g/L}$. The impact of severe hepatic impairment (Child-Pugh Class C) on everolimus pharmacokinetics has not been assessed but the effect on everolimus AUC is likely to be as large or larger compared with moderate impairment. [See *Dosage and Administration (2.5)*] No dosing adjustment is needed for patients with mild hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose needs to be reduced by one-half the recommended initial daily dose and blood concentrations should be monitored to make further adjustments as needed.

Renal Impairment

No pharmacokinetic studies in patients with renal impairment were conducted. Post-transplant renal function (creatinine clearance range 11 to 107 mL/min) did not affect the pharmacokinetics of everolimus, therefore, no dosage adjustments are needed in patients with renal impairment.

Pediatrics

The safety and efficacy of everolimus has not been established in pediatric patients.

Geriatrics

A limited reduction in everolimus oral CL of 0.33% per year was estimated in adults (age range studied was 16 to 70 years). There is no evidence to suggest that elderly patients will require a different dosage recommendation from younger adult patients.

Race

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is, on average, 20% higher in Black transplant patients.

12.5 Everolimus Whole Blood Concentrations Observed in Kidney Transplant Patients

Based on exposure-efficacy and exposure-safety analyses of clinical trials and using an LCMSMS assay method, kidney transplant patients achieving everolimus whole blood trough concentrations $\geq 3.0 \text{ ng/mL}$ have been found to have a lower incidence of treated biopsy-proven acute rejection compared with patients whose trough concentrations were below 3.0 ng/mL. Patients who attained everolimus trough concentrations within the range of 6 to 12 ng/mL had similar efficacy and more adverse events than patients who attained lower trough concentrations between 3 to 8 ng/mL. [See *Dosage and Administration (2.2)*]

In the clinical trial [See *Clinical Studies (14.1)*], everolimus whole blood trough concentrations were measured at Days 3, 7, and 14 and Months 1, 2, 3, 4, 6, 7, 9, and 12. The proportion of patients receiving 0.75 mg twice daily everolimus treatment regimen who had everolimus whole blood trough concentrations within the protocol specified target range of 3 to 8 ng/mL at Days 3, 7, and 14 were 55%, 71% and 69%, respectively. Approximately 80% of patients had everolimus whole blood trough concentrations within the 3 to 8 ng/mL target range by Month 1 and remained stable within range through Month 12. The median everolimus trough concentration for the 0.75 mg twice daily treatment group was between 3 and 8 ng/mL throughout the study duration.

12.6 Cyclosporine Concentrations Observed in Kidney Transplant Patients

In the clinical trial [See *Clinical Studies (14.1)*], the target cyclosporine whole blood trough concentration for the everolimus treatment arm of 0.75 mg twice daily were 100 to 200 ng/mL through Month 1 post-transplant, 75 to 150 ng/mL at Months 2 and 3 post-transplant, 50 to 100 ng/mL at Month 4 post-transplant, and 25 to 50 ng/mL from Month 6 through Month 12 post-transplant. Table 3 below provides a summary of the observed cyclosporine whole blood trough concentrations during the study.

Table 3 Cyclosporine Trough Concentrations Over 12 Months – Renal Study A2309 Median Values (ng/mL) with 10th and 90th Percentiles

Treatment group	Visit	N	Target (ng/mL)	Median	10 th Percentile	90 th Percentile
Everolimus 0.75 mg twice daily	Day 3	242	100-200	172	46	388
	Day 7	265	100-200	185	75	337
	Day 14	243	100-200	182	97	309
	Month 1	245	100-200	161	85	274
	Month 2	232	75-150	140	84	213
	Month 3	220	75-150	111	68	187
	Month 4	208	50-100	99	56	156
	Month 6	200	25-50	75	43	142
	Month 7	199	25-50	59	36	117
	Month 9	194	25-50	49	28	91
Month 12	186	25-50	46	25	100	

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Everolimus was not carcinogenic in mice or rats when administered daily by oral gavage for 2 years at doses of 0.9 mg/kg. In these studies, AUCs in mice were much higher (at least 20 times) than those in humans receiving 0.75 mg twice daily, and AUCs in rats were in the same range as those in humans receiving 0.75 mg twice daily.

Everolimus was not mutagenic in the bacterial reverse mutation, the mouse lymphoma thymidine kinase assay, or the chromosome aberration assay using V79 Chinese hamster cells, or *in vivo* following two daily doses of 500 mg/kg in the mouse micronucleus assay.

