For the use of Registered Medical Practitioner, hospital or laboratory only.

Biocon

Everolimus Tablets 0.25mg/ 0.5mg

Advacan®-0.25/0.5 एडवाकैन-०.२५/०.५

Composition:
Advacan® - 0.25
Each uncoated tablet contains:
Everolimus 0.25mg
Excipients q.s.
Advacan® - 0.5
Each uncoated tablet contains:
Everolimus 0.5mg
Excipients q.s.

ATC code: LO4AA18
Pharmaceutical Form: Tablets

Clinical Pharmacology
Pharmacodynamics
Everolimus, a proliferation signal inhibitor, prevents allograft rejection in allotransplantation. It exerts its immunosuppressive effect by inhibiting the proliferation, and thus clonal expansion, of antigen-activated T cells which is driven by T cell-specific interleukins, e.g. interleukin-2 and interleukin-15. Everolimus inhibits an intracellular signalling pathway which is triggered upon binding of these T cell growth factors to their respective receptors, and which normally leads to cell proliferation. The blockage of this signal by everolimus leads to an arrest of the cells at the G1 stage of the cell cycle.

At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus the growth factor-stimulated phosphorylation of the p70 S6 kinase is inhibited. Since p70 S6 kinase phosphorylation is under the control of FRAP (also called m-TOR), this finding suggests that the everolimus-FKBP-12 complex binds to and thus interferes with the function of FRAP. FRAP is a key regulatory protein which governs cell metabolism, growth and proliferation; disabling FRAP function thus explains the cell cycle arrest caused by everolimus.
Everolimus, thus, has a different mode of action than cyclosporine. In preclinical models of allotransplantation, the combination of everolimus and cyclosporine was more effective than either compound alone.
The effect of everolimus is not restricted to T cells. It rather inhibits in general growth factor-stimulated proliferation of hematopoietic as well as non-hematopoietic cells, like, for instance, that of vascular smooth muscle cells. Growth factor-stimulated vascular smooth muscle cell proliferation, triggered by injury to endothelial cells and leading to neointima formation, plays a key role in the pathogenesis of chronic rejection.

Pharmacokinetic properties
Absorption: After oral dosing, peak everolimus concentrations occur 1 to 2 h postdose. Everolimus blood concentrations are dose proportional over the dose range 0.25 to 15 mg in transplant patients. The relative bioavailability of the dispersible tablet compared with the tablet is 0.90 (90 % CI 0.76-1.07) based on the AUC-ratio. Food effect: Everolimus C_{max} and AUC are reduced by 60 % and 16 % when the tablet formulation is given with a high fat meal. 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 to 5000 ng/ml. Plasma protein binding is approximately 74 % in healthy subjects and patients with moderate hepatic impairment. The distribution volume associated with the terminal phase (Vz/F) in maintenance renal transplant patients is 342 ± 107.

Metabolism: Everolimus is a substrate of CYP3A4 and P-glycoprotein. The main metabolic pathways identified in human were mono-hydroxylations 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 are likely to contribute significantly to the immunosuppressive activity of everolimus.

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

Steady-state pharmacokinetics: Pharmacokinetics were comparable for kidney and heart transplant patients receiving everolimus twice daily simultaneously with cyclosporine microemulsion. 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. T_{max} occurs at 1 to 2 h postdose. C_{max} averages 11.1 ± 4.6 and 20.3 ± 8.0 ng/mL and AUC averages 75 ± 31 and 131 ± 59 ng.h/mL at 0.75 and 1.5 mg bid, respectively. Predose trough blood levels (C_{min}) average 4.1 ± 2.1 and 7.1 ± 4.6 ng/mL at 0.75 and 1.5 mg bid, respectively. Everolimus exposure remains stable over time in the first post-transplant year. C_{min} is significantly correlated with AUC yielding a correlation coefficient between 0.86 and 0.94. Based on a population pharmacokinetic analysis oral clearance (CL/F) is 8.8 L/h (27 % interpatient variation) and the central distribution volume (Vc/F) is 110 L (36 % interpatient variation). Residual variability in blood concentrations is 31%. The elimination half-life is 28 ± 7 h.

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 mol/L, INR was >1.3 (prothrombin time >4sec prolongation, and/or albumin concentration was <35 g/L. The impact of severe hepatic impairment (Child-Pugh Class C) has not been assessed but the effect on everolimus AUC is likely to be as large or larger compared with moderate impairment.

