Xevirol
Everolimus

COMPOSITION
Xevirol 5 Tablet : Each tablet contains Everolimus INN 5 mg.
Xevirol Tablet : Each tablet contains Everolimus INN 10 mg.

PHARMACOLOGICAL INFORMATION
The chemical name of Everolimus is 40-O-(2-hydroxyethyl)-rapamycin or 40-O-(2-hydroxyethyl)-sirolimus. Its molecular formula is $C_{53}H_{83}NO_{14}$ and its molecular weight is 958.2.

Mechanism of Action
Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin) or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signalling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream on the PI3K/AKT pathway, which is dysregulated in the majority of human cancers.

Two primary regulators of mTORC1 signalling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (TSC1, TSC2). Loss or inactivation of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signalling cascade, including activation of the S6K1. In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

Pharmacodynamics
Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signalling capacity. mTORC1 signalling is effected through modulation of the phosphorylation of downstream effectors, the best characterised of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumour growth and expression of hypoxia-inducible factors (e.g. HIF-1 transcription factors); the later resulting in reduced expression of factors involved in the potentiation of tumour angiogenic processes (e.g. the vascular endothelial growth factor VEGF). Everolimus is an inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells.

PHARMACOKINETICS
Absorption
In patients with advanced solid tumours, 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. AUC shows dose-proportionality over the 5 to 70 mg dose range.

Effects of Food
In healthy subjects, high fat meals reduced systemic exposure to Everolimus 10 mg (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 profile.

Distribution
The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 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 10 mg/day of Everolimus. Plasma protein binding is approximately 74% both in healthy subjects and patients with moderate hepatic impairment.

Following intravenous administration in a rat model, everolimus was shown to cross the blood-brain barrier in a non-linear dose-dependent manner, suggesting saturation of an efflux pump at the blood-brain barrier.

Metabolism
Everolimus is a substrate of CYP3A4 and P-glycoprotein (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. 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
No specific excretion studies have been undertaken in cancer patients; however, data are available from the transplant setting. Following the administration of a single dose of radiolabeled everolimus in conjunction with cyclosporin, 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in the urine or faeces.

CLINICAL INFORMATION
Indication
Everolimus is a kinase inhibitor indicated for the treatment of:
- postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic.
- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
- adults with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery.
- adults and children 3 years of age with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of EVEROLIMUS is based on an analysis of change in SEGA volume.

DOSAGE AND ADMINISTRATION
Treatment with Everolimus should be initiated by a physician experienced in the use of anticancer therapies.
Everolimus should be administered orally once daily at the same time every day (preferably in the morning), either consistently in a fasting state or consistently after no more than a light fat-free meal . Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. For patients unable to swallow tablets, Everolimus tablets should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Advanced HR +ve BC, Advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:
The recommended dose of Everolimus is 10 mg to be taken once daily with or without food.
Management of severe and/or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of Everolimus therapy. If dose reduction is required, the suggested dose is 5 mg daily.
Moderate CYP3A4 or PgP inhibitors: If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the dose to 5 mg daily. Further dose reduction to 5 mg every other day or 2.5 mg daily may be required to manage adverse reactions.
Strong CYP3A4 or PgP inducers: Avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration of a strong CYP3A4 inducer, an Everolimus dose increase from 10 mg daily up to 20 mg daily should be considered (based on pharmacokinetic data), using 5 mg increments.

SEGA associated with TS :
Initial dose based on body surface area with subsequent titration to attain trough concentrations of 5-10 ng/mL. Titration may be required to obtain the optimal therapeutic effect. Doses that are tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus and may contribute to this variance.
Recommended starting dose of Everolimus for treatment of patients with SEGA

Body Surface Area (BSA)*	Starting daily dose
1.2 m^2	2.5 mg
1.3 m^2 to 2.1 m^2	5 mg
2.2 m^2	7.5 mg

*BSA = sqrt ((Height (cm) x Weight (kg))/3600

Therapeutic drug monitoring for patients treated for SEGA
Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for SEGA using a validated bioanalytical LC/MS method.
Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL. If concentrations are below 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability.
SEGA volume should be evaluated approximately 3 months after commencing Everolimus therapy, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration and tolerability. Responses have been observed at trough concentrations as low as 2 ng/mL; as such, once acceptable efficacy has been achieved, additional dose increase may not be necessary.
If dose reduction is required for patients receiving 2.5 mg daily, alternate day dosing should be considered.
Moderate CYP3A4 or PgP inhibitors: If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the daily dose by approximately 50%. Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4 or PgP inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later.
Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. Patients receiving concomitant strong CYP3A4 inducers (e.g., enzyme inducing antiepileptic drug) may require an increased Everolimus dose to attain trough concentrations of 5 to 10 ng/mL. If concentrations are below 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, checking the trough level and assessing tolerability before increasing the dose. If the strong inducer is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later.

There is limited safety experience with patients having trough concentrations > 10 ng/mL. If concentrations are between 10 to 15 ng/mL and the patient has demonstrated adequate tolerability and tumour response, no dose reductions are needed. The dose of Everolimus should be reduced if trough concentrations > 15 ng/mL are observed.

Use in special population
Paediatric population
- Advanced renal cell carcinoma: Everolimus is not recommended for use in paediatric cancer patients.
- SEGA: Dosing recommendations for paediatric patients with SEGA are consistent with those for the adult SEGA population. Everolimus has not been studied in paediatric SEGA patients < 3 years of age and is currently not recommended for use in this age group.

