PRODUCT MONOGRAPH

PrTEVA-EVEROLIMUS

everolimus tablets

2.5 mg, 5 mg, 7.5 mg and 10 mg

Antineoplastic Agent
(mTOR kinase inhibitor)

Teva Canada Limited
30 Novopharm Court
Toronto, ON
M1B 2K9

Date of Revision: July 18, 2019

Submission Control Number: 226200

Table of Contents

PrTEVA-EVEROLIMUS
everolimus tablets
2.5 mg, 5 mg, 7.5 mg and 10 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 2.5 mg, 5 mg, 7.5 mg and 10 mg	Butylhydroxytoluene, crospovidone, hypromellose, lactose anhydrous, lactose monohydrate and magnesium stearate

INDICATIONS AND CLINICAL USE

TEVA-EVEROLIMUS is indicated for the treatment of postmenopausal women with hormone receptor-positive, HER2- negative advanced breast cancer in combination with exemestane after recurrence or progression following treatment with letrozole or anastrozole.

> The effectiveness of everolimus in advanced breast cancer is based on a demonstration of progression-free survival (PFS) benefit. Clinical benefit such as prolongation of overall survival (OS) or improvement in quality-of-life (QOL) has not been demonstrated (see **CLINICAL TRIALS**).

TEVA-EVEROLIMUS is indicated for the treatment of well- or moderately differentiated neuroendocrine tumours of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease that has progressed within the last 12 months.

> The effectiveness of everolimus in PNET is based on demonstrated progression-free survival (PFS) benefit in a phase III placebo-controlled study in patients with documented progressive disease within 12 months of randomization. There was no evidence of an overall survival (OS) benefit and quality of life (QOL) was not measured (see **CLINICAL TRIALS**).

TEVA-EVEROLIMUS is indicated for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults with progressive disease.

> The effectiveness of everolimus in gastrointestinal or lung NET is based on demonstrated progression-free survival (PFS) benefit in a phase III placebo-controlled study in patients whose disease had progressed within 6 months of randomization. An overall survival (OS) benefit or improvement in quality of life (QOL) has not been demonstrated.

Subgroup analyses suggested that patients with better prognosis benefited less from everolimus treatment (see **CLINICAL TRIALS**).

TEVA-EVEROLIMUS in combination with a somatostatin analogue is not indicated for the treatment of patients with neuroendocrine tumours from gastrointestinal or lung origin.

TEVA-EVEROLIMUS is not indicated for the treatment of patients with functional carcinoid tumours (see **WARNINGS AND PRECAUTIONS** and **CLINICAL TRIALS**).

TEVA-EVEROLIMUS is indicated for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell morphology, after failure of initial treatment with either of the VEGF-receptor TKIs[1] sunitinib or sorafenib.

The effectiveness of everolimus is based on PFS. Prolongation of OS was not demonstrated for everolimus in RCC nor were quality-of-life differences shown between patients receiving everolimus versus placebo in the pivotal phase III trial (see **CLINICAL TRIALS**).

TEVA-EVEROLIMUS is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required.

The effectiveness of everolimus is based on an analysis of change in SEGA volume. Prescribers should take into consideration that surgical resection can be curative, while treatment with everolimus has been shown only to reduce the SEGA volume.

TEVA-EVEROLIMUS is indicated for the treatment of adult patients (≥ 18 years of age) with renal angiomyolipoma associated with tuberous sclerosis complex (TSC); who do not require immediate surgery.

The effectiveness of everolimus in the treatment of renal angiomyolipoma is based on an analysis of objective responses in patients treated for a median of 8.3 months in the pivotal phase III placebo-controlled trial (see **CLINICAL TRIALS**).

Geriatrics (≥ 65 years of age):
In the advanced breast cancer study, 40% of everolimus-treated patients were ≥ 65 years of age, while 15% were 75 years of age and over. No overall differences in effectiveness were observed between elderly and younger patients. Differences in the incidence of deaths due to any cause within 28 days of the last everolimus dose and in the incidence of adverse reactions leading to permanent treatment discontinuation were observed between elderly and younger patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics** and **CLINICAL TRIALS**).

[1] VEGF receptor TKIs = vascular endothelial growth factor receptor tyrosine kinase inhibitors

In two other randomized trials (metastatic RCC and advanced PNET), no overall differences in safety or effectiveness were observed between elderly and younger patients. In the randomized metastatic RCC study, 41% of everolimus treated patients were ≥ 65 years of age, while 7% were 75 years of age and over. In the randomized advanced PNET study, 30% of everolimus-treated patients were ≥ 65 years of age, while 7% were 75 years of age and over (see **CLINICAL TRIALS**).

In the randomized advanced GI/Lung NET study, 47% of everolimus-treated patients were ≥ 65 years of age, while 16% were 75 years of age and above. No overall differences in effectiveness were observed between elderly and younger patients. Adverse events reported with 1.5-fold the incidence in older patients receiving everolimus relative to those aged < 65 years included cardiac failure, lower respiratory tract infections (pneumonia, lung infection, bronchitis), cough and decreased appetite.

Pediatrics (< 18 years of age):
TEVA-EVEROLIMUS is not recommended for use in pediatric cancer patients.

TEVA-EVEROLIMUS has not been studied in pediatric patients with SEGA < 1 year of age and is not recommended for use in this age group. There is limited efficacy and safety data in patients 1 to 3 years of age with everolimus in patients with SEGA (see **WARNINGS AND PRECAUTIONS, Special Populations**).

TEVA-EVEROLIMUS is not recommended for use in pediatric patients with renal angiomyolipoma.

CONTRAINDICATIONS

- TEVA-EVEROLIMUS is contraindicated in patients who are hypersensitive to the drug, to other rapamycin derivatives or to any of the excipients. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** (see also **WARNINGS AND PRECAUTIONS**).
- TEVA-EVEROLIMUS is contraindicated for the treatment of seizures (of any type).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hormone receptor-positive, HER2-negative advanced breast cancer, advanced NET and metastatic kidney cancer:
- TEVA-EVEROLIMUS should be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy.

SEGA associated with TSC:
- Treatment with TEVA-EVEROLIMUS should be initiated by a qualified healthcare

professional experienced in the treatment of patients with TSC and with access to everolimus therapeutic drug monitoring services.
- Therapeutic drug monitoring of everolimus blood concentrations is **required** for patients treated for SEGA (see **DOSAGE AND ADMINISTRATION, Therapeutic drug monitoring for SEGA associated with TSC**).
- The optimal duration of TEVA-EVEROLIMUS therapy for patients with SEGA is not known; however, SEGA re-growth has been reported to occur once therapy is discontinued (see **DOSAGE AND ADMINISTRATION, SEGA volume monitoring for patients treated with TEVA-EVEROLIMUS** and **CLINICAL TRIALS, SEGA associated with Tuberous Sclerosis Complex**).
- Non-clinical data suggests that there is a risk of delayed developmental landmarks and delayed reproductive development in patients taking everolimus (see **Special Populations, Paediatrics** below and **TOXICOLOGY**).

Renal Angiomyolipoma associated with TSC:
- Treatment with TEVA-EVEROLIMUS should be initiated by a qualified healthcare professional experienced in the treatment of patients with TSC. The optimal time to initiate therapy is not known.
- The optimal duration of TEVA-EVEROLIMUS therapy for patients who have renal angiomyolipoma associated with TSC is not known (see **CLINICAL TRIALS, Renal Angiomyolipoma associated with Tuberous Sclerosis Complex**).
- Clinical trial data suggest that there is a potential risk of secondary amenorrhoea in females taking everolimus (see **Special Populations, Women of childbearing potential** below).

The following are clinically significant adverse events:
- Non-infectious pneumonitis, including fatalities (see **Respiratory** section below)
- Infections, including fatalities (see **Immune** section below)
- Renal failure, including fatalities (see **Renal** section below)

General

Drug-Drug Interactions

Co-administration with strong inhibitors of CYP3A4 and/or PgP should be avoided (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

Use caution when administered in combination with moderate inhibitors of CYP3A4 and/or PgP. If TEVA-EVEROLIMUS must be co-administered with a moderate inhibitor of CYP3A4 and/or PgP, the patient should be carefully monitored for undesirable effects and the dose reduced (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

Co-administration with strong inducers of CYP3A4 and/or PgP should be avoided due to the risk of reduced effectiveness of the drug. If TEVA-EVEROLIMUS must be co-administered with a strong inducer of CYP3A4 and/or PgP, the patient should be carefully monitored for clinical response. Consider a dose increase of TEVA-EVEROLIMUS when co-administered with anticonvulsants that are strong inducers of CYP3A4 if alternative treatment is not possible. However, there are limited clinical data with this dose adjustment in patients with renal

angiomyolipoma receiving an anticonvulsant that is a strong inducer of CYP3A4 (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS)**.

Exercise caution when TEVA-EVEROLIMUS is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions that may increase blood levels of CYP3A4 substrates. Interaction between TEVA-EVEROLIMUS and non-orally administered CYP3A4 substrates has not been studied (see **DRUG INTERACTIONS**).

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment). A review of pooled clinical trial data in the oncology setting revealed that angioedema occurred in 3.2% and 2.9% of everolimus patients treated with concomitant ACE inhibitors during double-blind and open-label treatment, respectively. In contrast, angioedema occurred in 0.5% and 0.7% of everolimus patients NOT treated with ACE inhibitors, in double-blind and open-label treatment, respectively.

Carcinogenesis and Mutagenesis

Genotoxicity studies 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 3.9 and 0.2 times the estimated clinical exposure from a 10 mg daily dose.

Functional Carcinoid Tumour

In a randomized, double-blind, multi-centre trial in 429 patients with functional carcinoid tumours, everolimus plus depot octreotide was compared to placebo plus depot octreotide. The study did not meet the primary efficacy endpoint (PFS) and the OS interim analysis numerically favoured the placebo plus depot octreotide arm. Therefore, the use of TEVA-EVEROLIMUS in patients with functional carcinoid tumours is not recommended outside an investigational study.

Endocrine and Metabolism

Hyperlipidaemia: Hypercholesterolaemia and hypertriglyceridaemia have been reported in patients taking everolimus (see **ADVERSE REACTIONS**). Monitoring of fasting lipid profile is recommended prior to the start of TEVA-EVEROLIMUS therapy and periodically thereafter. Consider dose reduction, dose interruption or discontinuation, as well as management with appropriate medical therapy (see **DOSAGE AND ADMINISTRATION, Dosing Considerations;** Table 13).

Hyperglycaemia: Hyperglycaemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of TEVA-EVEROLIMUS therapy and periodically thereafter (see **Monitoring and Laboratory Tests** below). More frequent monitoring is recommended when TEVA-EVEROLIMUS is co-administered with other drugs that may induce hyperglycaemia. Optimal glycaemic control should be achieved before starting a

patient on TEVA-EVEROLIMUS. New onset type 2 diabetes has occurred with everolimus treatment (see **ADVERSE REACTIONS**).

Gastrointestinal

Stomatitis including mouth ulceration, is a common adverse event in patients treated with everolimus. Across the clinical trial experience, 44% to 86% of the patients receiving everolimus experienced stomatitis (see **ADVERSE REACTIONS**). Stomatitis mostly occurs within the first 8 weeks of treatment.

For mouth ulcers and stomatitis, topical treatments are recommended, but alcohol- hydrogen peroxide-, iodine- or thyme-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless oral fungal infection has been diagnosed (see **DOSAGE AND ADMINISTRATION;** Table 13 and **DRUG INTERACTIONS**).

A single arm study suggested that an alcohol-free corticosteroid oral solution, administered as a mouthwash during the initial 8 weeks of treatment with everolimus plus exemestane, may decrease the incidence and severity of stomatitis in postmenopausal breast cancer patients.

Haematologic

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in patients taking everolimus (see **ADVERSE REACTIONS**). Monitoring of complete blood count is recommended prior to the start of TEVA-EVEROLIMUS therapy and periodically thereafter.

Haemorrhage

Clinical trials in patients with advanced cancers treated with everolimus have reported all grades of haemorrhage. In the RCC trial, gastrointestinal (GI) haemorrhage, retinal haemorrhage, vaginal haemorrhage, pulmonary alveolar haemorrhage, melaena and haematuria were reported as adverse events. In the hormone receptor-positive, HER2-negative advanced breast cancer trial, a single case of tumour haemorrhage was reported as a fatal adverse drug reaction. Post-marketing surveillance reported GI, tumour, pulmonary and cerebral haemorrhage as adverse events. Some cases were fatal (GI haemorrhage and cerebral haemorrhage). In the renal angiomyolipoma with TSC trial, low grade epistaxis, vaginal haemorrhage and menorrhagia were reported (see **ADVERSE REACTIONS**).

Caution is advised in patients taking TEVA-EVEROLIMUS during concomitant use with active substances known to affect platelet function or that can increase the risk of haemorrhage and in patients with a history of bleeding disorders. Be vigilant for signs and symptoms of bleeding throughout the treatment period, especially if risk factors for haemorrhage are combined.

Immune

Hypersensitivity reactions: Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see **CONTRAINDICATIONS**). Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

Infections: Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see **ADVERSE REACTIONS**). Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis, candidiasis, or *pneumocystis jirovecii* pneumonia (PJP) and viral infections including reactivation of hepatitis B virus have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to sepsis [including septic shock], respiratory or hepatic failure) and occasionally have had a fatal outcome in adult and pediatric patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Physicians and patients should be aware of the increased risk of infection with TEVA-EVEROLIMUS. Pre-existing infections should be treated and fully resolved prior to starting treatment with TEVA-EVEROLIMUS. Be vigilant for signs and symptoms of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of TEVA-EVEROLIMUS.

If a diagnosis of invasive systemic fungal infection is made, discontinue TEVA-EVEROLIMUS and treat with appropriate antifungal therapy (see **DOSAGE AND ADMINISTRATION**).

Cases of pneumocystis jirovecii pneumonia (PJP), some with fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

Vaccinations: The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with TEVA-EVEROLIMUS (see **DRUG INTERACTIONS**). For pediatric patients with SEGA who do not require immediate treatment, complete the recommended childhood series of live vaccinations prior to the start of therapy according to local treatment guidelines (e.g. updated Canadian Immunization Guide).

Musculoskeletal and Connective Tissue Disorders

Rhabdomyolysis: There have been unconfirmed reports of rhabdomyolysis presenting as myalgia, muscle pain and weakness with significantly elevated creatine kinase in patients treated with everolimus. During TEVA-EVEROLIMUS therapy, patients should be monitored for the possible development of rhabdomyolysis especially if they are prescribed a concomitant statin. Patients on treatment with TEVA-EVEROLIMUS should be advised to report promptly symptoms including muscle pain, weakness, or dark urine. If rhabdomyolysis is diagnosed,

institute treatment promptly and consider interruption or discontinuation of TEVA-EVEROLIMUS (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

In a clinical trial of 118 patients with renal angiomyolipoma associated with TSC, one patient (< 1%) receiving everolimus reported an adverse event of rhabdomyolysis.

Peri-operative Considerations

Impaired wound healing is a class effect of rapamycin derivatives, including everolimus. Caution should therefore be exercised with the use of TEVA-EVEROLIMUS in the peri-surgical period.

Renal

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus (see **ADVERSE REACTIONS**). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of TEVA-EVEROLIMUS therapy and periodically thereafter. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function (see also **Monitoring and Laboratory Tests** below).

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus (see **ADVERSE REACTIONS**).

Respiratory

Non-infectious pneumonitis: Non-infectious pneumonitis is a class effect of rapamycin derivatives, including TEVA-EVEROLIMUS. Cases of non-infectious pneumonitis (including interstitial lung disease) were reported in up to 19% of patients treated with everolimus (see **ADVERSE REACTIONS**). Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with nonspecific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jirovecii pneumonia (PJP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see **Immune**, **Infections**). Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue TEVA-EVEROLIMUS therapy without dose alteration.

If symptoms are moderate (Grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. TEVA-EVEROLIMUS

may be reintroduced at a daily dose approximately 50% lower than the dose previously administered (see **DOSAGE AND ADMINISTRATION,** Table 14).

For cases of Grade 3 non-infectious pneumonitis, interrupt TEVA-EVEROLIMUS until, resolution to less than or equal to Grade 1. TEVA-EVEROLIMUS may be reintroduced at a daily dose approximately 50% lower than the dose previously administered, depending on the individual clinical circumstances. If toxicity recurs at Grade 3, consider discontinuation of TEVA-EVEROLIMUS. For cases of Grade 4 non-infectious pneumonitis, TEVA-EVEROLIMUS therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) should be considered. The development of pneumonitis has also been reported at a reduced dose (see **DOSAGE AND ADMINISTRATION,** Table 14).

Sporadic Lymphangioleiomyomatosis (LAM)

The safety and effectiveness of TEVA-EVEROLIMUS in the treatment of patients with renal angiomyolipoma associated with sporadic LAM has not been established.

Vascular

Deep vein thrombosis (DVT) and pulmonary embolism (PE) events have been reported with everolimus use in clinical trials (see **ADVERSE REACTIONS**).

Special Populations

Pregnant women: Fetal harm may occur when administered to pregnant women. Apprise women of potential harm to the fetus. Animal studies have shown post-implantation loss in rats and rabbits as well as fetal toxicity at below clinical exposures (see **TOXICOLOGY**).

Nursing women: 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 TEVA-EVEROLIMUS should therefore not breastfeed during treatment and for 2 weeks after the last dose.

Women of childbearing potential: Women of childbearing potential, including pre-pubertal women, should be advised to use a highly effective method of contraception while receiving TEVA-EVEROLIMUS, and for up to 8 weeks after ending treatment.

If amenorrhoea develops in a woman of childbearing potential who is receiving TEVA-EVEROLIMUS, use of a highly effective method of contraception should continue.

In the renal angiomyolipoma associated with TSC clinical trial, secondary amenorrhoea has been reported in 15% of females receiving everolimus and in 4% of females receiving placebo. In the SEGA associated with TSC trial, amenorrhea occurred in 17% of females receiving everolimus and in none of the females receiving placebo. The mechanism is unknown. Early referral of

patients with menstrual irregularities to endocrine specialists is recommended (see **ADVERSE REACTIONS**).

Fertility: Both female and male fertility may be compromised by treatment with TEVA-EVEROLIMUS. Secondary amenorrhoea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance have been observed in female patients receiving everolimus. Blood levels of FSH and LH increased, blood levels of testosterone decreased and azoospermia have been observed in male patients receiving everolimus. A reduction in male fertility has also been demonstrated in animal studies (see **TOXICOLOGY**).

Geriatrics (≥ 65 years of age): In the randomized hormone receptor-positive, HER2-negative advanced breast cancer study, the incidence of deaths due to any cause within 28 days of the last everolimus dose was 3.7% overall; 6.3% in patients ≥ 65 years of age compared to 2.1% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended (see **DOSAGE AND ADMINISTRATION**).

Other reported clinical experience has not identified differences in response between the elderly and younger patients (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Pediatrics (< 18 years of age): TEVA-EVEROLIMUS is not recommended for use in pediatric cancer patients.

TEVA-EVEROLIMUS has not been studied in pediatric patients with SEGA < 1 year of age and is not recommended for use in this age group. There are limited efficacy and safety data in patients 1 to 3 years of age everolimus in patients with SEGA.

The optimal duration of TEVA-EVEROLIMUS therapy for patients with SEGA is not known; however, SEGA re-growth has been reported to occur once therapy is discontinued (see **DOSAGE AND ADMINISTRATION**, **SEGA volume monitoring for patients treated with TEVA-EVEROLIMUS** and **CLINICAL TRIALS**, **SEGA associated with Tuberous Sclerosis Complex**).

Non-clinical data suggest that there is a risk of delayed developmental landmarks and delayed reproductive development in patients taking everolimus. In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females, and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day (see **TOXICOLOGY**). Although a conclusive determination cannot be made due to the lack of a comparator arm in the open label follow-up periods of two phase III studies and a phase II study, everolimus did not appear to adversely impact growth and pubertal development in the 409 pediatric patients treated with everolimus in clinical trials with an estimated exposure of 944.20 patient treatment years (PTY).

The effect of TEVA-EVEROLIMUS on neurological development is unknown; everolimus has not been associated with adverse effects on neurological development in children. Body weight, longitudinal growth and pubertal development should be monitored at regular intervals (every 12 months) and neurological development should be monitored according to TSC guidelines in paediatric patients. Therapy should be individualized for the patient and clinical situation.

TEVA-EVEROLIMUS is not recommended for use in pediatric patients with renal angiomyolipoma associated with TSC in the absence of TEVA-EVEROLIMUS treatment for SEGA.

The overall type, frequency and severity of adverse events across the age groups were similar, with the exception of infections, which occurred at a higher frequency and severity in patients < 6 years of age. A total of 46 out of 137 patients (34%) < 6 years had Grade 3/4 infections, compared to 49 out of 272 patients (18%) 6 to < 18 years and 24 out of 203 patients (12%) ≥ 18 years.