In a 13-week male fertility oral gavage study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone concentrations were diminished at 5 mg/kg which caused a decrease in male fertility. There was evidence of reversibility of these findings in animals examined after 13 weeks post-dosing. The 0.5 mg/kg dose in male rats resulted in AUCs in the range of clinical exposures, and the 5 mg/kg dose resulted in AUCs approximately 5 times the AUCs in humans receiving 0.75 mg twice daily. Everolimus did not affect female fertility in nonclinical studies, but everolimus crossed the placenta and was toxic to the conceptus. [See *Pregnancy (8.1)*]

14 CLINICAL STUDIES

14.1 Prevention of Organ Rejection after Renal Transplantation

A 24-month, multi-national, open-label, randomized (1:1:1) trial was conducted comparing two concentration-controlled everolimus regimens of 1.5 mg per day starting dose (targeting 3 to 8 ng/mL using an LCMSMS assay method) and 3.0 mg per day starting dose (targeting 6 to 12 ng/mL using an LCMSMS assay method) with reduced doses of cyclosporine and corticosteroids, to 1.44 gm per day of mycophenolic acid with standard doses of cyclosporine and corticosteroids. The mean cyclosporine starting dose was 5.2, 5.0 and 5.7 mg/kg body weight/day in the everolimus 1.5 mg, 3.0 mg and in mycophenolic acid groups, respectively. The cyclosporine dose in the everolimus group was then adjusted to the blood

trough concentration ranges indicated in Table 3, whereas in the Myfortic group the target ranges were 200-300 ng/mL starting Day 5: 200-300 ng/mL, and 100-250 ng/mL from Month 2 to Month 12.

All patients received basiliximab induction therapy. The study population consisted of 18 to 70 year old male and female low to moderate risk renal transplant recipients undergoing their first transplant. Low to moderate immunologic risk was defined in the study as an ABO blood type compatible first organ or tissue transplant recipient with anti-HLA Class I PRA <20% by a complement dependant cytotoxicity-based assay, or <50% by a flow cytometry or ELISA-based assay, and with a negative T-cell cross match. Eight hundred thirty-three (833) patients were randomized after transplantation; 277 randomized to the everolimus 1.5 mg per day group, 279 to the everolimus 3.0 mg per day group and 277 to the Myfortic 1.44 gm per day group. The study was conducted at 79 renal transplant centers across Europe, South Africa, North and South America, and Asia-Pacific. There were no major baseline differences between treatment groups with regard to recipient or donor disease characteristics. The majority of transplant recipients in all groups (70% to 76%) had three or more HLA mismatches; mean percentage of panel reactive antibodies ranged from 1% to 2%. The rate of premature treatment discontinuation at 12 months was 30% and 22% in the everolimus 1.5 mg and Myfortic groups, respectively, (p=0.03, Fisher's exact test) and was more prominent between groups among female patients. Results at 12 months indicated that everolimus 1.5 mg per day is comparable to Myfortic with respect to efficacy failure, defined as treated biopsy-proven acute rejection, graft loss, death or loss to follow-up. The percentage of patients experiencing this endpoint and each individual variable in the everolimus and Myfortic groups is shown in Table 4. The incidence of efficacy failure was 25% and 24% in the everolimus and Myfortic groups, respectively.

Table 4 Efficacy Failure by Treatment Group (ITT Population) at 12 Months

	Zortress (everolimus) 1.5 mg/day With reduced dose CsA N=277 n (%)	Mycophenolic Acid 1.44 gm/day With standard dose CsA N=277 n (%)
Efficacy Endpoints³		
Primary Efficacy Failure Endpoint ¹	70 (25.3)	67 (24.2)
Treated Biopsy Proven Acute Rejection	45 (16.2)	47 (17.0)
Death	7 (2.5)	6 (2.2)
Graft Loss	12 (4.3)	9 (3.2)
Loss to Follow-up	12 (4.3)	9 (3.2)
Graft Loss or Death or Loss to Follow-up ²	32 (11.6)	26 (9.4)
Graft Loss or Death	18 (6.5)	15 (5.4)
Loss to Follow-up ²	14 (5.1)	11 (4.0)

¹ Includes treated BPAR, graft loss, death or loss to follow-up by Month 12 where loss to follow-up represents patient who did not experience treated BPAR, graft loss or death and whose last contact date is prior to 12 month visit

² Loss to follow-up (for Graft Loss, Death, or Loss to Follow-up) represents patient who did not experience death or graft loss and whose last contact date is prior to 12 month visit

³ The difference in rates (everolimus – mycophenolic acid) with 95% CI for primary efficacy failure endpoint is 1.1% (-6.1%, 8.3%); and for the graft loss, death or loss to follow-up endpoint is 2.2% (-2.9%, 7.3%).

The calculated mean glomerular filtration rate (using the MDRD equation) for everolimus 1.5 mg (target trough concentrations 3 to 8 ng/mL) and mycophenolic acid were comparable at Month 12 in the ITT population (Table 5).

**Table 5 Calculated Glomerular Filtration Rates (mL/min/1.73m²) by MDRD
At 12 Months Post-Transplant***

	Zortress (everolimus)	Mycophenolic Acid
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Month 12 GFR (MDRD)	1.5 mg/day with reduced dose CsA n=276	1.44 gm/day with standard dose CsA n=277
Mean (SD)**	54.6 (21.7)	52.3 (26.5)
Median (Range)	55.0 (0 – 140.9)	50.1 (0.0-366.4)

* Analysis based on using a subject's last observation carried forward for missing data at 12 months due to death or lost to follow-up data, a value of zero is used for subjects who experienced a graft loss.

