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

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Everolimus Tablets

Evertor™ 5/10 एवरटोर ५/१०

COMPOSITION

Evertor 5mg tablet:

Each uncoated tablet contains:

Everolimus 5 mg

Colour: Indigo Carmine

Evertor 10mg tablet:

Each uncoated tablet contains:

Everolimus 10 mg

INDICATIONS

Evertor is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

DOSAGE AND ADMINISTRATION

Treatment with Evertor should be initiated by an experienced oncologist. Evertor should be administered orally daily at the same time every day (preferably in the morning), either in a fasting state or after no more than a light fat free meal. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Evertor tablets should be swallowed with a glass of water and should not be chewed or crushed.

Advanced Renal Cell Carcinoma

The recommended dose of Evertor for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily. Management of severe and/or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of Evertor therapy. If dose reduction is required, the suggested dose is 5 mg daily.

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 embryotoxicity and foetotoxicity. The potential risk for humans is unknown. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk to the foetus. It is not known whether Everolimus is excreted in breast milk. However, in animal studies Everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking Everolimus should therefore not breast-feed. Women of childbearing potential should be advised to use an effective method of contraception while receiving Everolimus and for up to 8 weeks after ending treatment.

Fertility

Based on non-clinical findings with Everolimus, male fertility may be compromised by the treatment.

Dosing in Special Population

No dosage adjustment is required in elderly patients (≥ 65 years) and in patients with renal impairment. For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment and is not recommended for use in this patient population.

Not recommended for use in paediatric patients.

SIDE EFFECTS AND DRUG INTERACTIONS

Preclinical Safety Data

The preclinical safety profile of Everolimus had been assessed in various animal models. The major target organs reported were male and female reproductive systems in several species and minor kidney changes were seen in the rat and mouse. There was no indication of kidney toxicity in monkeys or minipigs. Everolimus appeared to exacerbate background diseases like chronic myocarditis in rats, coxsackie virus infection in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys.

Everolimus showed no evidence of clastogenic or mutagenic activity. Administration of Everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure.

Clinical Studies Experience

The safety data described below reflect exposure to Everolimus (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib The median age of patients was 61 years (range 27-85), 88% were caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19451) for patients receiving Everolimus and 60 days (range 21-295) for those receiving placebo.

- The most common adverse reactions (incidence 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea.
- The most common grade 3/4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia.
- The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine.
- The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia.
- Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the Everolimus arm but none on the placebo arm.
- The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the Everolimus and placebo treatment groups, respectively.
- The most common adverse reactions leading to treatment discontinuation were pneumonitis and dyspnea, for treatment delay or dose reduction were infections, stomatitis, and pneumonitis
- The most common medical interventions required during Everolimus treatment were for infections, anemia, and stomatitis.

Table 1 Compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ l0% for patients receiving Everolimus 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table I Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the Everolimus Arm than in the Placebo Arm

	Everolimus 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	**97**	**52**	**13**	**93**	**23**	**5**
Gastrointestinal Disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrheao	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and Infestations[b]	37	7	3	18	1	0
General Disorders and Administration Site Conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	30	<1	0	16	0	0
Dyspnoea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and Nutrition Disorders						
Anorexia	25	1	0	14	<1	0
Nervous System Disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	10	1	0	7	0	0
Median Duration Treatment (d)		**141**			**60**	

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[a]Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b]Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%),urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Table 2 Other notable adverse reactions occurring more frequently with Everolimus than with Placebo, but with an incidence of <10% include

System Organ Class	Description
Gastrointestinal disorders	Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)
General disorders and administration site conditions	Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (<1%)
Respiratory, thoracic and mediastinal disorders	Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)
Skin and subcutaneous tissue disorders	Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%) , nail disorder (5%), erythema (4%), onychoclasis (4%) , skin lesion (4%), acneiform dermatitis (3%)
Metabolism and nutrition disorders	Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (<1%)
Psychiatric disorders	Insomnia (9%)
Nervous system disorders	Dizziness (7%), paresthesia (5%)
Eye disorders	Eyelid edema (4%), conjunctivitis (2%)
Vascular disorders	Hypertension (4%)
Renal and urinary disorders	Renal failure (3%)
Cardiac disorders	Tachycardia (3%), congestive cardiac failure (1%)
Musculoskeletal and connective tissue disorders	Jaw pain (3%)
Hematologic disorders	Hemorrhage (3%)

Key treatment-emergent laboratory abnormalities are presented in Table 3.