Hepatic impairment: Exposure to everolimus is increased in patients with hepatic impairment. TEVA-EVEROLIMUS is recommended at a reduced dose in patients with hormone receptor-positive, HER2-negative advanced breast cancer, advanced NET, metastatic RCC or renal angiomyolipoma associated with TSC who have severe hepatic impairment only if the potential benefits outweigh the risks. For patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, TEVA-EVEROLIMUS is recommended at a reduced dose (see **DOSAGE AND ADMINISTRATION, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer, Advanced NET, Metastatic RCC and Renal Angiomyolipoma associated with TSC** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**).

No data are available in a pediatric population with hepatic impairment. Everolimus clearance, normalized to body-surface area, may be higher in younger patients than in adults and therefore the available adult data in hepatic impairment cannot be used to predict pediatric dosing (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics**). TEVA-EVEROLIMUS is not recommended for use in patients < 18 years of age with SEGA and concomitant hepatic impairment (Child-Pugh A, B or C). TEVA-EVEROLIMUS is not recommended for use in patients ≥ 18 years of age with SEGA and severe hepatic impairment (Child-Pugh C). For patients ≥ 18 years of age with SEGA who have mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, TEVA-EVEROLIMUS is recommended at a reduced dose (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**).

Monitoring and Laboratory Tests

Evaluation of CBC and serum chemistries (including blood glucose, lipids, liver function tests, creatinine, BUN, electrolytes, magnesium, calcium and phosphate) and urinary protein should be performed at the beginning of treatment with TEVA-EVEROLIMUS and periodically thereafter.

Body weight, longitudinal growth and pubertal development should be monitored at regular intervals (every 12 months) and neurological development should be monitored according to TSC guidelines in paediatric patients (see **Special Populations, Paediatrics**).

ADVERSE REACTIONS

Adverse Events in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

Adverse Reaction Overview

The data described below reflect exposure to everolimus (10 mg/day) in combination with exemestane (25 mg/day) (n=482) and placebo in combination with exemestane (25 mg/day) (n=238) in a randomized, placebo-controlled phase III study (BOLERO-2) for the treatment of postmenopausal women with estrogen receptor-positive, HER 2-neu/non-amplified locally advanced breast cancer[2] or metastatic breast cancer. The median age of patients was 61 years (range 28 - 93) and 75% were Caucasian. Safety results are based on a median follow-up of approximately 13 months. As of the data cut-off date of the updated analysis, the median duration of treatment with everolimus was 23.9 weeks (range: 1 to 100) with a median dose intensity of 8.7 mg/day; the median duration of placebo therapy was 13.4 weeks (range: 1 to 79).

The most common treatment-emergent adverse events irrespective of causality (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhoea and decreased appetite. Grade 3-4 events were observed more frequently among patients receiving everolimus plus exemestane than patients receiving placebo plus exemestane [grade 3 (40.9% vs. 22.3%, respectively) and grade 4 (8.7% vs. 5.0%, respectively)]. The most common grade 3-4 adverse events (incidence ≥ 3%) were stomatitis, infections, fatigue, dyspnoea and pneumonitis. Specific grade 3 or grade 4 infections were: pneumonia (1.2%), sepsis (0.3%), gastroenteritis (0.6%), and primary atypical pneumonia (0.4%). The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolaemia, hyperglycaemia, increased AST, anaemia, leukopenia, thrombocytopenia, lymphopenia, increased ALT and hypertriglyceridaemia. The most common grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, anaemia, hyperglycaemia, increased gamma-glutamyltransferase, decreased potassium, increased AST, increased ALT and thrombocytopenia. Fatal adverse reactions occurred in 7/482 (1.5%) of patients who received everolimus plus exemestane, with one death each due to pneumonia, sepsis, staphylococcal sepsis, tumour haemorrhage, ischemic stroke, completed suicide and renal failure. One death (0.4%) due to pneumonia occurred among 238 patients on the placebo plus exemestane arm.

The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the everolimus plus exemestane and placebo plus exemestane treatment groups, respectively. The most commonly reported AEs leading to discontinuation in the everolimus plus exemestane arm were: pneumonitis (4.4% of patients), stomatitis (2.5%), dyspnoea (1.9%), fatigue (1.9%), decreased appetite (1.7%), anaemia (1.7%) and rash (1.5%). The incidence of

[2] N=2 patients (0.4%) in the everolimus plus exemestane arm only

dose adjustments was 64% among patients receiving everolimus in the everolimus plus exemestane arm and 21% among patients receiving placebo in the placebo plus exemestane arm. Adverse events necessitating dose adjustments (interruptions or reductions) were more frequent among patients in the everolimus plus exemestane arm than in the placebo plus exemestane arm (60% versus 12%, respectively). The most commonly reported AEs that necessitated dose interruption or reduction for the everolimus plus exemestane arm were stomatitis (23.7% of patients), pneumonitis (7.3%) and thrombocytopenia (5.2%).

Clinical Trial Adverse Reactions

Table 1 compares the incidence of treatment-emergent adverse events reported with an incidence of ≥ 10% for patients receiving everolimus 10 mg daily versus placebo.

Treatment-emergent adverse events in Table 1 are listed according to MedDRA system organ class. Within each system organ class, the adverse events are ranked by frequency, with the most frequent events first.

Table 1: Adverse events, irrespective of causality, reported in at least 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (Hormone Receptor-Positive, HER2- Negative Advanced Breast Cancer)

	Everolimus + exemestane N = 482			Placebo + exemestane N = 238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any Adverse Event	**100**	**41**	**9**	**90**	**22**	**5**
Gastrointestinal Disorders						
Stomatitis[a]	67	8	0	11	0.8	0
Diarrhoea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0
Constipation	14	0.4	0	13	0.4	0
Dry Mouth	11	0	0	7	0	0
General Disorders and Administration Site Conditions						
Fatigue	36	4	0.4	27	1	0
Oedema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
Infections and Infestations						
Infections[b]	50	4	1	25	2	0
Investigations						
Weight decreased	25	1	0	6	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycaemia	14	5	0.4	2	0.4	0
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0

	Everolimus + exemestane N = 482			Placebo + exemestane N = 238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Pain in extremity	9	0.4	0	11	2	0
Nervous System Disorders						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
Psychiatric Disorders						
Insomnia	13	0.2	0	8	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	24	0.6	0	12	0	0
Dyspnoea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis[c]	19	4	0.2	0.4	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	39	1	0	6	0	0
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
Vascular Disorders						
Hot flush	6	0	0	14	0	0

CTCAE Version 3.0

a Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

b Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), and also including candidiasis (< 1%), sepsis (< 1%) and hepatitis C (< 1%).

c Includes pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis

Other treatment-emergent adverse reactions occurring more frequently with everolimus than with placebo, but with an incidence of < 10% and considered clinically relevant include:

Cardiac disorders: Tachycardia (3%)

Ear and labyrinth disorders: Deafness (0.8%)

Gastrointestinal disorders: Abdominal pain (5%), dysphagia (2%), gingivitis (2%)

Metabolism and nutrition disorders: Diabetes mellitus (1%), dehydration (3%)

Nervous system disorders: Ageusia (1%)

Renal and urinary disorders: Renal failure (1%), renal failure acute (0.8%), renal impairment (1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (4%), pulmonary embolism (2%), haemoptysis (1%)

Skin and subcutaneous tissue disorders: Nail disorder (8%), erythema (4%), acne (3%), hand-foot syndrome (reported as palmar-plantar erythrodysaesthesia syndrome) (0.6%), angioedema (0.2%)

Vascular disorders: Hypertension (8%), lymphoedema (6%), muscle haemorrhage (0.8%), rectal haemorrhage (0.8%), haemorrhoidal haemorrhage (0.6%), intra-abdominal haematoma (0.6%), deep vein thrombosis (1%)

Abnormal Haematologic and Clinical Chemistry Findings

Clinically relevant laboratory abnormalities are presented in Table 2.

Table 2: Clinically relevant laboratory abnormalities reported in > 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (Hormone Receptor-Positive, HER2- Negative Advanced Breast Cancer

Laboratory parameter	Everolimus + exemestane N=482			Placebo + exemestane N=238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Haematology[a]						
Haemoglobin decreased	68	6	0.6	40	0.8	0.4
WBC decreased	58	1	0	28	0	0.8
Platelets decreased	54	3	0.2	5	0	0.4
Lymphocytes decreased	54	11	0.6	37	5	0.8
Neutrophils decreased	31	2	0	11	0.8	0.8
Clinical chemistry						
Glucose increased	69	9	0.4	44	0.8	0.4
Cholesterol increased	70	0.6	0.2	38	0.8	0.8
Aspartate transaminase (AST) increased	69	4	0.2	45	3	0.4
Gamma- glutamyl transferase increased	59	10	3	54	13	3
Alanine transaminase (ALT) increased	51	4	0.2	29	5	0
Triglycerides increased	50	0.8	0	26	0	0
Albumin decreased	33	0.8	0	16	0.8	0
Potassium decreased	29	4	0.2	7	1	0
Creatinine increased	24	2	0.2	13	0	0

CTCAE Version 3.0

a Reflects corresponding adverse drug reaction reports of anaemia, leukopenia, lymphopenia, neutropenia and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency

Adverse Events in Advanced Pancreatic Neuroendocrine Tumours

Adverse Reaction Overview

In a randomized, controlled trial of everolimus (n=204) versus placebo (n=203) in patients with advanced pancreatic neuroendocrine tumours (PNET) the median age of patients was 58 years (range 23-87 years), 79% were Caucasian and 55% were male. The median duration of blinded study treatment was 37 weeks (range 1-130) for patients receiving everolimus and 16 weeks (range 0-146) for those receiving placebo. Patients on the placebo arm could cross over to open-label everolimus upon disease progression.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, rash, diarrhoea, fatigue, oedema, abdominal pain, nausea, fever and headache. The most common grade 3/4 adverse reactions (incidence ≥ 5%) were stomatitis and diarrhoea. The most common laboratory abnormalities (incidence ≥ 50%) were decreased haemoglobin, hyperglycaemia, alkaline phosphatase increased, hypercholesterolaemia, bicarbonate decreased and increased aspartate transaminase (AST). The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were hyperglycaemia, lymphopenia, decreased haemoglobin, hypophosphataemia, increased alkaline phosphatase, neutropenia, increased aspartate transaminase (AST), potassium decreased and thrombocytopenia.

On-treatment deaths due to infections (1%), renal failure (0.5%), cardiac arrest (0.5%), death (0.5%), hepatic failure (0.5%) and acute respiratory distress (0.5%) were observed in the everolimus arm, but none in placebo arm. There was 1 on-treatment death due to pulmonary embolism (0.5%) in the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 20.1% and 5.9% for the everolimus and placebo treatment groups, respectively.

The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis, infections and pyrexia. Infections, stomatitis, pneumonitis, thrombocytopenia and pyrexia were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during everolimus treatment were for infections, stomatitis, rash, diarrhoea and peripheral oedema.

Clinical Trial Adverse Reactions

Table 3 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% 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 3: Adverse reactions reported in at least 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (PNET)

	Everolimus N=204			Placebo N=203		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
	%	**%**	**%**	**%**	**%**	**%**
Any adverse reaction	**100**	**49**	**13**	**98**	**32**	**8**
Gastrointestinal disorders						
Stomatitis[a]	70	7	0	20	0	0

	Everolimus N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Diarrhoea[b]	50	5	0.5	25	3	0
Abdominal pain	36	4	0	32	6	1
Nausea	32	2	0	33	2	0
Vomiting	29	1	0	21	2	0
Constipation	14	0	0	13	0.5	0
Dry mouth	11	0	0	4	0	0
General disorders and administration site conditions						
Fatigue/malaise	45	3	0.5	27	2	0.5
Oedema (general and peripheral)	39	1	0.5	12	1	0
Fever	31	0.5	0.5	13	0.5	0
Asthenia	19	3	0	20	3	0
Infections and infestations						
Nasopharyngitis/rhinitis/URI	25	0	0	13	0	0
Urinary tract infection	16	0	0	6	0.5	0
Investigations						
Weight decreased	28	0.5	0	11	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	18	1	0
Diabetes mellitus	10	2	0	0.5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	1	0.5	7	0.5	0
Back pain	15	1	0	11	1	0
Pain in extremity	14	0.5	0	6	1	0
Muscle spasms	10	0	0	4	0	0
Nervous system disorders						
Headache/migraine	30	0.5	0	15	1	0
Dysgeusia	19	0	0	5	0	0
Dizziness	12	0.5	0	7	0	0
Psychiatric disorders						
Insomnia	14	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough/productive cough	25	0.5	0	13	0	0
Epistaxis	22	0	0	1	0	0
Dyspnoea/dyspnoea exertional	20	2	0.5	7	0.5	0
Pneumonitis[c]	17	3	0.5	0	0	0
Oropharyngeal pain	11	0	0	6	0	0
Skin and subcutaneous disorders						
Rash	59	0.5	0	19	0	0
Nail disorders	22	0.5	0	2	0	0
Pruritus/pruritus generalized	21	0	0	13	0	0
Dry skin/xeroderma	13	0	0	6	0	0
Vascular disorders						
Hypertension	13	1	0	6	1	0
Median duration of treatment	**37**			**16**		

	Everolimus N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
(weeks)						

CTCAE Version 3.0

a Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration and mucosal inflammation.

b Includes diarrhoea, enteritis, enterocolitis, colitis, defecation urgency and steatorrhoea.

c Includes pneumonitis, interstitial lung disease, pulmonary fibrosis and restrictive pulmonary disease.

Other treatment-emergent adverse reactions occurring more frequently with everolimus than with placebo, but with an incidence of < 10% and considered clinically relevant include:

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pulmonary embolism (2%), pulmonary oedema (1%)

General disorders and administration site conditions: Chills (6%), chest pain (3%), generalized oedema (2%)

Psychiatric disorders: Depression (6%)

Skin and subcutaneous tissue disorders: Acne (6%), erythema (5%), hand-foot syndrome (reported as palmar-plantar erythrodysaesthesia syndrome) (3%), angioedema (0.5%)

Gastrointestinal disorders: Dysphagia (3%), oral pain (3%), small intestinal obstruction (0.5%)

Cardiac disorders: Angina pectoris (2%), cardiac failure (1%)

Renal and urinary disorders: Proteinuria (4%), renal failure (2%)

Haematologic disorders: Pure red cell aplasia (0.5%)

Metabolism and nutrition disorders: Dehydration (6%)

Reproductive system and breast disorders: Menstruation irregular (3%)

Abnormal Haematological and Clinical Chemistry Findings

Clinically relevant laboratory abnormalities are presented in Table 4.

Table 4: Clinically relevant laboratory abnormalities reported in ≥ 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (PNET)

Laboratory parameter	Everolimus N=204		Placebo N=203	
	All grades	Grade 3-4	All grades	Grade 3-4
	%	%	%	%
Haematology				
Haemoglobin decreased	86	15	63	1
Lymphocytes decreased	45	16	22	4
Platelets decreased	45	3	11	0
WBC decreased	43	2	13	0
Neutrophils decreased	30	4	17	2
Clinical chemistry				
Alkaline phosphatase increased	74	8	66	8
Glucose (fasting) increased	75	17	53	6
Cholesterol increased	66	0.5	22	0
Bicarbonate decreased	56	0	40	0
Aspartate transaminase (AST) increased	56	4	41	4
Alanine transaminase (ALT) increased	48	2	35	2
Phosphate decreased	40	10	14	3
Triglycerides increased	39	0	10	0
Calcium decreased	37	0.5	12	0
Potassium decreased	23	4	5	0
Creatinine increased	19	2	14	0
Sodium decreased	16	1	16	1
Albumin decreased	13	1	8	0
Bilirubin increased	10	1	14	2
Potassium increased	7	0	10	0.5

CTCAE Version 3.0

Adverse Events in Advanced Non-Functional Neuroendocrine Tumours of Gastrointestinal or Lung Origin

Adverse Reaction Overview

The data described below reflect exposure to everolimus (n=205) and placebo (n=97) in a randomized, controlled phase III study (RADIANT-4) in patients with advanced non-functional NET of GI or lung origin. The median duration of blinded study treatment was 40 weeks for patients receiving everolimus and 20 weeks for those receiving placebo.

Serious adverse events (SAEs) were reported more frequently in everolimus-treated group (42.1%) than in the placebo group (19.4%). While the incidence of specific individual SAEs was low for both treatment groups, the most commonly reported SAEs in everolimus group, irrespective of causal relationship to the study drug, were abdominal pain (5.4%), pyrexia (4.5%), diarrhea (4.0%), anemia (3.0%), pneumonia (3.0%), small intestinal obstruction (3.0%), asthenia (2.5%), fatigue (2.5%), vomiting (2.5%), and pneumonitis (2.0%).

Deaths during double-blind treatment where an adverse event was the primary cause occurred in three patients on everolimus (1.5%) and two patients on placebo (2.0%). Causes of death due to an adverse event on the everolimus arm included one case of each of the following: cardiac failure, respiratory failure and septic shock. Causes of death on the placebo arm due to an adverse event included one case of lung infection and one case of dyspnea. The rates of treatment-emergent adverse events resulting in permanent discontinuation were 29% and 7% for the everolimus and placebo treatment groups, respectively. Dose delay or reduction was necessary in 70% of everolimus patients and 19% of placebo patients.

The most frequent adverse events (AEs) (≥5%), irrespective of causality, requiring dose adjustment or interruption were anaemia, stomatitis, diarrhea, fatigue, oedema peripheral, pyrexia, pneumonitis. The most frequent AEs (irrespective of causality) leading to treatment discontinuation were stomatitis (3.0%), GGT increased (1.5%) and diarrhea (1.5%). Other AEs occurred in ≤ 1% of patients each.
The most common (≥ 10%) adverse events (irrespective of causality) requiring medical intervention during everolimus treatment were anemia, stomatitis, diarrhea, abdominal pain, nausea, pyrexia, oedema peripheral, urinary tract infection, pneumonitis, cough, rash and hypertension.

Table 5 compares the incidence of treatment-emergent adverse events reported with an incidence of ≥ 10% for patients receiving everolimus 10 mg daily plus best supportive care versus placebo plus best supportive care. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Clinical Trial Adverse Reactions

Table 5 Adverse events reported in at least 10% of patients with advanced non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin and at a higher rate in the everolimus arm than in the placebo arm

	Everolimus N=202			Placebo N=98		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any Adverse Reaction	**99**	**57**	**12**	**89**	**21**	**7**
Blood and Lymphatic System Disorders						
Anaemia	22	5	1	12	3	0
Gastrointestinal Disorders						
Stomatitis[a]	63	9	0	22	0	0
Diarrhea	41	8	1	31	2	0
Nausea	26	3	1	17	1	0
Vomiting	15	4	0	12	2	0
General Disorders and Administration Site Conditions						
Edema peripheral	39	3	0	6	1	0
Fatigue	37	4	1	36	1	0
Asthenia	23	2	1	8	0	0

	Everolimus N=202			Placebo N=98		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Pyrexia	23	1	1	8	0	0
Infections and Infestations						
Infections[b]	58	8	3	29	1	1
Investigations						
Weight decreased	22	2	0	11	1	0
Metabolism and Nutrition Disorders						
Decreased appetite	22	1	0	17	1	0
Hyperglycaemia	12	5	0	3	0	0
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	12	1	0	8	0	0
Nervous System Disorders						
Dysgeusia	18	1	0	4	0	0
Psychiatric disorders						
Insomnia	10	0	0	7	1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	27	0	0	20	0	0
Dyspnoea	20	3	0	11	1	1
Pneumonitis[c]	16	2	0	2	0	0
Epistaxis	13	1	0	3	0	0
Skin and Subcutaneous Disorders						
Rash	30	1	0	9	0	0
Pruritus	17	1	0	9	0	0
Vascular disorders						
Hypertension	12	4	0	8	3	0

Grading according to CTCAE Version 4.03

a Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration and mucosal inflammation

b Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock and viral myocarditis.

c Includes pneumonitis and interstitial lung disease

Other clinically relevant treatment-emergent adverse events with an incidence of < 10% in everolimus group but occurring more frequently than with placebo, include:

Blood and lymphatic system disorders: Thrombocytopenia (4%), neutropenia (3%)

Cardiac disorders: Cardiac failure (3%), cardiac failure congestive (1%), cardiac failure chronic (1%), left ventricular dysfunction (1%)

Eye disorders: Eyelid oedema (4%)

Gastrointestinal disorders: Small intestinal obstruction (3%), intestinal obstruction (2%), dysphagia (3%)

General disorders and administration site conditions: Impaired healing (1%)

Investigations: Alanine aminotransferase increased (5%), blood cholesterol increased (5%), gamma-glutamyltransferase increased (5%), aspartate aminotransferase increased (4%), blood creatinine increased (4%)

Metabolism and nutrition disorders: Hypokalaemia (10%), hypercholesterolaemia (6%), hypertriglyceridaemia (5%), hypophosphataemia (5%), diabetes mellitus (4%), type 2 diabetes mellitus (1%), hypocalcaemia (4%)

Musculoskeletal and connective tissue disorders: Pain in extremity (9%), myalgia (6%)

Nervous system disorders: Lethargy (4%), Paraesthesia (2%)

Renal and urinary disorders: Proteinuria (8%), renal failure (1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (5%)

Skin and subcutaneous tissue disorders: Dermatitis acneiform (9%), dry skin (9%), nail disorder (6%), erythema (6%), acne (5%), palmar-plantar erythrodysaesthesia syndrome (4%)

Vascular disorders: Deep vein thrombosis (1%), phlebitis (1%)

Abnormal Haematological and Clinical Chemistry Findings

Clinically relevant laboratory abnormalities are presented in Table 6.