Renal impairment: Post-transplant renal impairment did not affect the pharmacokinetics of everolimus.
Paediatrics: Everolimus CL/F increased in a linear manner with patient age (1 to 16 years), body surface area (0.49-1.92 m^2), and weight (11-77 kg). Steady-state CL/F was 10.2 ± 3.0 L/h/m^2 and elimination half-life was 30 ± 11 h. Nineteen paediatric de novo renal transplant patients (1 to 16 years) received Everolimus dispersible tablets at a dose of 0.8 mg/m^2 (maximum 1.5 mg) twice-daily with cyclosporine. They achieved an everolimus AUC of 87 ± 27 ng·h/ml which is similar to adults receiving 0.75 mg twice daily. Steady-state trough levels were 4.4 ± 1.7 ng/ml.

Elderly: A limited reduction in everolimus oral CL by 0.33 % per year was estimated in adults (age range studied was 16-70 years). No dose adjustment is considered necessary.

Ethnicity: Based on a population pharmacokinetic analysis, oral clearance (CL/F) of everolimus is, on average, 20 % higher in black transplant patients.

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

Contraindications
Everolimus is contraindicated in patients with a known hypersensitivity to everolimus, sirolimus, or to any of the excipients.

Warnings & Precautions for its Use
Everolimus has been administered in clinical trials concurrently with cyclosporine, basiliximab and corticosteroids. Everolimus in combination with immunosuppressive agents other than these has not been adequately investigated. Everolimus has not been adequately studied in patients at high immunological risk. The pharmacokinetics of everolimus have not been studied in patients with severe hepatic impairment. It is recommended that everolimus whole blood trough levels be closely monitored in patients with impaired hepatic function.

Co-administration with strong CYP3A4-inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir) and inducers (e.g. rifampicin, rifabutin) is not recommended unless the benefit outweighs the risk. It is recommended that everolimus whole blood trough levels be monitored whenever inducers or inhibitors of CYP3A4 are concurrently administered and after their discontinuation.

Patients receiving a regimen of immunosuppressive medicinal products, including everolimus, are at increased risk of developing lymphomas or other malignancies, particularly of the skin. The absolute risk seems related to the duration and intensity of immunosuppression rather than to the use of a specific medicinal product. Patients should be monitored regularly for skin neoplasms and advised to minimise exposure to UV light, sunlight and use appropriate sunscreen. Patients on a regimen of immunosuppressive medicinal products, including everolimus, are at increased risk of developing infections, especially with opportunistic pathogens. Fatal infections and sepsis have been reported in patients treated with Everolimus .

In clinical trials with everolimus, antimicrobial prophylaxis for Pneumocystis jiroveci (carinii) pneumonia was administered for the first 12 months following transplantation. Cytomegalovirus (CMV) prophylaxis was recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease. The use of Everolimus with cyclosporine for microemulsion in transplant patients has been associated with increased serum cholesterol and triglycerides that may require treatment. Patients receiving everolimus should be monitored for hyperlipidemia and if necessary, treated with lipid-lowering medicinal products and appropriate dietary adjustments. The risk/benefit should be considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Everolimus. Similarly the risk/benefit of continued everolimus therapy should be re-evaluated in patients with severe refractory hyperlipidemia. Patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of adverse effects.

Regular monitoring of renal function is recommended in all patients. Appropriate adjustment of the immunosuppressive regimen, in particular reduction of the cyclosporine dose should be considered in patients with elevated serum creatinine levels. Caution should be exercised when co-administering other medicinal products that are known to have a deleterious effect on renal function. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Vaccination: Immunosuppressants may affect response to vaccination. During treatment with immunosuppressants, including everolimus, vaccination may be less effective. The use of live vaccines should be avoided. A diagnosis of interstitial lung disease (ILD) should be considered in patients presenting with symptoms consistent with infectious pneumonia but not responding to antibiotic therapy and in whom infectious, neoplastic and other non-drug causes have been discounted through appropriate investigations. Cases of ILD have been reported with everolimus which resolve on drug interruption with or without glucocorticoid therapy.

Drug Interactions
Everolimus is mainly metabolised 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 CYP3A4-inhibitors and inducers is not recommended. Inhibitors of P-glycoprotein 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. All *in vivo* interaction studies were conducted without concomitant cyclosporine.