Table 3 Key Laboratory Abnormalities Reported at a Higher rate in the Everolimus Arm than the Placebo Arm.

Laboratory parameter	Everolimus 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Haematology[a]						
Haemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholestrol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ATS) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

[a]Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

DRUG INTERACTION

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of Everolimus may be influenced by products that affect CYP3A4 and/or PgP. Co-administration with strong or moderate inhibitors of CYP3A4 or P-glycoprotein (PgP) should be avoided where possible. If Everolimus must be co-administered with a strong CYP3A4 or (PgP) inhibitor, the patient should be carefully monitored for undesirable effects.

In vitro, Everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Agents that may Increase Everolimus Blood Concentrations

Everolimus blood concentrations may be increased by substances that inhibit CYP3A4 activity, thus by decreasing Everolimus metabolism and by inhibitors of PgP by decreasing the efflux of Everolimus from intestinal cells.

Concurrent treatment with inhibitors of CYP3A4/PgP like ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, telithromycin, fluconazole, calcium channel blockers (diltiazem), grapefruit, grapefruit juice and other foods etc. that are known to affect CYP 450 and PgP should be avoided during the treatment.

There was an increase in exposure to Everolimus in healthy subjects when Everolimus was administered with:

- Ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 3.9 and 15.0 fold, respectively).
- Erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.0 and 4.4 fold, respectively).
- Verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.3 and 3.5 fold, respectively).
- Ciclosporin (a CYP3A4 substrate and a PgP inhibitor; C_{max} and AUC increased by 1.8 and 2.7 fold, respectively).

Agents that may Decrease Everolimus Blood Concentrations

The concurrent administration of substances that are inducers of CYP3A4 or PgP like rifampicin, anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin) and anti HIV agents (e.g. efavirenz, nevirapine), St. John's wort (Hypericum perforatum)and may decrease Everolimus blood concentrations by either increasing metabolism or by increasing the efflux of Everolimus from intestinal cells, require caution and should be avoided when possible.

Studies with Everolimus in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between Everolimus and the HMG-CoA reductase inhibitors like atorvastatin, simvastatin etc.

Immunosuppressants may affect the response to vaccination by making it less effective. The use of live vaccines like intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines etc., should be avoided during treatment with Everolimus.

WARNINGS AND PRECAUTIONS

Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives including Everolimus. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Everolimus therapy without dose alteration. If symptoms are moderate, consideration should be given to interruption therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at 5 mg daily.

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Infections
Everolimus has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have occurred in patients taking Everolimus.

Oral Ulceration
Mouth ulcers, stomatitis, and oral mucositis have seen in patients treated with Everolimus. In such cases topical treatments are recommended, but alcohol or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition.

Laboratory Tests and Monitoring
Renal Function
Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine is recommended prior to the start of Everolimus therapy and periodically thereafter.

Blood Glucose and Lipids
Hyperglycemia has been reported in clinical trials with Everolimus. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of Everolimus therapy and periodically thereafter.

Hematological Parameters
Decreased hemoglobin, neutrophils, and platelets have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of Everolimus therapy and periodically thereafter.

Hepatic Impairment
Everolimus is not recommended in patients with severe hepatic impairment (Child-Pugh class C).

Vaccinations
The use of live vaccines and close contact with those who have received live vaccines like intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines etc., should be avoided during treatment with Everolimus.

OVERDOSEAGE AND CONTRAINDICATIONS
Overdose
In animal studies, Everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2,000 mg/kg (limit test). Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability.

General supportive measures should be initiated in all cases of overdose.

Contraindications
Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.

CLINICAL PHARMACOLOGY
PHARMACOKINETICS
Absorption
In patients with advanced solid tumors, peak Everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg Everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose -proportional between 5 and 10 mg in the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in is less than dose proportional, however AUC shows dose-proportionality over the 5 to 70 mg dose range.

Food effect
In healthy subjects, high fat meals reduced systemic exposure to Everolimus 10 mg tablet (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time

Distribution
The blood-to-plasma ratio of Everolimus; which is concentration-dependent over the range of 5 to 5000 ng/ml, is 17% to 73%. The amount of Everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given Everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

In animal models Everolimus was shown to cross the blood-brain barrier in a non-linear dose-dependent manner when given either with intravenous or oral route.

Metabolism
Everolimus is a substrate of CYP3A4 and PgP. 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.