Table 6: Clinically relevant laboratory abnormalities reported in ≥ 10% of patients with advanced non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin and at a higher rate in the everolimus arm than in the placebo arm

	Everolimus N=202			Placebo N=98		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology						
Hemoglobin decreased	81	5	0	41	2	0
Lymphocytes decreased	66	15	2	32	2	0
White blood cell count decreased	49	2	0	17	0	0
Platelets decreased	33	2	1	11	0	0
Neutrophils decreased	32	2	0	15	3	0
Clinical chemistry						
Creatinine increased	82	2	1	82	1	1
Cholesterol increased	71	0	0	37	0	0
Aspartate transaminase (AST) increased	57	1	1	34	2	0
Glucose (fasting) increased	55	6	0	36	1	0

Alanine transaminase (ALT) increased	46	5	1	39	1	0
Phosphate decreased	43	4	0	15	2	0
Triglycerides increased	30	3	1	8	1	0
Potassium decreased	27	4	2	12	3	0
Albumin decreased	18	0	0	8	0	0

Grading according to CTCAE Version 4.03

Adverse Events in Metastatic RCC

Adverse Reaction Overview

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomized phase III study for the treatment of metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥ 4 months. The median age of patients was 61 years (range 27 to 85 years), 90% were Caucasian and 78% were males. The median duration of blinded study treatment was 141 days (range 19 to 451) for patients receiving everolimus and 60 days (range 21 to 295) for those receiving placebo.

The most common treatment-emergent adverse events irrespective of causality (incidence ≥ 30%) were stomatitis, anaemia, infections, asthenia, fatigue, cough and diarrhoea. The most common grade 3-4 adverse events (incidence ≥ 3%) were anaemia, infections, dyspnoea, hyperglycaemia, stomatitis, fatigue, dehydration, pneumonitis, abdominal pain, asthenia and hypercholesterolaemia.

The rates of treatment-emergent adverse events resulting in permanent discontinuation were 14% and 3% for the everolimus and placebo treatment groups, respectively. Most treatment-emergent adverse events were grade 1 or 2 in severity.

Clinical Trial Adverse Reactions

Table 7 compares the incidence of treatment-emergent adverse events reported with an incidence of ≥ 10% for patients receiving everolimus 10 mg/day versus placebo.

Treatment-emergent adverse events in Table 7 are listed according to MedDRA system organ class. Within each system organ class, the adverse events are ranked by frequency, with the most frequent events first.

Table 7: Adverse events, irrespective of causality, reported in at least 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (mRCC)

	Everolimus 10 mg/day N=274			**Placebo N=137**		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
	%	**%**	**%**	**%**	**%**	**%**
Any Adverse Event	**97**	**52**	**13**	**93**	**23**	**5**

	Everolimus 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Gastrointestinal Disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhoea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Blood and Lymphatic System Disorders						
Anaemia	38	9	<1	15	4	<1
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
Oedema 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
Hypercholesterolaemia	20	3	0	2	0	0
Hypertriglyceridaemia	15	1	0	2	0	0
Hyperglycaemia	12	6	0	2	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 of Treatment (d)	**141**			**60**		

CTCAE Version 3.0

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 haemorrhage, pulmonary toxicity and alveolitis

Other treatment-emergent adverse events occurring more frequently with everolimus than with placebo, but with an incidence of < 10% and considered clinically relevant include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), haemorrhoids (5%), dyspepsia (4%), dysphagia (4%), anal haemorrhage (< 1%) haematochezia (< 1%), melaena (< 1%) and rectal haemorrhage (< 1%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Investigations: Blood creatinine increased (9%)

Blood and lymphatic system disorders: Lymphopenia (8%), thrombocytopenia (7%), leucopenia (3%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhoea (3%), pulmonary alveolar haemorrhage (< 1%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysaesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%), acne (< 1%), angioedema (0.7%)

Metabolism and nutrition disorders: Dehydration (5%), hypophosphataemia (5%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), hypocalcaemia (3%), exacerbation of pre-existing diabetes mellitus (2%), new-onset diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paraesthesia (5%), ageusia (1%)

Eye disorders: Eyelid oedema (4%), conjunctivitis (2%), retinal haemorrhage (< 1%)

Vascular disorders: Hypertension (4%), haemorrhage (3%)[§], deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%), acute renal failure (1%), increased daytime urination (2%), haematuria (2%)

Reproductive system and breast disorders: Vaginal haemorrhage (< 1%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

§Excluding epistaxis

Abnormal Haematological and Clinical Chemistry Findings

Clinically relevant laboratory abnormalities are presented in Table 8.

Table 8: Clinically relevant laboratory abnormalities reported at a higher rate in the everolimus arm than in the placebo arm (mRCC)

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						
Cholesterol 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 (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

a Includes reports of anaemia, leucopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia

Adverse Events in Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

Adverse Reaction Overview

The data described below reflect exposure to everolimus (10 mg/day) (n=79) vs. placebo (n=39) in a randomized double-blind, parallel-group, placebo-controlled, multi-centre phase III study for the treatment of patients who have renal angiomyolipoma associated with TSC (n=113) or with sporadic lymphangioleiomyomatosis (LAM) (n=5). The median age of patients was 31 years (range: 18 to 61 years), 89% were Caucasian, and 34% were male. The median duration of blinded study treatment was 48 weeks (range: 2 to 115 weeks) for patients receiving everolimus and 45 weeks (range: 9 to 115 weeks) for those receiving placebo.

The most common treatment-emergent adverse reaction irrespective of causality (incidence ≥ 30%) was stomatitis. The most common grade 3-4 adverse events (incidence ≥ 2%) were stomatitis, amenorrhoea and convulsion. The most common clinically relevant laboratory abnormalities (incidence ≥ 50%) were increased cholesterol and triglycerides and decreased haemoglobin. The most common clinically relevant grade 3/4 laboratory abnormality (incidence

≥ 2%) was decreased phosphate. A single death was reported in the everolimus arm as a result of status epilepticus in a patient with a prior history of intractable seizures.

The rates of treatment-emergent adverse events resulting in permanent discontinuation were 4% and 10% for the everolimus and placebo treatment groups, respectively. Adverse reactions leading to permanent discontinuation in the everolimus arm were hypersensitivity/angioedema/ bronchospasm, convulsion and decreased blood phosphorus. Dose adjustments (interruptions or reductions) due to adverse reactions were more frequent among patients in the everolimus arm than in the placebo arm (52% versus 21%, respectively). The most commonly occurring adverse reaction leading to everolimus dose adjustment or need for medical intervention was stomatitis.

Clinical Trial Adverse Reactions

Table 9 compares the incidence of treatment-emergent adverse events reported with an incidence of ≥ 10% for patients receiving everolimus 10 mg daily or placebo and occurring more frequently with everolimus than with placebo.

Treatment-emergent adverse events in Table 9 are listed according to MedDRA system organ class. Within each system organ class, the adverse events are ranked by frequency, with the most frequent events first.

Table 9: Adverse events, irrespective of causality, reported in at least 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (Renal Angiomyolipoma associated with TSC)

	Everolimus 10 mg/day N=79			Placebo N=39		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any Adverse Event	**100**	**25**	**5**	**97**	**8**	**5**
Blood and Lymphatic System Disorders						
Anaemia	11	0	0	3	0	0
Leukopenia	10	0	0	8	0	0
Gastrointestinal Disorders						
Stomatitis[a]	78	6	0	23	0	0
Nausea	16	0	0	13	0	0
Vomiting	15	0	0	5	0	0
Diarrhoea	14	0	0	5	0	0
Abdominal pain	11	0	0	8	3	0
General Disorders and Administration Site Conditions						
Oedema peripheral	13	1	0	8	0	0
Infections and Infestations						
Upper respiratory tract infection	11	0	0	5	0	0
Investigations						
Blood lactate dehydrogenase increased	11	0	0	3	0	0
Metabolism and Nutrition Disorders						

	Everolimus 10 mg/day N=79			Placebo N=39		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Hypercholesterolaemia	23	1	0	3	0	0
Hypophosphataemia	11	0	0	3	0	0
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	13	0	0	5	0	0
Nervous System Disorders						
Headache	22	0	0	21	3	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	20	0	0	13	0	0
Skin and Subcutaneous Tissue Disorders						
Acne	22	0	0	5	0	0
Rash[b]	11	0	0	0	0	0
Eczema	10	0	0	8	0	0

Grading according to CTCAE Version 3.0

a Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis and glossodynia.

b Includes rash, erythema, rash erythematous, palmar erythema, rash macular

Amenorrhoea (secondary) occurred in 15% of everolimus-treated females (8 of 52) and 4% (1 of 26) of females in the placebo group. Other adverse reactions involving the female reproductive system were menorrhagia (10%), menstrual irregularities (10%), vaginal haemorrhage (8%), menstruation delayed (2%) and oligomenorrhoea (2%).

Other treatment-emergent adverse reactions occurring more frequently with everolimus than with placebo, but with an incidence of < 10% and considered clinically relevant include:

Blood and lymphatic system disorders: Thrombocytopenia (8%)

Gastrointestinal disorders: Flatulence (6%), oral pain (1%)

Immune system disorders: Hypersensitivity (3%)

Infections and infestations: Otitis media (6%), sinusitis (6%), rash pustular (5%), oral herpes (4%), pneumonia (4%), gingivitis (1%)

Investigations: Carbon monoxide diffusing capacity decreased (9%), blood alkaline phosphatase increased (9%), gamma-glutamyltransferase increased (6%), blood phosphorus decreased (5%)

Metabolism and nutrition disorders: Hyperlipidaemia (8%), decreased appetite (6%), iron deficiency (6%)

Nervous system disorders: Migraine (5%), dysgeusia (4%), ageusia (1%)

Psychiatric disorders: Depression (5%), insomnia (4%), aggression (1%)

Respiratory, thoracic and mediastinal disorders: Epistaxis (9%), pneumonitis (1%)

Reproductive system and breast disorders: Blood luteinising hormone increased (4%), blood follicle stimulating hormone increased (3%), ovarian cyst (3%)

Skin and subcutaneous tissue disorders: Dry skin (9%), dermatitis acneiform (8%), angioedema (1%)

Vascular disorders: Hypertensive crisis (1%)

Abnormal Haematological and Clinical Chemistry Findings

Clinically relevant laboratory abnormalities are presented in Table 10 below.

Table 10: Clinically relevant laboratory abnormalities reported in at a higher rate in the everolimus arm than in the placebo arm (Renal Angiomyolipoma associated with TSC)

Laboratory parameter	Everolimus 10 mg/day N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Haematology						
Haemoglobin decreased	61	0	0	49	0	0
White blood cells (WBC) decreased	37	0	0	21	0	0
Lymphocytes decreased	20	1	0	8	0	0
Platelets decreased	19	0	0	3	0	0
Clinical chemistry						
Cholesterol increased	85	1	0	46	0	0
Triglycerides increased	52	0	0	10	0	0
Phosphate decreased	49	5	0	15	0	0
Alkaline phosphatase increased	32	1	0	10	0	0
Aspartate transaminase (AST) increased	23	1	0	8	0	0
Alanine transaminase (ALT) increased	20	1	0	15	0	0
Glucose (fasting) increased	14	0	0	8	0	0

Grading according to CTCAE Version 3.0

Further long term follow-up with a median duration of exposure of 47 months resulted in the following additional key laboratory abnormalities; partial thromboplastin time increased (63%), prothrombin time increased (40%), fibrinogen decreased (38%), and notable adverse events; nasopharyngitis (44.6%), urinary tract infection (31%), proteinuria (18%), bronchitis (14.3%), pyrexia (13%), oropharyngeal pain (13%), pruritus (12%), gastroenteritis (12%), blood lactate dehydrogenase increased (11%), dizziness (11%) and myalgia (11%), dental conditions (tooth abscess [7.1%], tooth infection [6.3%], and periodontitis [5.4%]), and metrorrhagia (5.4%).

Blood follicle stimulating hormone (FSH) increased and blood luteinizing hormone (LH) increased was reported in 2 male patients (5.1%; 2/39 male patients). One of these 2 patients also reported blood testosterone decreased (2.6%; 1/39 male patients).

Adverse Events in SEGA associated with Tuberous Sclerosis Complex

Adverse Reaction Overview

The data described below reflect exposure to everolimus (n=78) or placebo (n=39) in a randomized (2:1), double-blind, placebo-controlled, phase III trial in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) (N=117). The median age of patients was 9.5 years (range: 0.8 to 26.6 years), 93% were Caucasian and 57% were male. The median duration of blinded study treatment was 52 weeks (range: 24 to 89 weeks) for patients receiving everolimus and 47 weeks (range: 14 to 88 weeks) for those receiving placebo.

In the double-blind period of the trial, the most common treatment-emergent adverse event irrespective of causality reported for everolimus (incidence ≥ 30%) was stomatitis. The most common grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pyrexia, pneumonia, viral gastroenteritis, aggression, agitation, neutropenia and amenorrhoea. The most common key laboratory abnormalities (incidence ≥ 50%) were cholesterol increased and elevated partial thromboplastin time. The most common grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutrophil count decreased

There were no adverse events resulting in permanent discontinuation. Dose adjustments (interruptions or reductions) due to adverse events occurred in 55% of everolimus-treated patients. The most common adverse event leading to everolimus dose adjustment was stomatitis.

Clinical Trial Adverse Reactions

Table 11 compares the incidence of treatment-emergent adverse events irrespective of causality reported with an incidence of ≥ 10% for patients receiving everolimus and occurring more frequently with everolimus than with placebo.

Treatment-emergent adverse events in Table 11 are listed according to MedDRA system organ class. Within each system organ class, the adverse events are ranked by frequency, with the most frequent events first.

Table 11: Adverse events, irrespective of causality, reported in at least 10% of patients and at a higher rate in the everolimus arm than in the placebo arm (SEGA associated with TSC– Phase III Trial)

	Everolimus N=78			Placebo N=39		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Any adverse reaction	**97**	**36**	**3**	**92**	**23**	**3**
Gastrointestinal disorders						
Stomatitis[a]	62	9	0	26	3	0
Vomiting	22	1	0	13	0	0
Diarrhoea	17	0	0	5	0	0
Constipation	10	0	0	3	0	0
Infections and infestations						
Respiratory tract infection[b]	31	1	1	23	0	0
Gastroenteritis[c]	10	4	1	3	0	0
Pharyngitis streptococcal	10	0	0	3	0	0
Ear infection[f]	18	3	0	15	3	0
General disorders and administration site conditions						
Pyrexia	23	6	0	18	3	0
Fatigue	14	0	0	3	0	0
Psychiatric and behavioural disorder						
Anxiety, aggression or other behavioural disturbance[d]	21	5	0	3	0	0
Skin and subcutaneous tissue disorders						
Rash[e]	21	0	0	8	0	0
Acne	10	0	0	5	0	0

Grading according to CTCAE Version 3.0

a Includes mouth ulceration, stomatitis and lip ulceration

b Includes respiratory tract infection, upper respiratory tract infection and respiratory tract infection viral

c Includes gastroenteritis, gastroenteritis viral and gastrointestinal infection

d Includes agitation, anxiety, panic attack, aggression, abnormal behaviour and obsessive compulsive disorder

e Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic and urticaria

f Includes otitis media, ear infection, ear infection bacterial, otitis media acute

Amenorrhoea (secondary) occurred in 17% (3 out of 18) of everolimus-treated females aged 10 to 55 years (age of oldest patient in this target range was 27 years) and in none of the females in the placebo group. For this same group of everolimus-treated females, the following menstrual abnormalities were reported: dysmenorrhoea (6%), menorrhagia (6%), metrorrhagia (6%) and unspecified menstrual irregularity (6%).

Other treatment-emergent adverse events occurring with everolimus with an incidence of < 10% and considered clinically relevant include:

Blood and Lymphatic Disorders: Neutropenia (6%), anaemia (5%)

Gastrointestinal disorders: Nausea (8%), oral pain (5%)

General disorders and administrative site conditions: Irritability (5%)

Immune system disorders: Hypersensitivity (3%)

Infections and infestations: Urinary tract infection (4%), gingivitis (4%), herpes zoster (1%)

Investigations: Blood luteinising hormone increased (1%)

Metabolism and Nutrition Disorders: Decreased appetite (9%), hypercholesterolaemia (6%)

Musculoskeletal and connective tissue disorder: Pain in extremity (8%)

Psychiatric disorders: Aggression (8%), insomnia (6%)

Respiratory, thoracic and mediastinal disorders: Pneumonia (6%), epistaxis (5%), pneumonitis (1%)

Abnormal Haematological and Clinical Chemistry Findings

Key laboratory abnormalities reported more frequently with everolimus than placebo are presented in Table 12.

Table 12: Laboratory abnormalities reported in at a higher rate in the everolimus arm than in the placebo arm (SEGA associated with TSC - Phase III Trial)

	Everolimus N=78			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Haematology						
Elevated partial thromboplastin time	72	3	0	44	5	0
Neutrophils decreased	46	9	0	41	3	0
Haemoglobin decreased	41	0	0	21	0	0
Clinical chemistry						
Hypercholesterolemia	81	0	0	39	0	0
Elevated aspartate transaminase (AST)	33	0	0	0	0	0
Hypertriglyceridemia	27	0	0	15	0	0
Elevated alanine transaminase (ALT)	18	0	0	3	0	0
Hypophosphatemia	9	1	0	3	0	0

Grading according to CTCAE Version 3.0

Further long-term follow-up with a medium duration of exposure of 47 months resulted in the following additional notable adverse events and key laboratory abnormalities: nasopharyngitis

(35%), cough (26%), pneumonia (25%), sinusitis (20%), bronchitis (18%), otitis media (18%), headache (15%), decreased appetite (14%), hyperglycemia (13%), hypertension (11%), urinary tract infection (9%), decreased fibrinogen (8%), oropharyngeal pain (6%), cellulitis (6%), abdominal pain (5%), weight decrease (5%), irritability (5%) and elevated creatinine (5%) and azoospermia (1%).

Post-Market Adverse Reactions

Other adverse drug reactions are presented below; some of them are reported spontaneously. Because spontaneous events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to everolimus exposure.

Blood and lymphatic system disorders:	Febrile neutropenia
Immune system disorders:	Hepatitis B reactivation, including fatal outcome (reactivation of infections is an expected event during periods of immunosuppression), angioedema with and without concomitant use of ACE inhibitors
Infections and infestations:	Pneumocystis jirovecii pneumonia (PJP)
Musculoskeletal and connective tissue disorders:	Rhabdomyolysis
Renal and urinary disorders:	Renal failure events, including fatal outcome (monitoring of renal function is recommended), proteinuria
Reproductive system and breast disorders:	Secondary amenorrhoea
Respiratory, thoracic and mediastinal disorders:	Pulmonary embolism

DRUG INTERACTIONS

Overview

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP.

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

Drug-Drug Interactions

Agents that may increase everolimus blood concentrations:
Everolimus blood concentrations may be increased by substances that inhibit CYP3A4 activity and thus decrease everolimus metabolism.

Everolimus blood concentrations may be increased by inhibitors of PgP that may decrease the efflux of everolimus from intestinal cells.

Concurrent treatment with strong inhibitors of CYP3A4 and/or PgP (including but not limited to ketoconazole, itraconazole, voriconazole, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone, clarithromycin and telithromycin) should be avoided.

There was a significant increase in exposure to everolimus (C_{max} and AUC increased by 3.9- and 15.0-fold, respectively) in healthy subjects when everolimus was co-administered with ketoconazole (a strong inhibitor of CYP3A4 and PgP).

Concomitant treatment with moderate inhibitors of CYP3A4 (including, but not limited to, erythromycin, verapamil, cyclosporine, fluconazole, diltiazem, amprenavir, fosamprenavir or aprepitant) and moderate PgP inhibitors requires caution. Reduce the TEVA-EVEROLIMUS dose if co-administered with moderate inhibitors of CYP3A4 and/or PgP (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

There was an increase in exposure to everolimus in healthy subjects when everolimus was co-administered with:

- erythromycin (a moderate inhibitor of CYP3A4 and an inhibitor of PgP; C_{max} and AUC increased by 2.0- and 4.4-fold, respectively)
- verapamil (a moderate inhibitor of CYP3A4 and an inhibitor of PgP; C_{max} and AUC increased by 2.3-and 3.5-fold, respectively)
- cyclosporine (a CYP3A4 substrate and an inhibitor of PgP; C_{max} and AUC increased by 1.8- and 2.7-fold, respectively)

Agents that may decrease everolimus blood concentrations:
Substances that are inducers of CYP3A4 and/or PgP may decrease everolimus blood concentrations by increasing the metabolism or the efflux of everolimus from intestinal cells.

Concurrent treatment with strong inducers of CYP3A4 and/or PgP should be avoided. If TEVA-EVEROLIMUS must be co-administered with a strong inducer of CYP3A4 and/or PgP (e.g. rifampicin and rifabutin), it may be necessary to adjust the TEVA-EVEROLIMUS dose (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Pre-treatment of healthy subjects with multiple doses of rifampicin (a strong inducer of CYP3A4 and PgP) 600 mg daily for 8 days followed by a single dose of everolimus, increased everolimus oral-dose clearance nearly 3-fold and decreased C_{max} by 58% and AUC by 63%.