For the use of Registered Medical Practitioner, hospital or laboratory only.

Biocon

Everolimus Tablets 0.25mg/ 0.5mg

Advacan®-0.25/0.5 एडवाकैन-०.२५/०.५

Cyclosporine (CYP3A4/PgP inhibitor): The bioavailability of everolimus was significantly increased by co-administration of cyclosporine. In a single-dose study in healthy subjects, cyclosporine increased everolimus AUC by 168 % (range, 46 % to 365 %) and C_{max} by 82 % (range, 25 % to 158 %) compared with administration of everolimus alone. Dose adjustment of everolimus might be needed if the cyclosporine dose is altered. Everolimus had a clinically minor influence on cyclosporine pharmacokinetics in renal and heart transplant patients receiving cyclosporine.

Rifampicin (CYP3A4 inducer): Pre-treatment of healthy subjects with multiple-dose rifampicin followed by a single dose of everolimus increased everolimus clearance nearly 3-fold, and decreased C_{max} by 58 % and AUC by 63 %. Combination with rifampicin is not recommended.

Atorvastatin (CYP3A4-substrate) and pravastatin (PgP-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.

Other possible interactions: Moderate inhibitors of CYP3A4 and PgP may increase everolimus blood levels (e.g. antifungal substances: fluconazole; macrolide antibiotics: erythromycin; calcium channel blockers: verapamil, nicardipin, diltiazem; protease inhibitors: nelfinavir, indinavir, amprenavir) Inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood levels (e.g. St. John's wort (Hypericum perforatum), anticonvulsants: carbamazepine, phenobarbital, phenytoin; anti HIV drugs: efavirenz, nevirapine).

Grapefruit and grapefruit juice affect cytochrome P450 and PgP activity and should therefore be avoided. **Vaccination:** Immunosuppressants may affect response to vaccination and vaccination during treatment with everolimus may be less effective. The use of live vaccines should be avoided.

Pregnancy and lactation
There are no adequate data from the use of Everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryo/foetotoxicity . The potential risk for humans is unknown. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk for the foetus. 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.
It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into milk of lactating rats. Therefore women who are taking everolimus should not breast feed.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Side effects
The adverse drug reactions listed below was derived from three clinical trials and represents the pooled data from 1,199 patients. These were 3 randomised, double blind, controlled, multi-centre trials: 2 de novo kidney transplant trials and 1 de novo heart transplant trial, in which Everolimus was administered at a dose of either 1.5 mg or 3.0 mg/day for at least 12 months together with cyclosporine and corticosteroids.

Infections and infestations: Viral , bacterial and fungal infections, sepsis; **Blood and lymphatic system disorders:** Leucopaenia, Thrombocytopaenia, anaemia, coagulopathy, thrombotic thrombocytopaenic purpura/haemolytic uraemic syndrome, haemolysis; **Cardiac disorder:** Pericardial effusion; **Endocrine disorders:** Hypogonadism male; **Metabolic and nutrition disorders** :Hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia; **Vascular disorders:** Hypertension, lymphocoele, venous thromboembolism; **Respiratory, thoracic and mediastinal disorders:** Pleural effusion pneumonia; **Gastrointestinal disorders:** Abdominal pain, diarrhoea, nausea, vomiting; **Hepato-biliary disorders:** Hepatitis, hepatic disorders, jaundice, liver; **Skin and subcutaneous tissue disorders:** Acne, surgical wound complication, rash; **Musculoskeletal system disorder:** Myalgia; **Renal and urinary disorders:** Urinary tract infection, Renal tubular necrosis , pyelonephritis; **General disorders:** Oedema, pain.
In controlled clinical trials in which patients were monitored for at least 1 year, lymphoma or lymphoproliferative disease developed in 1.4% of patients receiving everolimus (1.5 mg or 3.0 mg/day) in combination with other immunosuppressants. Malignancies of the skin developed in 1.3% of patients, and other types of malignancies developed in 1.2% of patients.

Overdosage
Reported experience with overdose in humans is very limited. There was a single case of accidental ingestion of 1.5 mg everolimus by a 2-year old child, but no adverse events were observed. Single doses of 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.