Excretion
No specific excretion studies have been undertaken in cancer patients; however, data are available from the transplantation setting. Following the administration of a single dose of radiolabelled Everolimus in conjunction with ciclosporin suggest that 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in urine or faeces.

Steady-State Pharmacokinetics
After daily or weekly administration of Everolimus in patients with advanced solid tumors, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg in the daily dosing regimen and 5 to 70 mg on the weekly regimen. Steady-state was achieved within two weeks with the daily dosing regimen. C_{max} is dose-proportional between 5 and 10 mg on the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on the daily regimen. The mean elimination half-life of Everolimus is approximately 30 hours.

Patients with hepatic impairment
The average AUC of Everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration.

Patients with renal impairment
In a population pharmacokinetic analysis of 168 patients with advanced cancer, no significant influence of creatinine clearance (25 - 178 ml/min) was detected on CL/F of Everolimus.

Paediatric patients
There is no indication for use of Everolimus in the paediatric cancer patients.

Elderly patients
No significant influence of age (27-85 years) on oral clearance of Everolimus was detected.

Mechanism of Action
Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, Everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-l) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by Everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies. Everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells.

PHARMACODYNAMICS
QT/QTc Prolongation Potential
The data from a randomized, placebo-controlled, crossover study with, 59 healthy subjects suggests that on administering a single oral dose of Everolimus (20 mg and 50 mg) versus placebo, there is no indication of a QT/QTc prolonging effect of Everolimus in single doses up to 50 mg.

CLINICAL STUDIES
An international, multicenter, randomized, double-blind trial comparing Everolimus 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score[1] and prior anticancer therapy.

Progression-free survival (PFS), documented using RECIST (Response Evaluation Criteria in Solid Tumors) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label Everolimus 10 mg daily.

In total, 416 patients were randomized 2:1 to receive Everolimus (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

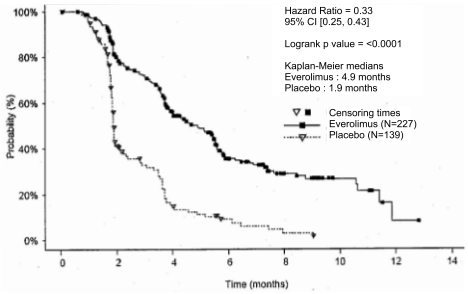
Everolimus was superior to placebo for progression-free survival (see Table 4 and Figure 1). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. The overall survival (OS) results were not mature and 32% of patients had died by the time of cut-off in this study.

Table 4 Efficacy Results by Central Radiologic Review

	Everolimus N=272	Placebo N=139	Hazard Ratio (95%CI)	p-value[a]
Median Progression Free Survival (95% CI)	4.9 months (4.0 to 5.5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 4.3)	<0.0001
Objective Response Rate	2%	0%	n/a[b]	n/a[b]

[a]Log-rank test startified by prognostic score
[b]Not applicable

Figure 1 Kaplan-Meier Progression-free Survival Curves



REFERENCE
Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell cancer. J Clin Oncol (2004) 22:454-63.

PRESENTATION AND STORAGE CONDITION
5mg tablets
Indigo carmine, round tablets with no score.
Each carton contains 3 blisters of 10 tablets each

10mg tablets
White color, round tablets with no score.
Each carton contains 3 blisters of 10 tablets each

Store below 25° C.
Protect from light and moisture.

Note: Evertor should be kept out of the reach and sight of children

INFORMATION FOR PATIENTS
Evertor comes in 5 mg and 10 mg tablets.

- Take Evertor exactly as your healthcare provider tells you.
- Swallow Evertor tablets whole with a glass of water. Do not crush or chew the tablets
- Take Evertor each day, at about the same time, with or without food.
- Do not take overdose of Evertor, if taken by mistake, contact your physician incharge.
- If you miss a dose of Evertor, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your Evertor, skip the dose for that day. The next day, take Evertor at your usual time.
- Do not take 2 doses to make up for the one that you missed. If you are not sure about what to do, call your healthcare provider.

For further details, please contact:
Biocon Limited
20th KM, Hosur Road, Electronics City, Bangalore 560100. India

In case of any product related complaints or adverse effect related to Biocon products

Call Toll Free No: 1800 102 9465
Or
Visit our website **www.biocon.com** and fill voluntary reporting form available under Report Adverse Events/ Side Effects and product complaints & send the duly filled form to us at the address mentioned in the web mail address.