HOSPIMAX
Maximising Life

Suregraft™ 0.5 mg 0.25 mg

Everolimus Tablets

For Prolonged Graft Survival

Product Description:

- Suregraft 0.5: Each Tablet contains Everolimus B.P. 0.5 mg
- Suregraft 0.25: Each Tablet contains Everolimus B.P. 0.25 mg

General Information

Everolimus belong to the novel class of immunosuppressant agents known as proliferation signal inhibitors (PSIs)/mammalian target of rapamycin (mTOR) inhibitors. Everolimus is macrolide derivatives with half-life of 28 h reaches steady state in 4 days

Indication & Usage

Kidney and heart transplantation

- Everolimus tablet is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant in combination with cyclosporine for microemulsion and corticosteroids.

Liver transplantation

- Everolimus tablet is indicated for the prophylaxis of organ rejection in adult patients receiving a hepatic transplant in combination with tacrolimus and corticosteroids.

DOSAGE AND ADMINISTRATION

Route of administration: Oral

Adults

An initial dose regimen of 0.75 mg twice daily in co-administration with cyclosporine is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation.

The dose of 1.0 mg twice daily in co-administration with tacrolimus is recommended for the hepatic transplant population with the initial dose approximately 4 weeks after transplantation.

Patients receiving Everolimus tablets may require dose adjustments based on blood concentrations achieved, tolerability, individual response, change in co-medications and the clinical situation. Dose adjustments can be made at 4-5 day intervals.

Paediatric population

There is insufficient data in children and adolescents to recommend the use of Everolimus tablets in renal transplantation and no recommendation on a posology can be made. In hepatic transplant paediatric patients, Everolimus tablets should not be used

Mechanism of action

The immunosuppressive activity of Everolimus results from its ability to inhibit the interleukin stimulated proliferation and clonal expansion of antigen-activated T and B lymphocytes. In cells, Everolimus binds to a cytoplasmic protein, the FK506 Binding Protein-12 (FKBP-12), to form the active immunosuppressive principle. That is, the Everolimus: FKBP-12 complex binds to and inhibits the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase and central controller of cell growth and proliferation. 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 are prevented which results in cell cycle arrest and inhibition of cell proliferation. The Everolimus: FKBP-12 complex has no effect on calcineurin activity.

Pharmacokinetic

Absorption: After oral administration, peak Everolimus concentrations occur 1 to 2 h post dose. Over the dose range of 0.5 mg to 2 mg bid, Everolimus Cmax 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 Cmax by 60%, delayed tmax 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.

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 (Vz/F) from a single-dose pharmacokinetic study in maintenance kidney transplant patients is 342 + 107 L (range 128 to 589 L).

Metabolism:

Everolimus is a substrate of CYP3A4 and P-glycoprotein. Following oral administration, it 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. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than Everolimus itself. Hence, the parent substance is considered to contribute the majority of the overall pharmacological 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.

Use in Specific Population

Pregnancy: Should not be used during pregnancy unless clearly necessary.

Lactation: Should not be used by breast-feeding women.

Pediatric Use: The safety and effective use of Everolimus in pediatric kidney transplant patients has not been established.

Elderly patients (≥65 years): Clinical experience in patients >65 years of age is limited. Although data are limited, there are no apparent differences in the pharmacokinetics of Everolimus in patients ≥65-70 years of age.

Patients with renal impairment: No dosage adjustment is required.

Patients with impaired hepatic function

Everolimus whole blood trough concentrations should be closely monitored in patients with impaired hepatic function. The dose should be reduced to approximately two thirds of the normal dose for patients with mild hepatic impairment (Child-Pugh Class A), to approximately one half of the normal dose for patients with moderate hepatic impairment (Child Pugh Class B), and to approximately one third of the normal dose for patients with severe hepatic impairment (Child Pugh Class C). Further dose titration should be based on therapeutic drug monitoring . Reduced doses rounded to the nearest tablet strength are tabulated below:

Everolimus tablets dose reduction in patients with hepatic impairment-

	Normal hepatic function	**Mild hepatic impairment (Child -Pugh A)**	**Moderate hepatic impairment (Child -Pugh B)**	**Severe hepatic impairment (Child -Pugh C)**
Renal and cardiac transplantation	**0.75 mg b.i.d.**	**0.5 mg b.i.d.**	**0.5 mg b.i.d.**	**0.25 mg b.i.d.**
Hepatic transplantation	**1 mg b.i.d.**	**0.75 mg b.i.d.**	**0.5 mg b.i.d.**	**0.5 mg b.i.d.**

Contraindication: Everolimus tablet is contraindicated in patients with a known hypersensitivity to everolimus & sirolimus.

Warning & Precaution:

Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids.

Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly.
Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments.
Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Everolimus tablets.

Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter
Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines.
Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus

DRUG INTERACTIONS:

- Caution should be exercized when co-administering Everolimus with CYP3A4 and CYP2D6-substrates having a narrow therapeutic index.
- Caution with concomitant use of rifampicin, rifabutin or ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin or ritonavir, as it may be necessary to modify the dose of Everolimus tablet.
- Caution with inducers of CYP3A4 (e.g St. John's Wort, anticonvulsants, (e.g carbamazepine), phenobarbital, phenytoin, anti-HIV drugs (e.g efavirenz, nevirapine), erythromycin, verapamil, inhibitors of PgP, and moderate inhibitors of CYP3A4 (e.g. antifungal substances: fluconazole, calcium channel blockers: nicardipine, diltiazem, protease inhibitors: nelfinavir, indinavir, amprenavir, octreotide and midazolam.
- Avoid grapefruit juice, grapefruit
- Avoid use of live vaccines

SIDE EFFECTS:

Very common (>10%): Infections (viral, bacterial, fungal), lower respiratory tract infection, upper respiratory tract infection, urinary tract infections, anaemia/erythropenia, leukopenia, thrombocytopenia, hyperlipidaemia (cholesterol and triglycerides), new onset diabetes mellitus, hypokalaemia, insomnia, anxiety, headache, venous thromboembolic events, hypertension, cough, dyspnoea, diarrhoea, nausea, vomiting, abdominal pain, pericardial and pleural effusion, peripheral oedema, healing impairment, pain and pyrexia

Common (1 to 10%): Malignant and unspecified tumours, skin neoplasms, wound infection, sepsis, pancytopenia, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, tachycardia, epistaxis, lymphocele, renal graft thrombosis, stomatitis/mouth ulceration, oropharyngeal pain, myalgia angioedema, acne arthralgia, pancreatitis, proteinuria, erectile dysfunction, renal tubular necrosis, incisional hernia and hepatic enzyme abnormal.

Uncommon (0.1 to 1%): Lymphomas, male hypogonadism, interstitial lung disease, hepatitis (non-infectious) and jaundice.
Unknown: Pulmonary alveolar proteinosis, erythroderma, leukocytoclastic vasculitis, and ovarian cyst.

OVERDOSE:
In animal studies, Everolimus showed 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.
Reported experience with overdose in humans is very limited; there is a single case of accidental ingestion of 1.5 mg everolimus in a 2-year-old child where no adverse events were observed. Single doses up to 25 mg have been administered to transplant patients with acceptable acute tolerability.
General supportive measures should be initiated in all cases of overdose

PRESENTATION:
10 Tablets packed in Alu/Alu blister, such 03 Strip of 1 x10 tablets are packed in a printed carton along with pack insert.

STORAGE CONDITIONS:
Store at temperature not exceeding 30°C. Protect from light.