Other strong inducers of CYP3A4 and/or PgP that may increase the metabolism of everolimus and decrease everolimus blood levels include St. John's wort (*Hypericum perforatum*), anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin) and anti-HIV agents (e.g. efavirenz, nevirapine).

Agents whose plasma concentrations may be altered by everolimus:
Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses

also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus. However, these studies were carried out with a 2 mg oral dose of everolimus. The effects of a 10 mg dose have not been studied and therefore pharmacological interactions cannot be ruled out in this setting.

Everolimus may inhibit the metabolism of substrates of CYP3A4 including statins (HMG-CoA reductase inhibitors). Caution should be exercised if a statin is prescribed for hyperlipidaemia, since the risk of developing rhabdomyolysis may be increased with statin use (see **WARNINGS AND PRECAUTIONS**, **Musculoskeletal and Connective Tissue Disorders**).

In vitro, everolimus competitively inhibited the metabolism of the CYP3A4 substrate cyclosporine and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus C_{max} with an oral dose of 10 mg daily or 70 mg weekly is more than 12- to 36-fold below the Ki-values of the *in vitro* inhibition. An effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates was therefore considered to be unlikely.

The effect of everolimus on the pharmacokinetics of the CYP3A4 substrate midazolam has been studied in healthy subjects. Co-administration of an oral dose of midazolam with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-inf})}$, whereas the metabolic $AUC_{(0\text{-inf})}$ ratio (1-hydroxy-midazolam/midazolam) and the terminal $t_{1/2}$ of midazolam were not affected. This indicates that everolimus may increase the blood concentration of orally administered CYP3A4 substrates. Interaction between everolimus and non-orally administered CYP3A4 substrates has not been studied (see **WARNINGS AND PRECAUTIONS**).

Everolimus increased pre-dose concentrations of the antiepileptic drugs (AEDs) carbamazepine, clobazam, and the clobazam metabolite N-desmethylclobazam by about 10%. The increase in the pre-dose concentrations of these AEDs may not be clinically significant but dose adjustments for AEDs with a narrow therapeutic index e.g. carbamazepine may be considered.

CYP3A4 Substrates (AEDs)
Everolimus had no impact on pre-dose concentrations of AEDs that are substrates of CYP3A4 (clonazepam, diazepam, felbamate and zonisamide).

Other Anti-Epileptic Drugs (AEDs)
Everolimus had no impact on the pre-dose concentration of other AEDs, including valproic acid, topiramate, oxcarbazepine, phenobarbital, phenytoin and primidone.

Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47 (90% CI: 1.32 to 1.64).

Co-administration of everolimus and exemestane (a drug which is metabolized in part by CYP3A4) increased exemestane C_{min} and C_{2h} by 45% and 71%, respectively. However, the corresponding oestradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients

with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Pharmacodynamic drug interactions:
Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment). The nature of the pharmacodynamic interaction has not been established (see **WARNINGS AND PRECAUTIONS**, **General**, **Drug-Drug Interactions**).

Vaccinations:
Immunosuppressants may affect the response to vaccination and vaccination during treatment with TEVA-EVEROLIMUS may therefore be less effective. The use of live vaccines should be avoided during treatment with TEVA-EVEROLIMUS (see **WARNINGS AND PRECAUTIONS**). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21, a typhoid vaccine.

For pediatric patients with SEGA associated with TSC who do not require immediate treatment, complete the recommended childhood series of live vaccinations prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

Drug-Food Interactions

Grapefruit, grapefruit juice, star fruit, Seville oranges, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment.

Drug-Herb Interactions

St. John's wort (*Hypericum perforatum)* is an inducer of CYP3A4 that may increase the metabolism of everolimus and decrease everolimus blood levels and should be avoided.

Drug-Laboratory Test Interactions

Interactions between TEVA-EVEROLIMUS and laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TEVA-EVEROLIMUS should be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy and/or in the treatment of patients with TSC.

TEVA-EVEROLIMUS tablets may be used in all approved oncology indications and for the renal angiomyolipoma associated with tuberous sclerosis complex (TSC) and subependymal giant cell astrocytoma (SEGA) associated with TSC indications. For patients with SEGA

associated with TSC, TEVA-EVEROLIMUS must be used in conjunction with therapeutic drug monitoring (see **Therapeutic drug monitoring for SEGA associated with TSC**, below).

TEVA-EVEROLIMUS tablets have not been studied and should not be used in patients with seizures associated with TSC.

TEVA-EVEROLIMUS should be administered orally once daily at the same time every day (preferably in the morning), either consistently with food or consistently without food (see **ACTION AND CLINICAL PHARMACOLOGY**).

Management of Adverse Reactions:
Management of severe or intolerable suspected adverse drug reactions may require temporary dose interruption (with or without dose reduction) or discontinuation of TEVA-EVEROLIMUS therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered (see Table 13 and **WARNINGS AND PRECAUTIONS**). For dose reductions below the lowest available tablet strength, alternate day dosing should be considered.

Table 13 summarizes recommendations for dose interruption, reduction, or discontinuation of TEVA-EVEROLIMUS in the management of adverse reactions. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 13: TEVA-EVEROLIMUS dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[a]	TEVA-EVEROLIMUS Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, clinical or diagnostic observations only; intervention not indicated	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated; limiting instrumental ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1. Re-initiate treatment at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self-care ADL[c]; O_2 indicated	Interrupt treatment until symptoms resolve to ≤ grade 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.

Adverse Drug Reaction	Severity[a]	TEVA-EVEROLIMUS Dose Adjustment[b] and Management Recommendations
	compromise; urgent intervention indicated (e.g. tracheotomy or intubation),	
Stomatitis	Grade 1 Asymptomatic or mild symptoms, intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to grade ≤ 1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤ 1. Re-initiate treatment 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 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to grade ≤ 1. Re-initiate treatment 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 4 Life-threatening consequences; urgent intervention indicated.	Discontinue treatment and treat with appropriate medical therapy.
Other non-haematologic 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 treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤ 1. Re-initiate treatment at a lower dose.
	Grade 3	Temporary dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.

Adverse Drug Reaction	Severity[a]	TEVA-EVEROLIMUS Dose Adjustment[b] and Management Recommendations
	Grade 3	Temporary dose interruption. Re-initiate treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue TEVA-EVEROLIMUS and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 (<LLN[e] – 75.0 x 10^9/L)	No dose adjustment required.
	Grade 2 (<75.0 – 50.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose.
	Grade 3 (<50.0 – 25.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at lower dose.
	Grade 4 (<25.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at lower dose.
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN[e] – 1.5 x 10^9/L)	No dose adjustment required.
	Grade 2 (<1.5 – 1.0 x 10^9/L)	No dose adjustment required.
	Grade 3 (<1.0 – 0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at same dose.
	Grade 4 (<0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at lower dose.
Febrile neutropenia	Grade 3 ANC[f]<1.0 x 10^9/L with a single temperature of >38.3 °C (101 °F) or a sustained temperature of 38 °C (100.4 °F) for more than one house.	Temporary dose interruption until recovery of ANC to ≥ 1.25 x 10^9/L and no fever. Re-initiate treatment at lower dose.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

a Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.
Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

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 alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers. Antifungal agents should not be used, unless an oral fungal infection has been diagnosed, in which case oral topical antifungal agents are preferred.

e Lower limit of normal (LLN)
f Absolute Neutrophil Count (ANC)

Moderate inhibitors of CYP3A4 and/or PgP: Use caution when administering TEVA-EVEROLIMUS in combination with moderate inhibitors of CYP3A4 (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem) or PgP. If patients require co-administration of a moderate inhibitor of CYP3A4 or PgP, reduce the TEVA-EVEROLIMUS daily dose by approximately 50%. Further dose reduction may be required to manage adverse reactions. For dose reductions below the lowest available strength, alternate day dosing should be considered (see **WARNING AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Hormone receptor-positive, HER-2 negative advanced breast cancer, advanced NET, metastatic renal cell carcinoma and renal angiomyolipoma associated with TSC: If the moderate inhibitor of CYP3A4/PgP is discontinued; consider a washout period of at least 3 days, or four drug-elimination half-lives, before the TEVA-EVEROLIMUS dose is increased. The TEVA-EVEROLIMUS dose should be returned to the dose used prior to initiation of the moderate inhibitor of CYP3A4 or PgP (see **WARNING AND PRECAUTIONS** and **DRUG INTERACTIONS**).

SEGA associated with TSC: Everolimus trough concentrations should be assessed approximately 1 to 2 weeks after the addition of a moderate inhibitor of CYP3A4/PgP. If the moderate inhibitor is discontinued, the TEVA-EVEROLIMUS dose should be returned to the dose used prior to initiation of the inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Strong inhibitors of CYP3A4/PgP: Avoid the use of concomitant strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or PgP, due to the risk of reduced effectiveness of the drug (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Grapefruit, grapefruit juice, star fruit, Seville oranges and other foods that are known to inhibit cytochrome P450 and PgP activity should be avoided during treatment (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Strong inducers of CYP3A4: Avoid the use of concomitant strong inducers of CYP3A4 (e.g., anticonvulsants [such as carbamazepine, oxcarbazepine, phenobarbital and phenytoin]; St. John's Wort [*Hypericum perforatum*]; rifampin, rifabutin, rifapentine). If TEVA-EVEROLIMUS must be co-administered with a strong CYP3A4/PgP inducer, the patient should be carefully monitored for clinical response. Consider a dose increase of TEVA-EVEROLIMUS when co-administered with strong CYP3A4/PgP inducers if alternative treatment is not possible.

Renal angiomyolipoma associated with TSC:

If patients with renal angiomyolipoma associated with TSC require co-administration of an anticonvulsant that is a strong inducer of CYP3A4, consider increasing the TEVA-EVEROLIMUS recommended dose up to 20 mg daily, using increments of 5 mg or less. This dose of TEVA-EVEROLIMUS is predicted, based on pharmacokinetic data, to adjust the AUC to the range observed without inducers. However, there are limited clinical data with this dose adjustment in patients with renal angiomyolipoma receiving an anticonvulsant which is a strong inducer of CYP3A4. If the anticonvulsant that is a strong inducer of CYP3A4 is discontinued, the TEVA-EVEROLIMUS dose should be returned to the dose used prior to initiation of the anticonvulsant.

SEGA associated with TSC:
Patients who have SEGA associated with TSC who are receiving concomitant strong inducers of CYP3A4 at the start of everolimus treatment may require an increased TEVA-EVEROLIMUS dose to attain trough concentrations of 5 to 15 ng/mL. The daily dose may be increased by 2.5 mg every 2 weeks for TEVA-EVEROLIMUS (see **Therapeutic drug monitoring for SEGA with TSC** below, **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

For patients who have SEGA associated with TSC who are not receiving concomitant strong inducers at the start of everolimus treatment, the addition of a strong inducer may require an increased TEVA-EVEROLIMUS dose. Double the daily dose of TEVA-EVEROLIMUS and assess tolerability. Determine the everolimus trough level two weeks after doubling the dose. Further adjust the dose if necessary by increments of 1 to 4 mg as necessary to maintain the target trough concentration (see **Therapeutic drug monitoring for SEGA associated with TSC**, below).

The addition of another concomitant strong CYP3A4 inducer may not require additional dose adjustment. Determine the everolimus trough level two weeks after initiating the additional inducer. Adjust the dose in 1 to 4 mg increments as necessary to maintain the target trough concentration (see **Therapeutic drug monitoring for SEGA associated with TSC**, below).

Discontinuation of one of multiple strong CYP3A4 inducers may not require additional dose adjustment. Determine the everolimus trough level two weeks after discontinuation of one of multiple strong CYP3A4 inducers (see **Therapeutic drug monitoring for SEGA associated with TSC**, below). If all strong inducers are discontinued, impose a washout period of at least 5 days (reasonable time for significant enzyme de-induction) before the TEVA-EVEROLIMUS dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer. Determine the everolimus trough concentration approximately 2 weeks later (see **DRUG INTERACTIONS**).

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer, Advanced NET, Metastatic RCC and Renal Angiomyolipoma associated with TSC

Recommended Dose and Dosage Adjustment

The recommended dose of TEVA-EVEROLIMUS for the treatment of hormone receptor-positive, HER2- negative advanced breast cancer, advanced NET, metastatic RCC and renal angiomyolipoma associated with TSC is 10 mg, to be taken once daily.

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer: Treatment with TEVA-EVEROLIMUS and exemestane should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Advanced NET and Metastatic RCC: Treatment with TEVA-EVEROLIMUS should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Renal Angiomyolipoma associated with Tuberous Sclerosis Complex: Optimal duration of treatment with TEVA-EVEROLIMUS is not known.

Special Populations and Conditions

Geriatrics (≥ 65 years):
No dosage adjustment is required for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Pediatrics (< 18 years):
TEVA-EVEROLIMUS is not recommended for use in pediatric patients with renal angiomyolipoma associated with TSC.

Renal impairment:
No studies with everolimus in patients with impaired renal function have been carried out. However, given that renal metabolism and clearance of everolimus is minimal (< 5% of total), no dosage adjustment is recommended (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Impairment)**

Hepatic impairment:
- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated
- Severe hepatic impairment (Child-Pugh C) – if the potential benefit outweighs the risk, a dose of 2.5 mg daily may be used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Missed Dose

TEVA-EVEROLIMUS can still be taken up to 6 hours after the time it is normally taken. After more than 6 hours, the dose should be skipped for that day. The next day, TEVA-EVEROLIMUS should be taken at its usual time. Double doses should not be taken to make up for the one that was missed.

Administration

TEVA-EVEROLIMUS tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

SEGA associated with Tuberous Sclerosis Complex

Recommended Dose and Dosage Adjustment

Individualize dosing based on body surface area (BSA, in m^2), calculated using the Dubois formula.[3]

Ttiration may be required to attain target everolimus trough concentrations, followed by optimal therapeutic effect within this range. Doses that are tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus and may contribute to this variance (see **DRUG INTERACTIONS** and **Therapeutic drug monitoring for SEGA associated with TSC**).

Starting dose and target trough concentrations in SEGA associated with TSC
The recommended starting daily dose for TEVA-EVEROLIMUS for the treatment of patients with SEGA associated with TSC is 4.5 mg/m^2, rounded to the nearest strength of TEVA-EVEROLIMUS. Different strengths of TEVA-EVEROLIMUS can be combined to attain the desired dose.

Dosage should be titrated with the objective of attaining everolimus trough concentrations of 5 to 15 ng/mL, subject to tolerability.

Dose titration for SEGA associated with TSC
Individualized dosing should be titrated by increasing the dose by increments of 1 to 4 mg of everolimus to attain the target trough concentration for optimal clinical response. Efficacy, safety, concomitant medication, and the current trough concentration should be considered when planning for dose titration. Individualized dose titration can be based on simple proportion:

New everolimus dose = current everolimus dose x (target concentration/current concentration)

The trough concentration should then be assessed 1 to 2 weeks after this change in dose.

Therapeutic drug monitoring for SEGA associated with TSC
Therapeutic drug monitoring of everolimus whole blood concentrations is **required** for patients treated for SEGA associated with TSC. A validated bioanalytical assay that is specific for everolimus, for example LC/MS, should be used. When possible, the same assay and laboratory should be used for therapeutic drug monitoring throughout treatment.

Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after the initial dose, after any change in dose, after an initiation or change in co-administration

[3] BSA = ($W^{0.425}$x $H^{0.725}$) x 0.007184 (weight (W) is in kilograms and height (H) is in centimetres)

of inducers or inhibitors of CYP3A4 /PgP (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**) or after any change in hepatic (Child-Pugh) status (see **Recommended Dose and Dosage Adjustment, Patients with hepatic impairment** below and **ACTION AND CLINICAL PHARMACOLOGY**).

Long-term dose monitoring
For patients with SEGA associated with TSC, once a stable dose is attained, monitor trough concentrations every 3 to 6 months in patients with changing body surface area or every 6 to 12 months in patients with stable body surface area for the duration of treatment.

SEGA volume monitoring for patients treated with TEVA-EVEROLIMUS

SEGA volume should be evaluated approximately 3 months after commencing TEVA-EVEROLIMUS therapy and periodically thereafter. In the phase II and phase III clinical studies, SEGA volume monitoring was performed at baseline, Month 3, Month 6 and every 6 months thereafter. The optimal schedule of monitoring and the optimal duration of everolimus therapy are unknown, but SEGA progressions were reported in 13 of the 111 patients approximately 8 to 56 months after initiation of everolimus therapy by independent central review in the phase III study. Six patients progressed while on everolimus remained on treatment as they were considered to be experiencing clinical benefit. No patient required surgical intervention for SEGA during the course of the study. Subsequent dose adjustments should take 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 is not necessary.

Special Populations and Conditions

Hepatic impairment:
Patients with SEGA associated with TSC ≥ 18 years of age
- Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B) – 50% of the dose calculated based on BSA (rounded to the nearest strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended

Patients < 18 years of age
TEVA-EVEROLIMUS is not recommended for patients < 18 years of age with SEGA and concomitant hepatic impairment.

Pediatrics (< 18 years):
Dosing recommendations for pediatric patients with SEGA are consistent with those for the corresponding adult population.
TEVA-EVEROLIMUS is not recommended for patients < 18 years of age with SEGA who have any degree of hepatic impairment (see **Hepatic impairment** above**)**.

Missed Dose

TEVA-EVEROLIMUS can still be taken up to 6 hours after the time it is normally taken. After more than 6 hours, the dose should be skipped for that day. The next day, TEVA-EVEROLIMUS should be taken at its usual time. Double doses should not be taken to make up for the one that was missed.

Administration

TEVA-EVEROLIMUS tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

OVERDOSAGE

For management of suspected drug overdose, contact your regional poison control centre.

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was 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.

There is no specific treatment for TEVA-EVEROLIMUS overdose and general supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Everolimus is an 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 signaling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream of the PI3K/AKT pathway, which is dysregulated in the majority of human cancers. Consistent with the central regulatory role of mTORC1, its inhibition by everolimus has been shown to reduce cell proliferation, glycolysis and angiogenesis in solid tumours *in vivo*, both through direct anti-tumour cell activity and inhibition of the tumour stromal compartment.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the PI3K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (AI)-resistant and long-term oestrogen-deprived breast cancer cells. In *in*

vitro models of breast cancer cells, resistance to AIs due to Akt activation can be reversed by co-administration with everolimus.

In tuberous sclerosis complex, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body as well as seizures. In animal models of TSC, everolimus appears to exert inhibitory effects on phosphorylation of substrates of mTOR (see **DETAILED PHARMACOLOGY**).

Pharmacodynamics / Exposure response relationships

Exposure-response relationships: There was a moderate correlation between the decrease in the phosphorylation of 4E-BP1 (p4E-BP1) in tumour tissue and the average everolimus C_{min} at steady state in blood after daily administration of 5 or 10 mg everolimus. Further data suggest that the inhibition of phosphorylation of the S6 kinase is very sensitive to the mTOR inhibition by everolimus. Inhibition of phosphorylation of elF-4G was complete at all C_{min} values after the 10 mg daily dose.

Cardiac Electrophysiology: Everolimus was studied in a randomized, placebo- and active-controlled, crossover ECG assessment study performed in 64 healthy subjects who received 20 mg and 50 mg single doses of everolimus. The maximum placebo-adjusted mean difference from placebo in the QTcF interval [$QTcF=QT/RR^{0.33}$] was 4.15 (90% CI 2.33; 5.97) ms in the 20 mg treatment arm and 4.26 (90% CI 2.45, 6.07) ms in the 50 mg treatment arm, both at the 12 hour time point. The effects of repeat dosing were not tested.

Pharmacokinetics

Absorption: After administration of everolimus to 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 with daily dosing between 5 and 10 mg. With single doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional; however, AUC shows dose-proportionality over the 5 to 70 mg dose range. Steady-state was achieved within 2 weeks with the daily dosing regimen. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on the daily regimen.

Table 14: Summary Statistics of Main Pharmacokinetic Parameters of Everolimus in the Pivotal Phase III Trial

	C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	AUC_{0-T} (ng•h/mL)	CL/F (L/h)	CL/F ($L/h/m^2$)
Day 1 (n=13)	68.1 ± 29.8	1 (1-2)	7.9 ± 3.4	455.0 ± 168.5	-	-
CV	(43.7%)		(43.3%)	(37.0%)		
Day 15 (n=12)	76.7 ± 39.3	1 (1-5)	19.8 ± 12.3	729.1 ± 262.7	15.4 ± 5.3	7.5 ± 2.3
CV	(51.2%)		(61.8%)	(36.0%)	(34.3%)	(30.1%)

Food effect: In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak blood 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 elimination 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 everolimus 10 mg/day. Plasma protein binding is approximately 74%, both in healthy subjects and in 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. Brain penetration of everolimus has also been demonstrated in rats receiving oral doses of everolimus.

Biotransformation/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. 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.

Elimination: No specific elimination studies have been undertaken in cancer patients; however, data are available from the transplantation setting. Following the administration of a single dose of radio-labelled everolimus in conjunction with cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine over 10 days. The parent substance was not detected in urine or feces.