Elderly patients (≥ 65 years)
No dosage adjustment is required.
Patients with renal impairment
No dosage adjustment is required.
Patients with hepatic impairment
For patients with moderate hepatic impairment (Child-Pugh class B):
- Advanced renal cell carcinoma: the dose should be reduced to 5 mg daily.
- SEGA: the dose should be reduced by approximately 50% and titrate to trough concentrations of 5 to 15 ng/mL For patients with severe hepatic impairment (Child-Pugh class C): Everolimus has not been evaluated in patients with severe hepatic impairment and is not recommended for use in this patient population.

Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC and Renal Angiomyolipoma with TSC and Management of Adverse Reactions

Adverse Drug Reaction	Everolimus Dose Adjustment and Management Recommendations
a) Non-infectious pneumonitis	
Grade 1 : Asymptomatic, radiographic findings only	No dose adjustment required, Initiate appropriate monitoring.
Grade 2 : Symptomatic, not interfering with ADLc	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ grade 1. Re-initiate Everolimus at a lower dose. Discontinue treatment if failure to recover within 4 wks.
Grade 3 : Symptomatic, interfering with ADLc; O_2 indicated	Interrupt Everolimus until symptoms resolve to ≤ grade 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating Everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
Grade 4 : Life-threatening, ventilatory support indicated	Discontinue Everolimus, rule out infection and consider treatment with corticosteroids.
b) Stomatitis	
Grade 1 : Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
Grade 2 : Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to grade ≤1. Re-initiate Everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade≤1. Re-initiate Everolimus at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).d
Grade 3 : Symptomatic and unable to adequately aliment or hydrate orally	Temporary dose interruption until recovery to grade≤1. Re-initiate Everolimus at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).d
Grade 4 : Symptoms associated with life-threatening consequences	Discontinue Everolimus and treat with appropriate medical therapy.
c) Other non-hematologic toxicities (excluding metabolic events)	
Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤ 1. Re-initiate Everolimus at the same dose. If toxicity recurs at grade 2, interrupt Everolimus until recovery to grade ≤1. Re-initiate Everolimus at a lower dose.
Grade 3	Temporary dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Consider reinitiating Everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
Grade 4	Discontinue Everolimus and treat with appropriate medical therapy.
d) Metabolic events (e.g. hyperglycemia, dyslipidemia)	
Grade 1	No dose adjustment required. Manage with appropriate medical therapy and monitor.
Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
Grade 3	Temporary dose interruption. Re-initiate Everolimus at a lower dose. Manage with appropriate medical therapy and monitor.
Grade 4	Discontinue Everolimus and treat with appropriate medical therapy.

a Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.
b If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.
c Activities of daily living (ADL)
d Avoid using agents containing hydrogen peroxide, iodine and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

CONTRAINDICATIONS
Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. Hypersensitivity reactions manifested by symptoms including but not limited to anaphylaxis, dyspnea, flushing, chest pain or angioedema. (e.g., swelling of the airways or tongue with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

WARNINGS AND PRECAUTIONS
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 events: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Everolimus.
- 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.
- Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus.

Laboratory Tests and Monitoring
Renal Function: Elevations of serum creatinine and proteinuria have been reported in clinical trials .Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine is recommended prior to the start of Everolimus therapy and periodically thereafter.
Blood Glucose and Lipids: Hyperglycemia, hyperlipidemia and hypertriglyceridemia have been reported in clinical trials. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of Everolimus therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on Everolimus.
Hematologic Parameters: Decreased hemoglobin, lymphocytes, neutrophils and platelets have been reported in clinical trials of Everolimus. Monitoring of complete blood count is recommended prior to the start of Everolimus therapy and periodically thereafter.
Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother.
Hepatic impairment: Everolimus should not be used in patients with Child-Pugh class C hepatic impairment. For advanced PNET and advanced RCC patients with Child-Pugh class B hepatic impairment, reduce Everolimus dose. For SEGA patients with Child-Pugh class B hepatic impairment, adjustment to the starting dose may not be needed; however, subsequent dosing should be based on TDM.

ADVERSE REACTIONS
Advanced HR+ BC, Advanced PNET, Advanced RCC: Most common adverse reactions (incidence ≥ 30%) include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache and decreased appetite.
Renal angiomyolipoma with TSC: Most common adverse reaction (incidence ≥ 30%) is stomatitis.
SEGA: Most common adverse reactions (incidence ≥ 30%) are stomatitis, upper respiratory tract infection, sinusitis, otitis media and pyrexia.

DRUG INTERACTIONS
Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4 inhibitors should be avoided. A reduction of the Everolimus dose is recommended when co-administered with a moderate CYP3A4 and/or PgP inhibitor . An increase in the Everolimus dose is recommended when co-administered with a strong CYP3A4 inducer.

OVERDOSAGE
Reported experience with overdose in humans is very limited. Single dose of up to 70 mg have been given with acceptable acute tolerability. General supportive measures should be initiated in all cases of overdose.

PHARMACEUTICAL INFORMATION
Storage Conditions
Store in a cool and dry place (below 25°C), away from light. Keep out of the reach of children.

Presentation & Packaging
Xevirol 5 Tablet: Each commercial box contains 10's tablets in Alu-Alu blister pack.
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Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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