Dosage and Administration
Adults
An initial dose regimen of 0.75 mg twice daily is recommended for the general kidney and heart transplant population, administered as soon as possible after transplantation. The daily dose of Everolimus should always be given orally in two divided doses (b.i.d.). Everolimus should be consistently given either with or without food and at the same time as cyclosporine. Everolimus is for oral use only.

Everolimus tablets should be swallowed whole with water and not crushed before use. Patients receiving Everolimus may require dose adjustments based on blood levels achieved, tolerability, individual response, change in co-medications and the clinical situation. Dose adjustments can be made at 4-5 days intervals.

Use in children and adolescents
There are no adequate data of the use of everolimus in children and adolescents to support its use in patients in these age groups. Limited information is, however, available in renal transplant paediatric patients.

Elderly patients (≥ 65 years)
Clinical experience is limited in patients ≥ 65 years of age. Nevertheless, there are no apparent differences in the pharmacokinetics of everolimus in patients ≥ 65-70 years of age as compared with younger adults

Patients with renal impairment
No dosage adjustment is required .

Patients with hepatic impairment
Whole blood trough levels (C0) of everolimus should be closely monitored in patients with impaired hepatic function. For patients with mild or moderate hepatic impairment (Child-Pugh Class A or B), the dose should be reduced to approximately one half of the normal dose if two of the following conditions apply: bilirubin > 34 micro mol/L (> 2 mg/dL), albumin < 35 g/L (< 3.5 g/dL), prothrombin time > 1.3 INR (> 4 sec prolongation). Further dose titration should be based on therapeutic drug monitoring. everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C).

Therapeutic Drug Monitoring
Routine whole blood, therapeutic drug level monitoring of everolimus is recommended. Based on exposure-efficacy and exposure-safety analysis, patients achieving Everolimus whole blood trough levels (C0) ≥ 3.0 ng/mL have been found to have a lower incidence of biopsy-proven acute rejection in both renal and heart transplantation than patients whose trough levels (C0) are below 3.0 ng/mL. The recommended upper limit of the therapeutic range is 8 ng/mL. Exposure above 12 ng/mL has not been studied. These recommended ranges for everolimus are based on chromatographic methods. It is especially important to monitor Everolimus blood concentrations, in patients with hepatic impairment, during concomitant administration of strong CYP3A4 inducers and inhibitors, when switching formulation and/or if cyclosporine dosing is markedly reduced. Ideally, dose adjustments of everolimus should be based on trough levels (C0) obtained > 4-5 days after the previous dose change. Since cyclosporine interacts with everolimus, everolimus levels may decrease if cyclosporine exposure is markedly reduced (i.e.trough concentration (C0) < 50 ng/mL).

Cyclosporine dose recommendation in renal transplantation
Everolimus should not be used long-term together with full doses of cyclosporine. Reduced exposure to cyclosporine in everolimus-treated renal transplant patients improves renal function. Cyclosporine exposure reduction should be started after 1 month posttransplantation. Based on the experience gained from study, the following target ranges for cyclosporine exposure as defined per protocol (cyclosporine blood concentrations measured 2 hours after dose administration (C2) are recommended: weeks 0-4: 1000-1400 ng/mL, weeks 5-8: 700-900 ng/mL, weeks 9-12: 550-650 ng/mL, weeks 13-52: 350-450 ng/mL. In this study, measured cyclosporine trough blood concentrations (C0) (ng/mL) were: month 1: 239 ± 114; month 3: 131 ± 85; month 6: 82 ± 60; month 12: 61 ± 28.

It is important to ensure that both everolimus and cyclosporine levels do not fall below the therapeutic range early after transplantation to minimize the risk of efficacy failure. Prior to dose reduction of cyclosporine it should be ascertained that steady state whole blood trough concentrations (C0) are equal to or above 3 ng/mL. There are limited data regarding dosing with cyclosporine trough concentrations (C0) below 50 ng/mL, or C2 levels below 350 ng/mL, in the maintenance phase. If the patient cannot tolerate reduction of cyclosporine exposure, the continued use of everolimus should be reconsidered.

Storage: Store below 25°C. Protect from light and moisture.
Keep out of reach of children.

Shelf life: Please refer to carton/blister.

Presentation: Advacan®-0.25/0.5: Available in Alu-Alu blister pack of 10 Tablets

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

Leaflet revised July 2019

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**

D5634/2 / 1108069

BFILL/36682/01