Special Populations and Conditions

Pediatrics:
In patients who have SEGA associated with TSC receiving everolimus, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 - 18 years were lower by 54% and 40% respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults. Dosing in this population should be guided by Therapeutic Drug Monitoring (see **DOSAGE AND ADMINISTRATION**, **SEGA associated with Tuberous Sclerosis Complex**, **Therapeutic drug monitoring for SEGA associated with TSC**).

Geriatrics: In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27 to 85 years) on oral clearance (CL/F: range 4.8 to 54.5 litres/hour) of everolimus was detected.

Gender: Analyses of efficacy and safety data in male and female subgroups suggest that no dose adjustments are necessary based on patient gender.

Race: Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black transplant patients.

Hepatic Impairment: The influence of hepatic impairment on the pharmacokinetics of everolimus was assessed in two independent single oral dose studies in adult volunteers. One study evaluated the pharmacokinetics of everolimus in 8 volunteers with moderate hepatic impairment (Child-Pugh B) and 8 volunteers with normal hepatic function. Compared to normal volunteers, there was a 2.2-fold increase in exposure ($AUC_{0\text{-}inf}$) for subjects with moderate hepatic impairment. A second study evaluated the pharmacokinetics of everolimus in 7 volunteers with mild hepatic impairment (Child-Pugh A), 8 volunteers with moderate hepatic impairment (Child-Pugh B), 6 volunteers with severe hepatic impairment (Child-Pugh C) and 13 volunteers with normal hepatic function. Compared to normal volunteers, there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure ($AUC_{0\text{-}inf}$) for volunteers with mild, moderate and severe hepatic impairment, respectively. Simulations of multiple dose pharmacokinetics support the dosing recommendations in hepatic impaired patients based on their Child-Pugh status. Dose adjustment is recommended for patients with hepatic impairment. Dosing recommendations are based on the combined results of the two studies (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment: In a population pharmacokinetic analysis of 170 patients with advanced cancer, no significant influence of creatinine clearance (25 to 178 mL/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range 11 to 107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients.

STORAGE AND STABILITY

Store at room temperature (15 – 30°C).
Store in original package to protect from light and moisture.
Keep in a safe place out of the reach of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-EVEROLIMUS tablets are oblong and white with a
bevelled edge and no score. TEVA-EVEROLIMUS tablets are available in four strengths: 2.5 mg, 5 mg, 7.5 mg and 10 mg.

2.5 mg:	The tablets are engraved with “EV” on one side and “2.5” on the other
5 mg:	The tablets are engraved with “EV” on one side and “5” on the other
7.5 mg	The tablets are engraved with “EV” on one side and “7.5” on the other
10 mg:	The tablets are engraved with “EV” on one side and “10” on the other

Non-medicinal Ingredients
Butyhydroxytoluene, crospovidone, hypromellose, lactose anhydrous, lactose monohydrate and magnesium stearate

TEVA-EVEROLIMUS 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets are supplied in blister packs (10 blisters/card, 3 cards/carton).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

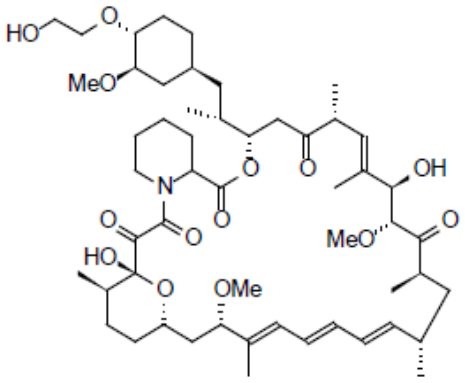
Common name: Everolimus

Chemical name: (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-azatricyclo [30.3.1.$0^{4,9}$]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

Molecular formula: $C_{53}H_{83}NO_{14}$

Molecular mass: 958.2 g/mol

Structural formula:



Physicochemical Properties:

Physical description: White to off-white powder

Solubility: Everolimus is freely soluble in chloroform, acetone and methanol, soluble in DMSO and ethanol and very poorly soluble in water.

pKa: No titratable aqueous pKa, the calculated pKa is 13.43.

Partition Coefficient: 7.4

Melting Point: 85°C - 105°C

CLINICAL TRIALS

Comparative Bioavailability Study

A blinded, pivotal, randomized, three-way crossover, single-dose, bioequivalence study comparing 1 x TEVA-EVEROLIMUS 10 mg Tablets (Teva Canada Limited) to 1 x AFINITOR® (everolimus) 10 mg Tablets (Novartis Pharmaceuticals Canada Inc.), was conducted in healthy male and female subjects (n=47) under fasting conditions. The results from measured data are summarized in the table below:

Everolimus (1 x 10 mg) From Measured Data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng*h/mL)	443.86 459.13 (25.2)	454.14 468.57 (23.7)	97.7	92.8 – 102.9
AUC_I (ng*h/mL)	507.83 525.78 (25.6)	519.68 537.18 (24.9)	97.7	92.9 – 102.7
C_{max} (ng/mL)	62.07 64.13 (24.0)	65.17 67.65 (26.4)	95.2	90.1 – 100.7
T_{max}§ (h)	1.00 (0.50 – 3.10)	1.00 (0.50 - 2.50)		
$T_{½}$Ψ (h)	27.42 (12.8)	27.42 (14.2)		

*TEVA-EVEROLIMUS (everolimus) 10 mg Tablets (Teva Canada Limited)
† AFINITOR® (everolimus) 10 mg Tablets (Novartis Pharmaceuticals Canada Inc.), were purchased in Canada
§ Expressed as median (range) only
Ψ Expressed as arithmetic mean (CV% only)

The results of comparative bioavailability studies for TEVA-EVEROLIMUS 10 mg tablets in which the drug product was administered either in the fasted state or following a high-calorie, high-fat meal indicate that the effect of food on TEVA-EVEROLIMUS tablets is comparable to that of the Canadian reference product.

Safety and Efficacy Studies

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer
Study Y2301 (BOLERO-2)

A randomized, double-blind, multicentre, international phase III study of everolimus plus exemestane versus placebo plus exemestane was conducted in postmenopausal women with oestrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole.

Refractory disease to NSAIs was defined as:

- Recurrence while on or within 12 months of the end of adjuvant treatment with letrozole or anastrozole

or

- Progression while on or within 1 month of the end of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer

Except for the prior use of exemestane and mTOR inhibitors, there were no restrictions as to the last anticancer treatment prior to randomization. Patients were permitted to have received 0-1 prior lines of chemotherapy in the advanced disease setting. Documented recurrence or progression on last therapy prior to randomization was required, but letrozole or anastrozole did not have to be the last line of therapy.

Patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) or matching placebo in addition to open-label exemestane (25 mg daily). Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumours (RECIST 1.0), based on the investigator's (local radiology) assessment. Supportive PFS analyses were based on a blinded, independent central radiology review.

Overall survival (OS) was the key secondary endpoint. Other secondary endpoints included Overall Response Rate (ORR), Clinical Benefit Rate (CBR), Safety, change in Quality of Life (QOL) [EORTC QLQ-C30] and time to ECOG PS deterioration.

A total of 724 patients were randomized to the combination everolimus plus exemestane (n = 485) or placebo plus exemestane (n = 239). The two treatment groups were generally balanced with respect to baseline demographics, tumour burden, disease characteristics and history of prior anti-neoplastic therapies (see Table 15). Overall, 84% of patients were considered to be sensitive to prior endocrine therapy. The median age of patients was 61 years (range 28 to 93 years). Patients in the placebo plus exemestane arm did not cross-over to everolimus at the time of progression.

Table 15: Demographic and Disease Characteristics (Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer)

Demographic or disease characteristic	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	All patients N=724 n (%)
Age category (years) (n [%])			
< 65 years	290 (59.8)	159 (66.5)	449 (62.0)
≥ 65 years to <75 years	123 (25.4)	58 (24.3)	181 (25.0)

Demographic or disease characteristic	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	All patients N=724 n (%)
≥ 75 years	72 (14.8)	22 (9.2)	94 (13.0)
Race			
Caucasian	361 (74.4)	186 (77.8)	547 (75.6)
Asian	98 (20.2)	45 (18.8)	143 (19.8)
Black	13 (2.7)	3 (1.3)	16 (2.2)
Other	13 (2.7)	5 (2.1)	18 (2.5)
Current disease status			
Metastatic	483 (99.6)	239 (100.0)	722 (99.7)
Locally advanced	2 (0.4)	0	2 (0.3)
Metastatic site of cancer			
Bone	370 (76.3)	184 (77.0)	554 (76.5)
Visceral (excluding CNS)	283 (58.4)	143 (59.8)	426 (58.8)
CNS	6 (1.2)	0	6 (0.8)
Other	245 (50.5)	137 (57.3)	382 (52.8)
ECOG performance status			
0	293 (60.4)	142 (59.4)	435 (60.1)
1	174 (35.9)	84 (35.1)	258 (35.6)
2	9 (1.9)	7 (2.9)	16 (2.2)
Missing	9 (1.9)	6 (2.5)	15 (2.1)
Prior anti-neoplastic therapy			
Any non-steroidal aromatase inhibitor (NSAI)	485 (100)	239 (100)	724 (100)
Prior hormonal therapy other than NSAI	281 (57.9)	146 (61.1)	427 (59.0)
Chemotherapy	337 (69.5)	156 (65.3)	493 (68.1)
Neoadjuvant /adjuvant setting	211 (43.5)	95 (39.7)	306 (42.3)
Advanced setting (one line)	125 (25.8)	58 (24.3)	183 (25.3)
Other therapy	38 (7.8)	13 (5.4)	51 (7.0)

At baseline, 218 patients (45.2%) to be randomized to everolimus plus exemestane and 130 patients (54.6%) to be randomized to placebo plus exemestane were taking a bisphosphonate. At update, 251 patients (52.1%) in the everolimus plus exemestane arm and 140 patients (58.8%) in the placebo plus exemestane arm were taking a bisphosphonate.

The trial met its primary PFS endpoint at a pre-planned interim efficacy analysis (median study follow-up of 7.6 months and documentation of 68% of targeted PFS events). A statistically significant clinical benefit of everolimus plus exemestane over placebo plus exemestane was demonstrated by a 2.4-fold prolongation in median PFS (median: 6.93 months versus 2.83 months), resulting in a 57% risk reduction of progression or death (PFS HR 0.43; 95% CI: 0.35, 0.54); one-sided log-rank test p-value <0.0001 per local investigator assessment.

Subsequently, the trial remained blinded to investigators and patients to permit OS data to mature. Updated efficacy results (excluding OS) with an additional 5 months of follow-up (overall median follow-up of 12.5 months and documentation of 87% of targeted PFS events)

demonstrated a significant clinical benefit of everolimus plus exemestane over placebo plus exemestane by a 2.3-fold prolongation in median PFS (median: 7.36 months versus 3.19 months), resulting in a 56 % risk reduction of progression or death (PFS HR 0.44; 95% CI: 0.36, 0.53); one-sided log-rank test p-value < 0.0001 per local investigator assessment (see Table 16 and Figure 1).

The analysis of PFS based on independent central radiological assessment was supportive (see Table 16).

No clinically or statistically significant differences were observed between the two treatment arms in terms of time to deterioration of ECOG PS (≥ 1 point) and median times to deterioration (≥ 5%) of QLQ-C30 domain scores.

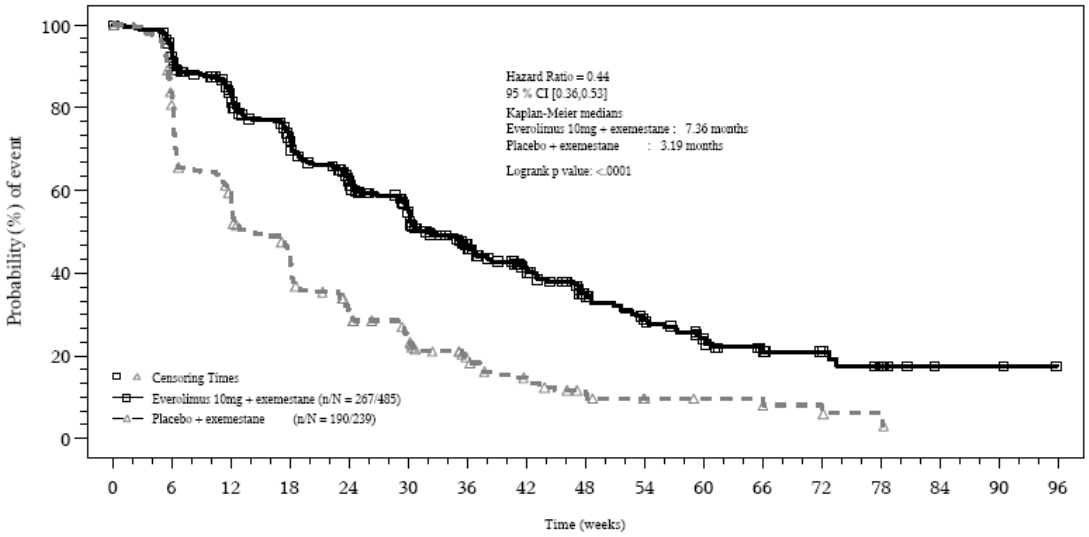
OS data were not mature at the time of a second interim analysis (additional 8 months of follow-up) based on 182 observed deaths (representing 23% and 29% of patient-deaths reported in the everolimus plus exemestane arm and placebo plus exemestane arm, respectively). No statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)]. The final OS analysis is planned at 398 deaths.

Table 16: Efficacy Results at a Median Follow-up of 12.5 Months (Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer)

Analysis	Everolimus + exemestane N=485	Placebo + exemestane N=239	Hazard Ratio (95%CI)	p-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.36 (6.93 to 8.48)	3.19 (2.76 to 4.14)	0.44 (0.36 to 0.53)	<0.0001
Independent radiological review	11.01 (9.56 to NA)	4.11 (2.83 to 5.55)	0.36 (0.28 to 0.45)	<0.0001
Best overall response (%, 95% CI)				
Objective response rate [Complete response (CR) or Partial response (PR)]	12% (7.0 to 12.4)	1.3% (0.3 to 3.6)	-	<0.0001[a]
Clinical benefit rate (CR or PR or stable disease ≥ 24 weeks	50.5% (46.0 to 55.1)	25.5% (20.1 to 31.5)	-	<0.0001[a]

a p-value is obtained from the exact Cochran-Mantel-Haenzel test using a stratified version of the Cochran-Armitage permutation test

Figure 1: Kaplan-Meier Progression-free Survival Curves at a Median Follow-up of 12.5 Months

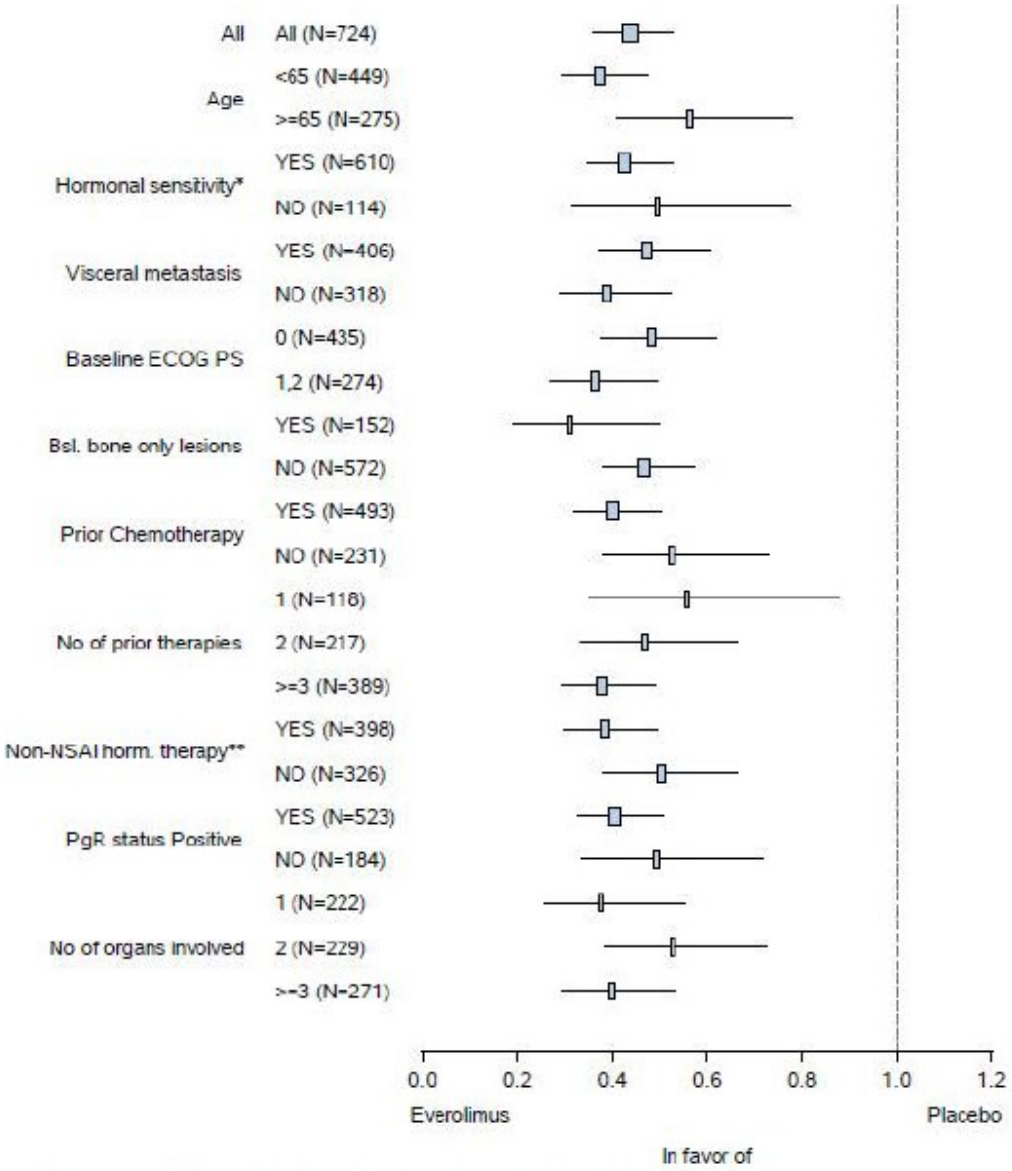


Number of Patients still at Risk

Time(weeks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Everolimus	485	436	365	303	246	188	136	96	64	45	34	21	13	9	2	2	0
Placebo	239	190	131	95	63	45	29	19	12	8	6	6	4	2	0	0	0

Planned exploratory subgroup analyses of PFS demonstrated a positive treatment effect for everolimus plus exemestane across all subgroups analyzed (see Figure 2).

Figure 2: Forest plot of PFS as per investigator by subgroup



Hazard ratio was obtained using unstratified Cox proportional hazard model.
* sensitivity to prior hormonal therapy
** anti-estrogens, LHRH analogs and progestins

Pancreatic Neuroendocrine Tumours (PNET)
Study C2324 (RADIANT-3)

A randomized, double-blind, multi-centre phase III study of everolimus plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with locally advanced or metastatic pancreatic neuroendocrine tumours (PNET) and disease progression within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes/no) and by WHO performance status (0 vs. 1 and 2). Treatment with somatostatin analogues was allowed as part of BSC.

The primary endpoint for the trial was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumours, version 1.0) as per investigator radiology review. After documented radiological progression, patients could be unblinded by the investigator; those randomized to placebo were then able to receive open-label everolimus. Crossover from placebo to open-label everolimus occurred in 73% (148/203) of patients.

Secondary endpoints include safety, objective response rate (ORR) (complete response [CR] or partial response [PR]) and overall survival.

Patients were randomized 1:1 to receive either everolimus 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 79% Caucasian).

Table 17: Demographic and Disease Characteristics (PNET)

Demographic or disease characteristic	**Everolimus N=207 n (%)**	**Placebo N=203 n (%)**	**Total N=410 n (%)**
Age (years)			
Mean (standard deviation) Median Range	57.1 (12.2) 58.0 23 - 87	56.2 (11.4) 57.0 20 - 82	56.5 (11.8) 58.0 20 - 87
Age group (years) (n [%])			
< 65 years	146 (70.5)	153 (75.4)	299 (72.9)
≥ 65 years	61 (29.5)	50 (24.6)	111 (27.1)
Gender			
Male	110 (53.1)	117 (57.6)	227 (55.4)
Female	97 (46.9)	86 (42.4)	183 (44.6)
Race			
Caucasian	146 (75.4)	166 (81.8)	322 (78.5)
Asian	40 (19.3)	34 (16.7)	74 (18.0)
Black	9 (4.3)	2 (1.0)	11 (2.7)
Other	2 (1.0)	1 (0.5)	3 (0.7)
Histologic grade			
Well differentiated	170 (82.1)	171 (84.2)	341 (83.2)
Moderately differentiated	35 (16.9)	30 (14.8)	65 (15.9)
Unknown	2 (1.0)	2 (1.0)	4 (1.0)
WHO performance status			
0	139 (67.1)	133 (65.5)	272 (66.3)
1	62 (30.0)	64 (31.5)	126 (30.7)
2	6 (2.9)	6 (2.9)	12 (2.9)
Prior long-acting somatostatin analogue therapy	101 (48.8)	102 (50.2)	203 (49.5)

The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001) (see Table 18 and Figure 3). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analogue use. The PFS results by

investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 18.