** SD=standard deviation

Two earlier studies compared fixed doses of everolimus 1.5 mg per day and 3 mg per day, without therapeutic drug monitoring, combined with standard doses of cyclosporine and corticosteroids to mycophenolate mofetil 2.0 gm per day and corticosteroids. Antilymphocyte antibody induction was prohibited in both studies. Both were multicenter, double-blind (for first 12 months), randomized trials (1:1:1) of 588 and 583 *de novo* renal transplant patients, respectively. The 12 month analysis of GFR showed increased rates of renal impairment in both the everolimus groups compared to the mycophenolate mofetil group in both studies. Therefore, reduced doses of cyclosporine should be used in combination with everolimus in order to avoid renal dysfunction and everolimus trough concentrations should be adjusted using therapeutic drug monitoring to maintain trough concentrations between 3 to 8 ng/mL. [See *Boxed Warning, Dosage and Administration (2.3) and Warnings and Precautions (5.5)*]

16 HOW SUPPLIED/STORAGE AND HANDLING

Zortress (everolimus) Tablets are packed in child-resistant blisters.

Description of Zortress (everolimus) Tablets

Dosage Strength	0.25 mg	0.5 mg	0.75 mg
Appearance	White to yellowish, marbled, round, flat tablets with beveled edge		
Imprint	“C” on one side and “NVR” on the other	“CH” on one side and “NVR” on the other	“CL” on one side and “NVR” on the other
NDC Number	0078-0417-20	0078-0414-20	0078-0415-20

Each strength is available in boxes of 60 tablets (6 blister strips of 10 tablets each).

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]

Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Administration

Inform patients that Zortress should be taken orally twice a day approximately 12 hours apart consistently either with or without food.

Inform patients to avoid grapefruit and grapefruit juice which increase blood drug concentrations of Zortress. [See *Warnings and Precautions (5.18)*]

Advise patients that Zortress should be used concurrently with reduced doses of cyclosporine and that any change of cyclosporine dose should be made under physician supervision and may also require a change in the dosage of Zortress.

Inform patients of the necessity of repeated laboratory tests according to physician recommendations while they are taking Zortress.

17.2 Development of Lymphomas and Other Malignancies

Inform patients they are at risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and using a sunscreen with a high protection factor. [*See Warnings and Precautions (5.2)*]

17.3 Increased Risk of Infection

Inform patients they are at increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression. Advise patients to contact their physician if they develop any symptoms of infection. [*See Warnings and Precautions (5.3, 5.11)*]

17.4 Graft Thrombosis

Inform patients that Zortress has been associated with an increased risk of kidney arterial and venous thrombosis, resulting in graft loss, usually within the first 30 days post-transplantation. [*See Warnings and Precautions (5.4)*]

17.5 Nephrotoxicity

Advise patients of the risks of impaired kidney function with the combination of Zortress and cyclosporine as well as the need for routine blood concentration monitoring for both drugs. Advise patients of the importance of serum creatinine monitoring. [*See Warnings and Precautions (5.5)*]

17.6 Angioedema

Inform patients of the risk of angioedema and that concomitant use of angiotensin converting enzyme (ACE) inhibitors may increase this risk. Advise patients to seek prompt medical attention if symptoms occur. [*See Warnings and Precautions (5.7)*]

17.7 Wound Healing Complications and Fluid Accumulation

Inform patients the use of Zortress has been associated with impaired or delayed wound healing, fluid accumulation and the need for careful observation of their incision site. [*See Warnings and Precautions (5.8)*]

17.8 Hyperlipidemia

Inform patients the use of Zortress has been associated with increased serum cholesterol and triglycerides that may require treatment and the need for monitoring of blood lipid concentrations. [*See Warnings and Precautions (5.9)*]

17.9 Proteinuria

Inform patients the use of Zortress has been associated with an increased risk of proteinuria. [*See Warnings and Precautions (5.10)*]

17.10 Pregnancy

Advise women of childbearing age to avoid becoming pregnant throughout treatment and for 8 weeks after Zortress therapy has stopped.

17.11 Medications that Interfere with Zortress

Some medications can increase or decrease blood concentrations of Zortress. Advise patients to inform their physician if they are taking any of the following: antifungals, antibiotics, anti-epileptic medicines including carbamazepine, phenytoin and barbiturates, herbal/dietary supplements (St. John's Wort), and/or rifampin. [*See Warnings and Precautions (5.12)*]

17.12 Non-Infectious Pneumonitis

Inform patients the use of Zortress may increase the risk of non-infectious pneumonitis. Advise patients to seek medical attention if they develop clinical symptoms consistent with pneumonia. [*See Warnings and Precautions (5.13)*]

17.13 New Onset Diabetes

Inform patients the use of Zortress may increase the risk of diabetes mellitus and to contact their physician if they develop symptoms. [*See Warnings and Precautions (5.15)*]

17.14 Immunizations

Inform patients that vaccinations may be less effective while they are being treated with Zortress. Advise patients live vaccines should be avoided. [*See Warnings and Precautions (5.17)*]

17.15 Patient with Hereditary Disorders

Advise patients to inform their physicians that if they have hereditary disorders of galactose intolerance (Lapp-lactase deficiency or glucose-galactose malabsorption) not to take Zortress. [*See Warnings and Precautions (5.19)*]

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