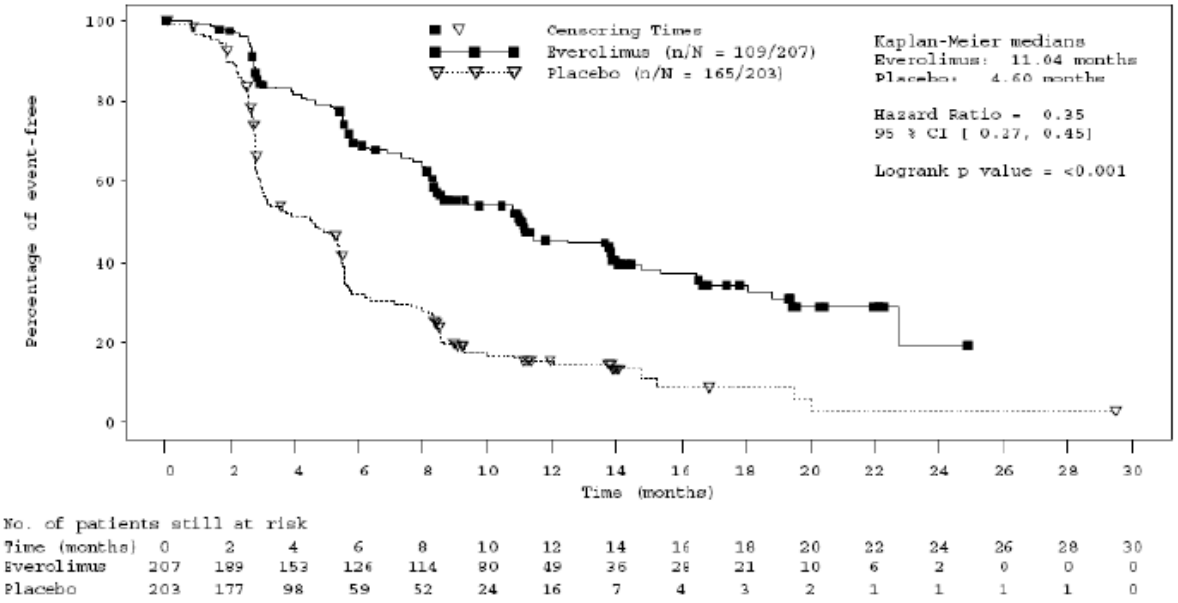
Table 18: Progression Free Survival Results (PNET)

Analysis	N 410	Everolimus N=207	Placebo N=203	Hazard Ratio (95%CI)	p-value[b]
Median progression-free survival (months) (95% CI)					
Investigator radiological review		11.0 (8.4 to 13.9)	4.60 (3.1 to 5.4)	0.35 (0.27 to 0.45)	<0.0001
Central radiological review		13.7 (11.2 to 18.8)	5.7 (5.4 to 8.3)	0.38 (0.28 to 0.51)	<0.001
Independent radiological review[a]		11.40 [10.84, 14.75]	5.39 [4.34, 5.55]	0.34 [0.26, 0.44]	<0.0001

a Includes adjudication for discrepant assessments between investigator radiological review and central radiological review.

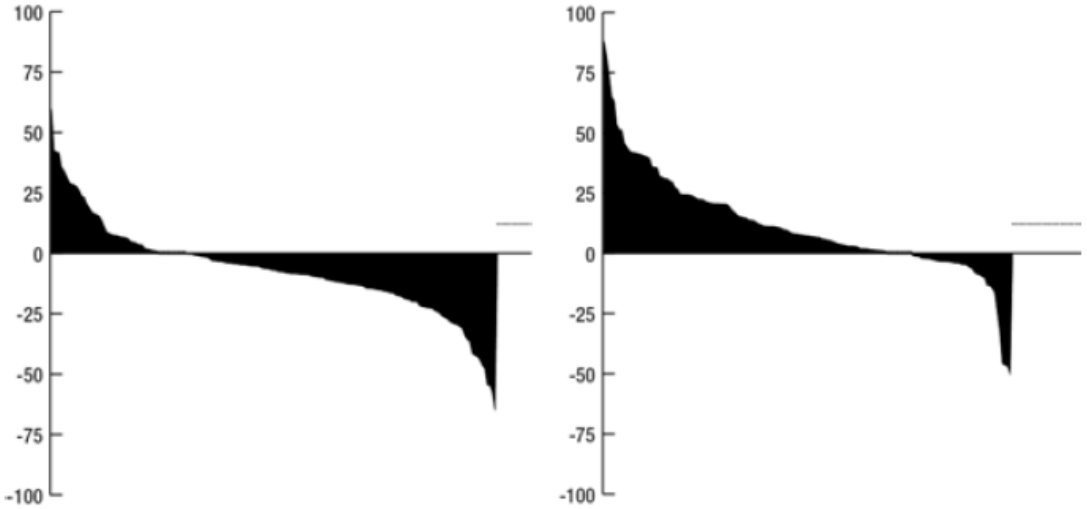
b one-sided p-value from a stratified log-rank test

Figure 3 Kaplan-Meier Investigator-Determined Progression-free Survival Curves



The objective response rate per investigator assessment was 4.8% for the everolimus arm vs. 2% for the placebo arm. Tumour reduction is also evident from the corresponding waterfall plot (Figure 4). Results indicate that 64.4% of patients in the everolimus arm experienced tumour shrinkage versus 20.6% for placebo.

Figure 4: Tumour shrinkage: best percentage change from baseline in sum of longest diameters as per investigator assessment



	n (%)	n (%)
Decrease in best percentage change from baseline	123 (64.4%)	39 (20.6%)
Zero change in best percentage change from baseline	11 (5.8%)	10 (5.3%)
Increase in best percentage change from baseline	43 (22.5%)	112 (59.3)
% Change in target lesion available but contradicted by overall lesion response = PD*	14 (7.3)	28 (14.8%)

* Patients for whom the best % change in target lesions was either unavailable or was contradicted by overall lesion response of "unknown" were excluded from this analysis. Percentages were derived using the remaining number of evaluable patients (n) as the denominator.

The overall survival results are not yet mature and no statistically significant treatment-related difference in OS was noted [HR=0.99 (95% CI: 0.68 to 1.43)]. Crossover of > 72% of patients from placebo to open-label everolimus following disease progression likely confounded the detection of any treatment-related difference in OS.

Advanced, Non-Functional Neuroendocrine Tumours of Gastrointestinal or Lung Origin Study T2302 (RADIANT-4)

A randomized, double-blind, multi-center study of everolimus plus best supportive care (BSC) versus placebo plus best supportive care was conducted in patients with unresectable, locally advanced or metastatic neuroendocrine tumours (NET) of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome. Patients enrolled in Study T2302 had well-differentiated (low or intermediate grade) histology and evidence of disease progression within 6 months prior to randomization. Randomization was stratified by prior somatostatin analog (SSA) use, tumour origin and WHO performance status. Best supportive care excluded the use of anti-tumour therapies such as SSAs.

The primary endpoint for the study was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumours (modified RECIST version 1.0) based on independent radiological assessment. Supportive PFS analysis was based on local investigator review.

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Safety, change in Quality of Life (QoL) via FACT-G and time to WHO PS deterioration.

A total of 302 patients were randomised in a 2:1 ratio to receive either everolimus (10 mg daily) (n = 205) or placebo (n = 97). The two treatment groups were generally balanced with respect to the baseline demographics, disease characteristics and history of prior somatostatin analog (SSA) use. The median duration of blinded treatment was 40.4 weeks for patients receiving everolimus and 19.6 weeks for those receiving placebo. Patients in the placebo arm did not cross-over to everolimus at the time of progression.

Table 19 Demographic and Disease Characteristics (GI or Lung NET)

Demographic variable	Everolimus N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
Age (years)			
Median (min-max)	65 (22 – 86)	60 (24 – 83)	63 (22 – 86)
Age category (years) – n (%)			
<65	100 (48.8)	59 (60.8)	159 (52.6)
≥ 65	105 (51.2)	38 (39.2)	143 (47.4)
Gender – n (%)			
Male	89 (43.4)	53 (54.6)	142 (47.0)
Female	116 (56.6)	44 (45.4)	160 (53.0)
WHO performance status – n (%)			
0	149 (72.7)	73 (75.3)	222 (73.5)
1	55 (26.8)	24 (24.7)	79 (26.2)
2	1 (0.5)	0	1 (0.3)
Primary tumour site			
Lung	63 (30.7)	27 (27.8)	90 (29.8)
Ileum	47 (22.9)	24 (24.7)	71 (23.5)
Rectum	25 (12.2)	15 (15.5)	40 (13.2)
CUP	23 (11.2)	13 (13.4)	36 (11.9)
Jejunum	16 (7.8)	6 (6.2)	22 (7.3)
Stomach	7 (3.4)	4 (4.1)	11 (3.6)
Duodenum	8 (3.9)	2 (2.1)	10 (3.3)
Colon	5 (2.4)	3 (3.1)	8 (2.6)
Other	6 (2.9)	2 (2.1)	8 (2.6)
Caecum	4 (2.0)	1 (1.0)	5 (1.7)
Appendix	1 (0.5)	0	1 (0.3)
Tumour Grade			
Grade 1	129 (62.9)	65 (67.0)	194 (64.2)
Grade 2	75 (36.6)	32 (33.0)	107 (35.4)
Time from initial diagnosis to randomization			
≤6 months	26 (12.7)	12 (12.4)	38 (12.6)
>6 months - ≤12 months	37 (18.0)	13 (13.4)	50 (16.6)
>12 months - ≤18 months	14 (6.8)	12 (12.4)	26 (8.6)
>18 months - ≤24 months	12 (5.9)	9 (9.3)	21 (7.0)
>24 months - ≤36 months	29 (14.1)	13 (13.4)	42 (13.9)
>36 months	87 (42.4)	38 (39.2)	125 (41.4)

Demographic variable	Everolimus N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
Previous treatments			
Any prior antineoplastictherapy[1]	159 (77.6)	82 (84.5)	241 (79.8)
Any prior radiotherapy	44 (21.5)	19 (19.6)	63 (20.9)
Any prior surgery	121 (59.0)	70 (72.2)	191 (63.2)
Any loco-regional therapy	23 (11.2)	10 (10.3)	33 (10.9)
Any prior medications	63 (30.7)	29 (29.9)	92 (30.5)
Any prior chemotherapy	54 (26.3)	23 (23.7)	77 (25.5)
Any prior hormonal therapy	1 (0.5)	1 (1.0)	2 (0.7)
Any prior immunotherapy	7 (3.4)	5 (5.2)	12 (4.0)
Any prior targeted therapy	2 (1.0)	0	2 (0.7)
Any prior other therapy	2 (1.0)	4 (4.1)	6 (2.0)
Prior SSA treatment			
Yes	109 (53.2)	54 (55.7)	163 (54.0)
Disease stage			
I	0	1 (1.0)	1 (0.3)
II	2 (1.0)	3 (3.1)	5 (1.7)
III	7 (3.4)	3 (3.1)	10 (3.3)
IV	196 (95.6)	90 (92.8)	286 (94.7)
Disease sites			
Liver	163 (79.5)	76 (78.4)	239 (79.1)
Lymph node/Lymphatic system	85 (41.5)	45 (46.4)	130 (43.0)
Lung	45 (22.0)	20 (20.6)	65 (21.5)
Bone	42 (20.5)	15 (15.5)	57 (18.9)
Peritoneum	25 (12.2)	8 (8.2)	33 (10.9)
Liver tumour burden			
0%	34 (16.6)	14 (14.4)	48 (15.9)
>0-10%	119 (58.0)	61 (62.9)	180 (59.6)
>10-25%	29 (14.1)	8 (8.2)	37 (12.3)
>25-50%	9 (4.4)	4 (4.1)	13 (4.3)
>50%	12 (5.9)	10 (10.3)	22 (7.3)
Unknown	2 (1.0)	0	2 (0.7)

1 Any prior antineoplastic therapy includes patients who have had prior medication (other than somatostatin analog), radiotherapy or surgery.

The efficacy results were obtained from the final analysis of PFS after 178 PFS events were observed per independent radiological review.

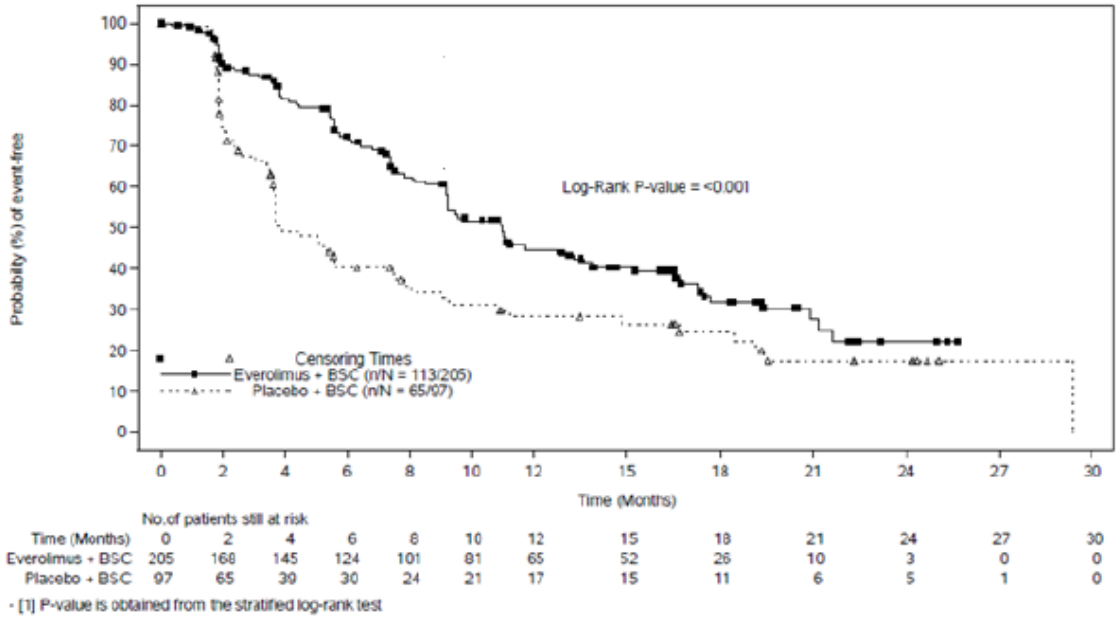
The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 52% risk reduction of progression or death (HR 0.48; 95% CI: 0.35, 0.67; one-sided stratified log-rank test p-value <0.001) per independent assessment (see Table 20 and Figure 5). The analysis of PFS based on local investigator assessment was supportive.

Table 20 RADIANT-4 – Progression Free Survival Results

Analysis	N 302	Everolimus N = 205	Placebo N = 97	Hazard Ratio[a] (95% CI)	p-value[b]
Median progression-free survival (months) (95% CI)					
Independent radiological review		11.0 (9.2 to 13.3)	3.9 (3.6 to 7.4)	0.48 (0.35 to 0.67)	< 0.001
Investigator radiological review		14.0 (11.2 to 17.7)	5.5 (3.7 to 7.4)	0.39 (0.28 to 0.54)	< 0.001

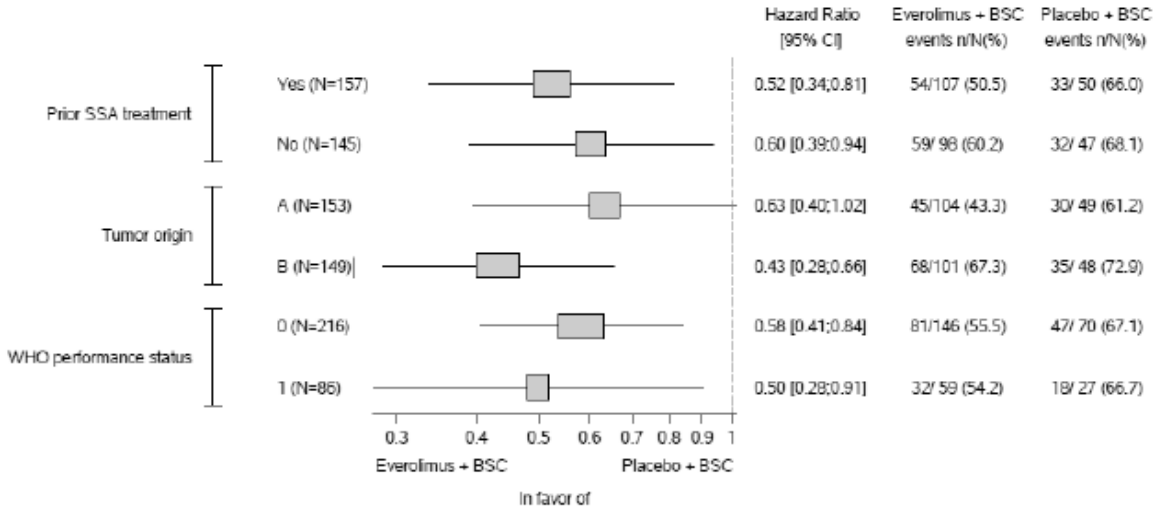
a Hazard ratio from a stratified Cox model
b One-sided p-value from a stratified log-rank test

Figure 5 RADIANT-4 – Kaplan-Meier progression-free survival curves (independent radiological review)



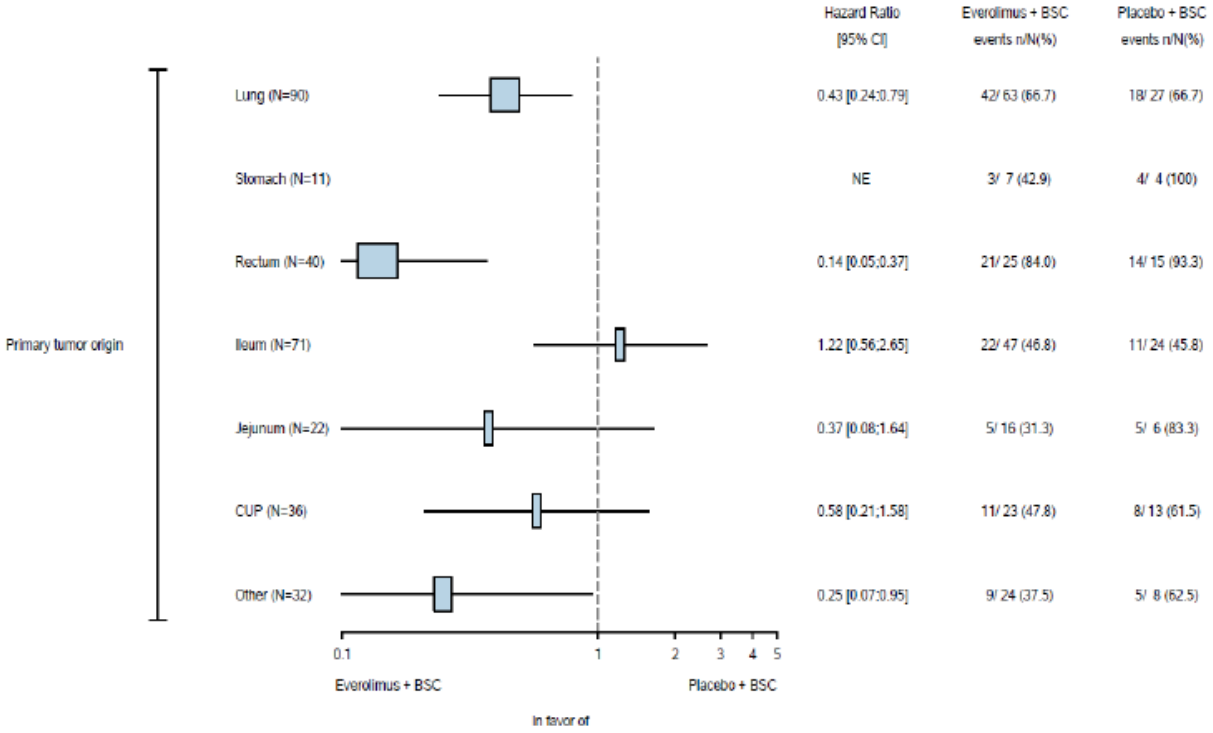
The overall PFS benefit favoured everolimus across demographic and prognostic stratification subgroups (see Figure 6). Stratum A (appendix, cecum, jejunum, ileum, duodenum, and carcinoma of unknown primary (CUP)) corresponds to better prognosis and that stratum B (lung, stomach, rectum and colon (with the exception of cecum) has worse prognosis. In an exploratory subgroup analysis of PFS for sites of tumour origin, a positive treatment effect has been observed in all subgroups with the exception of the subgroup of patients with ileum as primary site of tumour origin (Ileum: HR=1.22 [95% CI: 0.56 to 2.65]) (see Figure 7).

Figure 6 Forest plot of hazard ratio for PFS by subgroup based on stratification factors (independent radiological review)



- Hazard ratio is obtained from unstratified Cox model
- The somatostatin analogs (SSA) pretreated stratum is defined as patients who had continuously received SSA for >=12 weeks any time prior to study inclusion.
- The tumor origin stratum is A for appendix, caecum, jejunum, ileum, duodenum and carcinoma of unknown primary (CUP).
- The tumor origin stratum is B for lung, stomach, rectum, and colon except caecum.
- Stratification factors are as per IRT.

Figure 7 Forest plot of stratified hazard ratio for PFS treatment effect for patient subgroups (independent radiological review)



- Hazard ratio is obtained from stratified Cox model
- In Primary tumor origin category: Appendix, Caecum, Colon, Duodenum and Other are grouped as Other category.
- Cox model stratified by Prior SSA and WHO performance status as entered in the IRT at randomization.

The overall response rate as per independent assessment was 2% in the everolimus arm vs. 1% in the placebo arm. The overall survival (OS) analysis is not yet mature.

Clinically or statistically significant differences were not observed between the two treatment arms in terms of time to deterioration of WHO PS (≥1 point) and time to deterioration of FACT-G total score (≥7 points).

Lack of Efficacy in Locally Advanced or Metastatic Functional Carcinoid Tumours Study C2325 (RADIANT-2)
The safety and effectiveness of everolimus in patients with locally advanced or metastatic functional carcinoid tumours was not demonstrated in study C2325. In this randomized (1:1), double-blind, multi-center trial in 429 patients with carcinoid tumours, everolimus plus depot octreotide (Sandostatin LAR) was compared to placebo plus depot octreotide. After documented radiological progression, patients on the placebo arm could receive everolimus; of those randomized to placebo, 143 (67%) patients received open-label everolimus plus depot octreotide. The study did not meet its primary efficacy endpoint of a statistically significant improvement in PFS and the final analysis of OS favored the placebo plus depot octreotide arm.

Metastatic RCC
The safety and efficacy of everolimus in the treatment of metastatic renal cell carcinoma (mRCC) were studied in a single randomized phase III trial.

Study C2240 (RECORD-1)
A phase III, international, multi-centre, randomized, double-blind study comparing everolimus 10 mg/day (2 x 5 mg tablets) and placebo, both in conjunction with best supportive care, was conducted in patients with mRCC whose disease had progressed despite prior treatment with the VEGF (vascular endothelial growth factor)-receptor tyrosine kinase inhibitors (TKIs) sunitinib, sorafenib, or both sunitinib and sorafenib. Prior therapy with bevacizumab, interleukin-2 or interferon-alpha was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- vs. intermediate- vs. poor-risk groups) and prior anticancer therapy (1 vs. 2 prior VEGF-receptor TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms and quality of life. 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/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were randomized 2:1 to receive everolimus (n=277) or placebo (n=139). Demographics were well balanced (see Table 21).

Table 21: Demographic and Disease Characteristics (mRCC)

Demographic or disease characteristic	Everolimus N=277		Placebo N=139	
Age (years)				
Median (range)	61.0	(27 to 85)	60.0	(29 to 79)
Age group (years) (n [%])				
< 65 years	165	(59.6)	98	(70.5)
≥ 65 years	112	(40.4)	41	(29.5)
Gender (n [%])				
Male	216	(78.0)	106	(76.3)
Female	61	(22.0)	33	(23.7)
Race (n [%])				
Caucasian	246	(88.8)	121	(87.1)
Asian	16	(5.8)	11	(7.9)
Black	2	(0.7)	3	(2.2)
Native American	1	(0.4)	0	
Other/ Missing	9/4	(2.9/1.4)	3/1	(2.2/0.7)
MSKCC prognostic score [n (%)]				
Favourable risk	81	(29.2)	39	(28.1)
Intermediate risk	156	(56.3)	79	(56.8)
Poor risk	40	(14.4)	21	(15.1)
Prior VEGF-receptor TKI therapy [n (%)]				
One prior VEGF-receptor TKI	205	(74.0)	103	(74.1)
Two prior VEGF-receptor TKIs	72	(26.0)	36	(25.9)
Prior immunotherapy (n [%])	179	(64.6)	93	(66.9)

Results from a planned interim analysis showed that everolimus was superior to placebo for the primary endpoint of progression-free survival (PFS), with a statistically significant 67% reduction in the risk of progression or death. At 6 months, PFS rates were 36% for everolimus therapy compared with 9% for placebo (see Table 22 and Figure 8).

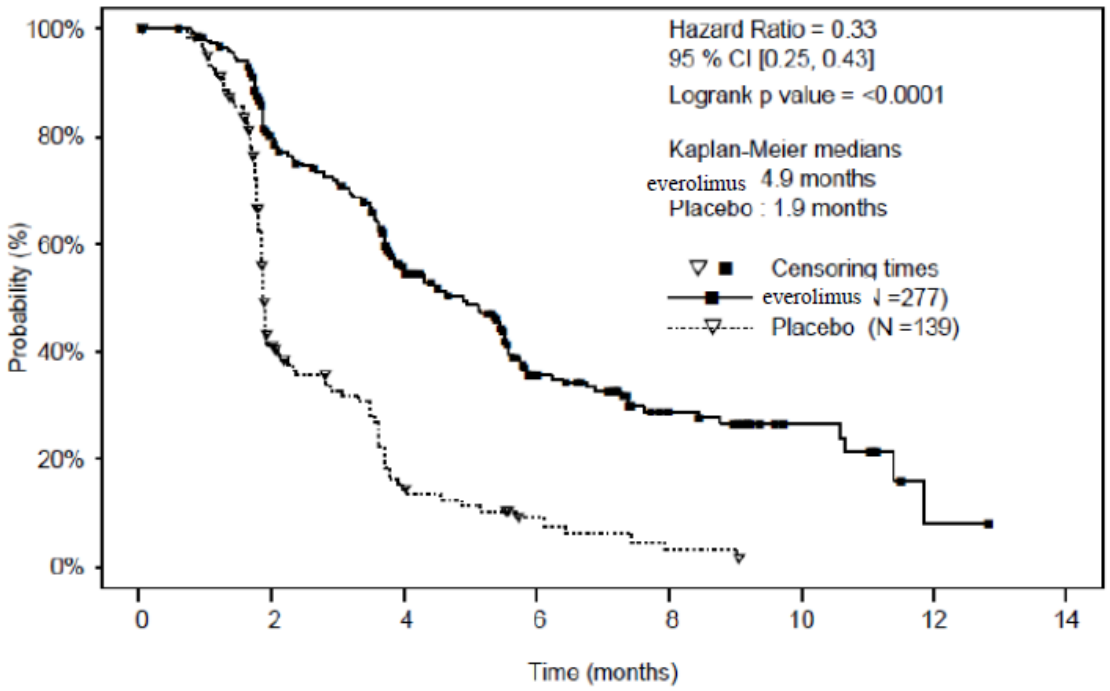
Table 22: Progression Free Survival results (mRCC)

Population	N	Everolimus N = 277	Placebo N = 139	Hazard Ratio (95% CI)	p-value
Median progression-free survival (months (95% CI)					
Primary Analysis					
All (blinded independent central review)	416	4.9 (4.0 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001[a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6 to 5.8)	1.9 (1.8 to 2.2)	0.32 (0.25 to 0.41)	<0.001[a]
MSKCC prognostic score					
Favourable risk	120	5.8 (4.0 to 7.4)	1.9 (1.9 to 2.8)	0.31 (0.19 to 0.50)	<0.001[b]
Intermediate risk	235	4.5 (3.8 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.001[b]
Poor risk	61	3.6	1.8	0.44	<0.001[b]

Population	N	Everolimus N = 277	Placebo N = 139	Hazard Ratio (95% CI)	p-value
		(1.9 to 4.6)	(1.8 to 3.6)	(0.22 to 0.85)	

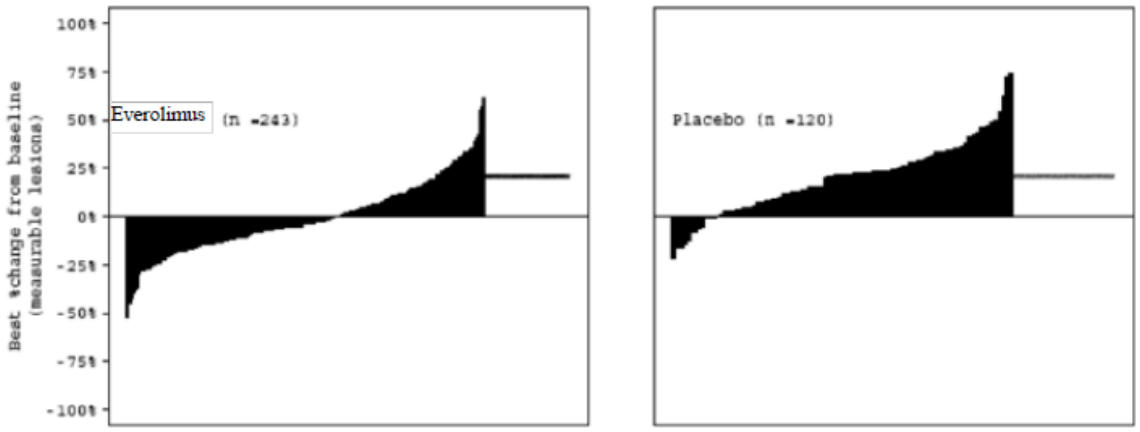
a Log-rank test stratified by prognostic score
b Unstratified, two-sided log-rank test

Figure 8: Kaplan-Meier progression-free survival curves



A low objective response rate (ORR) was observed with no significant differences apparent between the two treatment arms. ORR, based on RECIST, was documented in 1.8% (95% CI: 0.6-4.2%) of patients receiving everolimus therapy (*vs.* 0% for placebo); all 5 of these patients had partial responses. The progression-free survival advantage therefore primarily reflects the population with disease stabilization (corresponding to 67% of the everolimus treatment group) (see Figure 9).

Figure 9: Waterfall plot: best percentage change from baseline of target lesions by central radiology



	Everolimus n (%)	Placebo n (%)
Decrease in best percentage change from baseline	114 (46.9%)	12 (10.0%)
Increase in best percentage change from baseline	82 (33.7%)	80 (66.7%)
* % change in target lesion available but contradicted by Overall lesion response - PD	47 (19.3%)	28 (23.3%)
% change in target lesion available but contradicted by Overall lesion response - UNK	4	0
% change in target lesion not available	30	19

No statistically significant treatment-related difference in overall survival was noted, although there was a trend in favour of everolimus (HR 0.82; 95% CI: 0.57 to 1.17; p=0.137). Crossover to open-label everolimus following disease progression for patients allocated to placebo may have confounded the detection of any treatment-related difference in overall survival.

No difference in health-related quality of life was observed in patients receiving everolimus compared to placebo patients.

Renal Angiomyolipoma associated with Tuberous Sclerosis Complex
The safety and efficacy of everolimus in the treatment of renal angiomyolipoma associated with tuberous sclerosis complex (TSC) were studied in a phase III trial.

M2302 (EXIST-2)
A randomized, double-blind, multi-centre phase III study of everolimus versus placebo was conducted in patients who have renal angiomyolipoma associated with TSC (n=113) or with sporadic lymphangioleiomyomatosis (LAM) (n=5). Presence of at least one angiomyolipoma ≥ 3 cm in longest diameter using CT/MRI (based on local radiology assessment), no immediate indication for surgery, and age ≥ 18 years; were required for entry.

The primary efficacy endpoint for the trial was angiomyolipoma response rate based on independent central radiology review. Response was defined as: ≥ 50% reduction in the sum of angiomyolipoma volume relative to baseline, plus absence of new angiomyolipoma ≥ 1.0 cm in longest diameter, plus no increases in renal volume > 20% from nadir, plus absence of grade ≥ 2 angiomyolipoma-related bleeding. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Key secondary endpoints included time to angiomyolipoma progression and skin lesion response rate.

The primary analyses of efficacy endpoints were limited to the blinded treatment period which ended 6 months after the last patient was randomized. The median duration of follow-up was 8.3 months (range 0.7 to 24.8 months).

Patients initially treated with placebo were allowed to cross over to everolimus at the time of angiomyolipoma progression or after the primary analysis. At the time of the final analysis (4 years following the last patient randomization), the median duration of exposure to everolimus was 46.9 months (range 0.5 to 63.9 months).

A total of 118 patients were randomized in a 2:1 ratio to receive either everolimus 10 mg daily (n=79) or matching placebo (n=39) until disease progression or unacceptable toxicity. Demographic and baseline disease characteristics and history of prior anti-angiomyolipoma therapies were generally well balanced.

Table 23: Demographic and Disease Characteristics (Full Analysis Set) (Renal Angiomyolipoma associated with TSC)

Demographic or disease characteristic	Everolimus N=79	Placebo N=39
Age (years)		
N	79	39
Mean (SD)	32.5 (10.4)	31.0 (9.6)
Median	32.0	29.0
Range	18 – 61	18 - 58
Age (years), n (%]		
18 to < 30	35 (44.3)	20 (51.3)
≥ 30	44 (55.7)	19 (48.7)
Gender, n (%)		
Female	52 (65.8)	26 (66.7)
Male	27 (34.2)	13 (33.3)
Race, n (%)		
Caucasian	71 (89.9)	34 (87.2)
Asian	7 (8.9)	4 (10.3)
Other[1]	1 (1.3)	1 (2.6)
Diagnosis of TSC[2], n (%)		
At least two major features	77 (97.5)	36 (92.3)
Only one major feature and at least two minor features	0	0
EIAED use/EIAED non-use (n, %)		
EIAED use	13 (16.5)	7 (17.9)
EIAED non-use	66 (83.5)	32 (82.1)
Longest diameter of largest angiomyolipoma[2]		
≥ 8cm	22 (27.8)	12 (30.8)
≥ 4cm and < 8cm	45 (57.0)	19 (48.7)
≥ 3cm and < 4cm	6 (7.6)	4 (10.3)

Demographic or disease characteristic	Everolimus N=79	Placebo N=39
< 3cm	5 (6.3)	2 (5.1)
Number of target angiomyolipoma lesions ≥ 1cm in longest diameter (n, %)		
1-5	32 (40.5)	15 (38.5)
6-10	46 (58.2)	23 (59.0)
Number of patients with angiomyolipoma lesions present in (n, %)		
One kidney only	13 (16.7)	11 (28.9)
Both kidneys	65 (83.3)	27 (71.1)
Sum of volumes of target angiomyolipoma lesions (cm^3)[2]		
Median	85.4	119.8
Range	8.6 – 1611.5	3.0 – 4520.0
Prior anti-angiomyolipoma therapy (surgery/invasive procedure)		
Renal embolization	19 (24.1)	9 (23.1)
Nephrectomy	14 (17.7)	8 (20.5)
Number of patients with ≥ 1 skin lesion at baseline	77 (97.5)	37 (94.9)

1 Other was applied to patients of mixed race
2 Baseline kidney CT/MRI assessments were per central radiology review

Results showed that everolimus was statistically superior to placebo for the primary efficacy endpoint of angiomyolipoma response rate ($p<0.0001$). Best overall response rate was 41.8% (95% CI: 30.8, 53.4) for the everolimus arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (Figure 8). Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, age and race) at the primary efficacy analysis (Figure 10).

Figure 10: Forest plot of angiomyolipoma response by subgroup (Full Analysis Set) at primary analysis

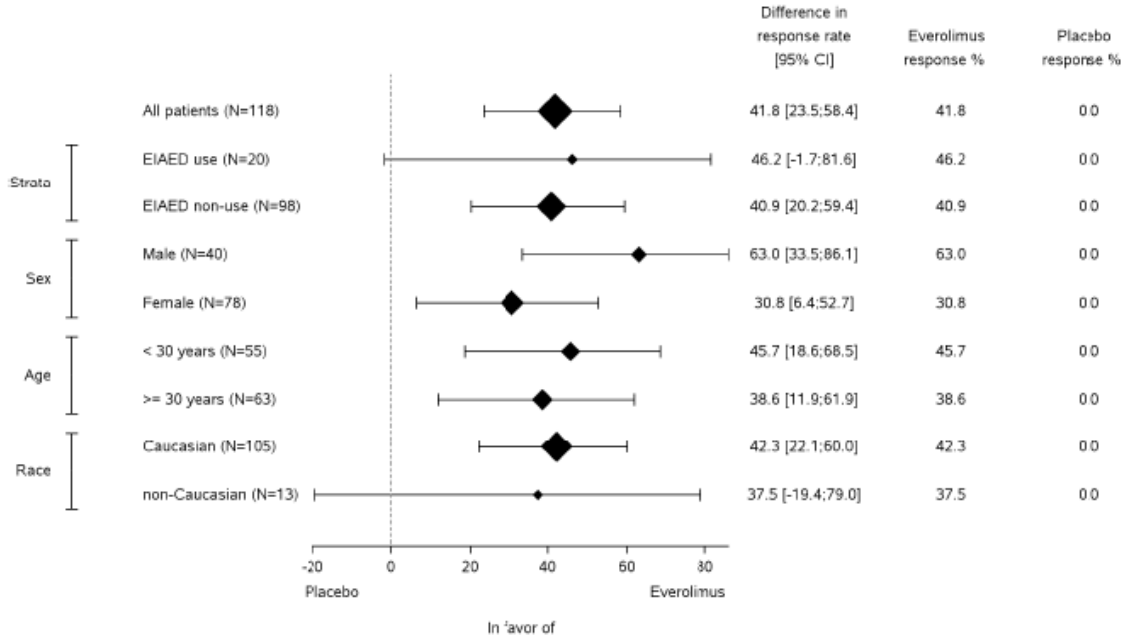
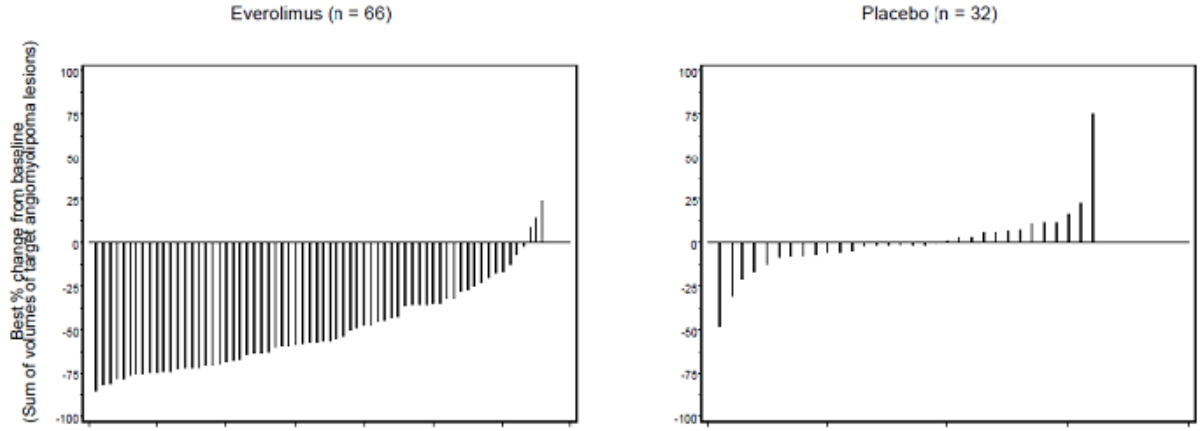


Table 24: Angiomyolipoma Response

	Primary Analysis			Final Analysis
	Everolimus N=79	**Placebo N=39**	**p-value**	**Everolimus N=112**
Angiomyolipoma response rate[a] % 95% CI	41.8 (30.8, 53.4)	0 (0.0, 9.0)	< 0.0001	58.0 (48.3, 67.3)

a Per independent central radiology review

Figure 11: Waterfall plot: Angiomyolipoma shrinkage: best percentage change from baseline (Full Analysis Set)[1,2] at primary analysis



1 Per independent central radiology review

2 Patients for whom the best % change in sum of volumes of target angiomyolipoma lesions was not available and patients with overall angiomyolipoma response = Not evaluable were excluded from the graph

At the primary analysis, progressions were observed in 3.8% (3/79) of patients in the everolimus arm compared with 20.5% (8/39) of patients in the placebo arm. Everolimus was associated with a statistically significant prolongation in time to angiomyolipoma progression (HR 0.08; 95% CI: 0.02, 0.37; p<0.0001). Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the everolimus arm.

At the final analysis, the angiomyolipoma best overall response rate had increased to 58.0% (95% CI: 48.3, 67.3). Median time to angiomyolipoma progression was not reached. Angiomyolipoma progressions were observed in 14.3% of the patients (16/112). The estimated angiomyolipoma progression-free rates at 24 months and 48 months were 91.6% (95% CI: 84.0%, 95.7%) and 83.1% (95% CI: 73.4%, 89.5%) respectively. No cases of angiomyolipoma-related nephrectomy and only one case of renal embolization were reported among patients treated with everolimus during the study.

At the primary analysis, everolimus also demonstrated improvements in skin lesion response (p=0.0002), with partial response rates of 26.0% (20/77) for the everolimus arm and 0% (0/37) for the placebo arm. At the final analysis, the overall skin lesion response rate had increased to 68.2% (73/107) (95% CI: 58.5%, 76.9%).

SEGA associated with Tuberous Sclerosis Complex
The safety and efficacy of everolimus in the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) were studied in a phase III trial.

Study M2301 (EXIST-1)
A randomized, double-blind, multicentre, phase III study of everolimus versus placebo was conducted in 117 patients with SEGA associated with TSC. Patients were randomized in a 2:1 ratio to receive either everolimus or placebo. Eligible patients had the presence of at least one SEGA lesion ≥ 1.0 cm in longest diameter using MRI (based on local radiology assessment) and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received everolimus at a starting dose of 4.5 mg/m^2 daily, with subsequent dose adjustments as needed, to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL, as tolerated.

The primary efficacy endpoint was SEGA response rate based on independent central radiology review. Analysis of SEGA response rate was limited to the blinded treatment period which ended 6 months after the last patient was randomized. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Key secondary endpoints included time to SEGA progression and skin lesion response rate. Renal angiomyolipoma response was an exploratory endpoint.

Of the 117 patients enrolled, 78 were randomized to everolimus and 39 were randomized to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies. The median duration of

blinded study treatment was 52.2 weeks (range 24 to 89 weeks) for patients receiving everolimus and 46.6 weeks (range 14 to 88 weeks) for those receiving placebo.

Table 25: Demographic and Disease Characteristics

Demographic or disease characteristic	Everolimus N=78 n (%)	Placebo N=39 n (%)	Total N=117 n (%)
Age (years)			
Mean (standard deviation) Median	10.1 (5.9) 9.5	10.3 (7.3) 7.1	10.2 (6.4) 9.5
Range	1.0 to 23.9	0. 8 to 26.6	0.8 to 26.6
Age group (years) (n [%])			
< 3	13 (16.7)	7 (17.9)	20 (17.1)
3 to < 18	55 (70.5)	26 (66.7)	81 (69.2)
≥ 18	10 (12.8)	6 (15.4)	16 (13.7)
Gender			
Male	49 (62.8)	18 (46.2)	67 (57.3)
Female	29 (37.2)	21 (53.8)	50 (42.7)
Race			
Caucasian	73 (93.6)	36 (92.6)	109 (93.2)
Black	3 (3.8)	1 (2.6)	4 (3.4)
Other[a]	1 (1.3)	2 (5.1)	3 (2.6)
Number of target SEGA lesions			
Bilateral SEGA	63 (80.8)	30 (76.9)	93 (79.5)
≥ 2	36 (46.2)	14 (35.9)	50 (42.7)
Brain MRI assessment			
Inferior growth	19 (24.4)	11 (28.2)	30 (25.6)
Evidence of deep parenchymal invasion	8 (10.3)	3 (7.7)	11 (9.4)
Radiographic evidence of hydrocephalus	8 (10.3)	0 (0.0)	8 (6.8)
Skin and subcutaneous tissue disorders			
At least one skin lesion	72 (92.3)	38 (97.4)	110 (94.0)
Prior SEGA-related surgery	6 (7.7)	2 (5.1)	8 (6.8)

a Other was applied to patients who were of mixed race.

Results showed that everolimus was superior to placebo for the primary endpoint of best overall SEGA response ($p<0.0001$) (Table 26). At the time of primary analysis, all SEGA responses were on-going and the median duration of response was 5.3 months (range 2.1 to 8.4 months).

Patients initially treated with placebo were allowed to cross over to everolimus at the time of SEGA progression and upon recognition that treatment with everolimus was superior to treatment with placebo. All patients receiving at least one dose of everolimus were followed until drug discontinuation or study completion. At the time of final analysis, the median duration of exposure to everolimus among all such patients was 204.9 weeks (range 8.1 to 253.7). The best

overall SEGA response rate had increased to 57.7% (95% CI: 47.9, 67.0) at the final analysis (Table 26).

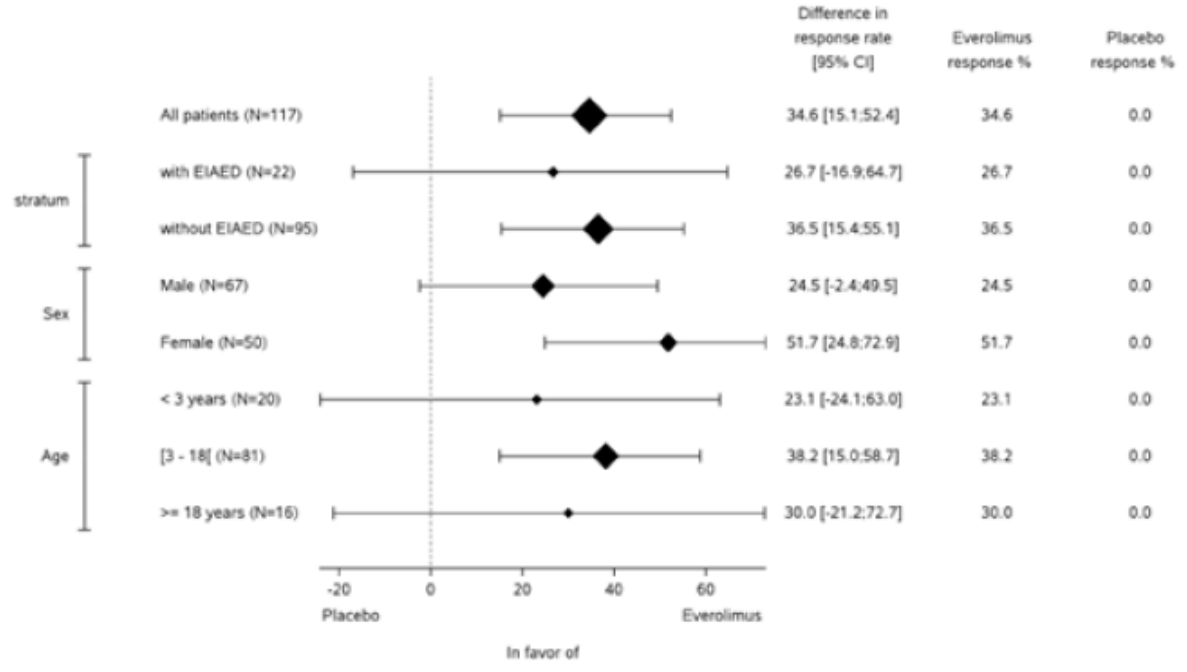
Table 26: SEGA response (Study EXIST-1)

	Primary analysis[3]			Final analysis[4]
	Everolimus N = 78	**Placebo N = 39**	**p-value**	**Everolimus**
SEGA response rate[1,2] (%)	34.6	0	< 0.0001	57.7
95% CI	24.2, 46.2	0.0, 9.0		47.9, 67.0

1 Per independent central radiological review
2 SEGA responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of SEGA volume relative to baseline, plus no unequivocal worsening of non-target SEGA lesions, plus absence of new SEGA ≥ 1 cm in longest diameter, plus no new worsening hydrocephalus
3 Primary analysis for double blind period
4 Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.9 weeks

Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex and age) at the primary analysis (Figure 12).

Figure 12: Forest plot of SEGA response by subgroup at primary analysis



During the double blind period, reduction of SEGA volume was evident within the initial 12 weeks of treatment with everolimus: 29.7% (22/74) of patients had ≥ 50% reductions in volume and 73.0% (54/74) of patients had ≥ 30% reductions in volume. At Week 24, 41.9% (31/74) of

patients had ≥ 50% reductions and 78.4% (58/74) of patients had ≥ 30% reductions in SEGA volume.

In the everolimus treated population (N=111) of the study, including patients who crossed over from the placebo group, tumour response, starting as early as after 12 weeks on everolimus, was sustained at later time points. The proportion of patients achieving at least 50% or at least 30% reductions in SEGA volume were 62.1% (41/66) and 77.3% (51/66) respectively, at Week 192 after start of everolimus treatment.

Progressions were only observed in the placebo arm (15.4%) during the blinded phase of the study. Thirteen of the 111 patients (11.7%) treated with everolimus had documented disease progression by the end of the follow-up period.

Everolimus demonstrated improvements in skin lesion response with response rates of 41.7% for the everolimus arm and 10.5% for the placebo arm. At the final analysis, the skin lesion response rate increased to 58.1% (95% CI: 48.1, 67.7).

At the time of the primary analysis, renal angiomyolipoma responses were only observed in the everolimus arm (n/N:16/30; 53.3%; 95% CI: 34.3, 71.7). At the time of final analysis, among the 41 TSC-SEGA patients with an angiomyolipoma lesion(s) present at start of treatment with everolimus, 30 patients (73.2%; 95% CI: 57.1, 85.8) achieved, as their best overall response, at least a 50% reduction in sum of angiomyolipoma volumes.

No patient required surgical intervention for SEGA during the entire course of the study.

DETAILED PHARMACOLOGY

This section includes animal data on everolimus pharmacology not derived from human studies.

Nonclinical Pharmacology

In vitro pharmacology

Everolimus binds with high affinity to the intracellular immunophilin, FKBP-12 resulting in inhibition of the mTORC1 complex and consequently, suppression of downstream events such as S6K and 4EBP activity and cell-cycle arrest from G1 to S phase. No activity was found against the following kinases: HER-1, HER-2, KDR, IGF1-R, FGFR-1, c-met, c-src, c-kit, and CDK1. Everolimus shows a very broad inhibition of tumour cell lines (i.e. inhibits tumour proliferation) of different histotypes *in vitro* with high sensitivity to anti-proliferative effects in some cells (as determined by measuring the number of cells) (IC_{50} < 1 nM) and insensitivity in others (IC_{50} >1 μM), although the majority of cell lines tested (80%) had IC_{50} values < 100 nM. Specifically, in renal cancer models, everolimus showed significant activity: a panel of 16 human RCC cell lines were tested *in vitro* for anti-proliferative activity of everolimus; 14 were sensitive to everolimus treatment with IC_{50}s in the low/sub nM range, while two renal cell lines were insensitive (IC_{50} > 2500 nM). The sensitivity of RCC cell lines was similar to that described for other histotypes *in vitro*. VHL genetic status did not affect the anti-proliferative response to everolimus in the renal

cell panel *in vitro*: three out of the four VHL wild-type lines were very sensitive to everolimus treatment with similar IC_{50}s (in the low/sub nM range) as observed in the VHL negative lines. Moreover, exogenous expression of VHL in a VHL negative background had little effect and the two lines defined as insensitive to everolimus treatment were VHL wild type (Caki-1) and VHL negative (Caki-2).

***In vivo* pharmacology**

Cell lines insensitive to everolimus *in vitro* responded to the drug when grown as tumours in mice. This was noted by a decrease in tumour-volume suggesting a significant anti-vascular/ angiogenic activity of everolimus consistent with the ability of this drug to decrease levels of HIF-1 and VEGF in tumours *in vivo*. Thus everolimus is expected to inhibit cancer cell growth by mechanisms directed against both tumour cells and the surrounding cellular milieu. Two of the human RCC cell lines (786-O and Caki-1) were also tested for sensitivity to everolimus *in vivo* by growing them subcutaneously (s.c.) in athymic nude mice. Everolimus showed significant dose-dependent inhibition of growth, and in the more sensitive cell line (786-O) caused tumour regression.

In a mouse neuronal model of TSC in which *TSC1* is ablated in most neurons during cortical development, everolimus improved median survival from 33 days to more than 100 days, and behaviour, phenotype and weight gain also markedly improved. There was brain penetration, with accumulation over time with repetitive treatment, and effective reduction of levels of phospho-S6, a downstream marker of mTORC1. Neurofilament abnormalities, myelination and cell enlargement were all improved by the treatment, although dysplastic neuronal features persisted, and there were only modest changes in dendritic spine density and length. Mice treated with everolimus for 23 days only (postnatal days 7–30) displayed a persistent improvement in phenotype, with median survival of 78 days. In summary, everolimus is highly active in this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 and Akt signaling and, consequently, cell size and myelination.

Safety Pharmacology

The studies related to safety pharmacology showed that everolimus was devoid of relevant effects on vital functions including the cardiovascular function, respiratory function and nervous systems.

In stably transfected HEK293 cells, everolimus inhibited hERG currents by 18% at 10 μM (concentration experimentally verified). Higher concentrations could not be tested because of solubility limitations. In sheep isolated Purkinje fibres, everolimus prolonged the action potential duration at 90% repolarization (APD90) by 5.0% at 1.04 μM and 4.7% at 10.0 μM (nominal concentrations). In male pigs (N=4) anaesthetized with ketamine and sodium pentobarbital, everolimus at escalating intravenous doses of 0, 0.01, 0.1 and 10 mg/kg was not observed to affect the mean arterial blood pressure, systolic blood pressure, diastolic blood pressure, heart rate, or ECG parameters over 30 minute post-dose observation periods. The study lacked a time-matched vehicle control arm.

Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behaviour of rodents, even after single oral doses up to 2000 mg/kg.

Based on these findings, the potential of everolimus to affect vital functions in patients is considered to be low.

Nonclinical Pharmacokinetics

See also **ACTION AND CLINICAL PHARMACOLOGY.**

Absorption/Bioavailability: The oral absorption of everolimus was low in mice (12%) and monkeys (18%) and medium in rats (~ 40%). The bioavailability of unchanged everolimus was 14-26% in the rat and 6% in the monkey, suggesting considerable first-pass metabolism. Everolimus is a substrate for P-glycoprotein mediated efflux systems (MDR1). After an intravenous dose to mice (0.9 mg/kg), rats (1 mg/kg) and monkeys (1 mg/kg), terminal half-lives of about 9.8 hours, 60 hours, and 27 hours were observed, respectively. After an oral dose of [^{3}H]everolimus to rats (1.5 and 15 mg/kg) and monkeys (5 mg/kg), terminal half-lives of about 61 and 47 hours in rats and 18 hours in monkeys were observed. Multiple oral dosing of [^{3}H]everolimus over 21 days (0.5 mg/kg/day) to rats increases 24-hour trough levels of radioactivity in blood by 4.4-fold compared to Day 1. In the rat, the blood clearance was moderate and corresponded to about 38% and 59% of the hepatic blood flow. In the mouse and monkey, the blood clearance was significantly lower, corresponding to about 0.9% and 7% of the hepatic blood flow, respectively.

Distribution: In plasma, the free fraction of everolimus was independent of concentration and averaged 7.6% in the rat, 16% in the monkey and 25% in human, but only 0.1% in the mouse. With the exception of the mouse, the blood distribution of everolimus was concentration-dependent. At a concentration of 5 ng/mL the distribution was 66%, 79% and 83% in rat, monkey and human, respectively. In the mouse blood, the majority of everolimus (~ 98%) was located in plasma. The volume of distribution at steady-state (V_{ss}) was species-dependent and ranged from high in the rat (44-52 L/kg) to very low in the mouse (0.37 L/kg). An intermediate value could be estimated for human (V_z/F= 14.2 L/kg). In rats, tissue distribution of radioactivity was essentially extravascular with highest levels found in heart, lung, liver, kidney, spleen, thyroid and adrenal gland. Everolimus and/or its metabolites displayed no special affinity to melanin-containing tissue of the pigmented rat. Unchanged everolimus was the major component of tissues radioactivity of rats after single oral or intravenous administration. In the rat, the blood-brain passage of everolimus and/or its metabolites was found to be dose-dependent. [^{3}H]Everolimus-related radioactivity passed the placenta of pregnant rats to a limited degree and was readily transferred into milk of lactating rats.

Metabolism: Everolimus is mainly eliminated by metabolism in the mouse, rat, monkey and human. Everolimus was the main circulating drug-related component in blood of all species. In all species everolimus formed a large number of metabolites. The metabolite patterns in the blood were comparable in all species including man. Everolimus is essentially metabolized through oxidation by CYP3A4 in the liver and to some extent in the gut wall. Therefore, co-medications that are strong inducers of CYP3A4 have the potential to reduce everolimus metabolism *in vivo*. Conversely, everolimus inhibited competitively the metabolism of the CYP3A4 substrate cyclosporine (K_i = 2.3 µmol/L) and was also a mixed inhibitor of the

metabolism of the CYP2D6 substrate dextromethorphan (K_i = 1.7 µmol/L) *in vitro*. Apart from parent drug, essentially five main metabolite peaks P36, P40, P42, P50 and P57, containing six metabolites were observed. The main metabolites P40, P36, P42, P50 and P57 were approximately two orders of magnitudes less active than everolimus in a mixed lymphocyte reaction (MLR) assay. Essentially the same metabolites of everolimus in humans were formed by at least one of the animal species *in vivo* and/or *in vitro*.

Elimination/Excretion: Everolimus was predominantly eliminated through metabolic biliary/fecal clearance in all animal species and in human. Excretion was essentially complete in all species. Renal excretion was a minor component (0.7-7%). No unchanged drug was detected in urine or feces.

Conclusion: Overall, the pharmacokinetic and metabolism data from mouse, rat and monkey indicate that these species are adequate for non-clinical pharmacology and toxicology studies with everolimus.

Human Pharmacology

Absorption and Distribution

Based on the amount of radioactivity excreted in urine in the mass balance study in maintenance renal transplant patients, the extent of absorption was estimated to be 11% or higher based on the amount of radio-labelled compounds present in blood at t_{max}. In patients with advanced solid tumours, the steady-state AUC0-τ is dose-proportional over the 5 mg and 10 mg dose range in the daily regimen and 5 mg to 70 mg in the weekly regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional. Pre-dose trough blood concentrations (C_{min}) correlate well with $AUC_{0-\tau}$ at steady-state during daily administration. The *in vitro* distribution of everolimus between human blood cells and plasma was concentration-dependent. The proportion of everolimus confined to plasma ranged from 17 to 73% over the concentration range of 5 to 5000 ng/mL. The saturation of blood cell uptake was evident at concentrations above 100 ng/mL. The proportion of everolimus confined to plasma was approximately 20% at blood concentrations observed in cancer patients given 10 mg/day of everolimus. Plasma protein binding is approximately 74% in healthy subjects as well as patients with moderate hepatic impairment.

Metabolism and Elimination

The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man is CYP3A4. Everolimus is a moderate inhibitor of PgP-like mediated efflux systems. After an oral ^{14}C-labelled dose of everolimus, 85% of the radioactivity was recovered within 10 days in feces (80%) and urine (5%). Unchanged everolimus accounted for about 40% of the AUC of total radioactivity in blood but was not detected in feces or urine. Japanese and Caucasian cancer patients with similar liver functions have similar CL/F values. Age and weight (both over the adult ranges) and gender do not have significant effects on pharmacokinetics of everolimus in cancer and transplant patients. Pharmacokinetics in healthy subjects are not altered by Japanese or Asian ethnicity. Black renal transplant patients have a 20% higher apparent clearance

compared with non-blacks. As expected from the low renal excretion of parent compound, post-transplant renal impairment does not affect the pharmacokinetics of everolimus. Mean exposure ($AUC_{0-\infty}$) to everolimus is increased in patients with hepatic impairment. In one study, compared to normal subjects, there was a 2.2-fold increase in exposure for subjects with moderate hepatic impairment (Child-Pugh B, score 7 to 9). In a second study there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure for subjects with mild (Child-Pugh A, score 5 to 6), moderate (Child-Pugh B, score 7 to 9) and severe (Child-Pugh C, score 10 to 15) hepatic impairment respectively, compared to normal subjects. The strong inhibitor of CYP3A4 and PgP, ketoconazole, increases everolimus AUC0-∞ 15.0-fold. The moderate inhibitors of CYP3A4 and PgP, erythromycin and verapamil, increase everolimus $AUC_{0-\infty}$ 4.4-fold and 3.5-fold, respectively. The CYP3A4 substrate and inhibitor of PgP, cyclosporine (NEORAL®), increases everolimus $AUC_{0-\infty}$ 2.7-fold. The CYP3A4 substrate atorvastatin did not influence the pharmacokinetics of everolimus. The CYP3A4 and PgP substrate paclitaxel did not influence the pharmacokinetics of everolimus. The everolimus doses used in these drug interaction studies ranged from 1 to 4 mg. Drug interaction studies at the 10 mg dose have not been conducted. The strong inducer rifampin decreases everolimus $AUC_{0-\infty}$ to 0.4-times the pre-treatment value.

Pravastatin and gemcitabine are not substrates of CYP3A4 and do not have effects on the pharmacokinetics of everolimus. Co-administration of everolimus and SANDOSTATIN LAR did not have clinically significant effects on the pre-dose trough concentrations of everolimus and octreotide.

TOXICOLOGY

Single Dose Toxicity Studies

Single dose toxicity studies were conducted in rats and mice. Everolimus showed a low acute toxic potential after oral administration in mice and rats. No lethality or severe toxicity was observed after single oral doses of 2000 mg/kg (limit test) in either mice or rats. The low oral acute toxicity indicates that there is a minimal risk of intoxication following accidental or deliberate overdosing.

Repeated Dose Toxicity Studies

Repeated dose toxicity studies were performed in mice over 13 weeks, in rats up to 26 weeks, in minipigs up to 4 weeks and in monkeys up to 52 weeks. The study design and major findings of the repeated dose toxicity studies are shown in Table 27. The monkey was selected as a non-rodent species because gastrointestinal intolerability of everolimus was seen in the oral rising-dose study in the dog, precluding this species from treatment for longer periods. Similar findings have been reported with rapamycin in this species.

Table 27: Repeated dose toxicity studies

Species (strain)	Duration	Route	No./group	Dose (mg/kg)	Major Findings
Mouse	13 weeks	Oral, gavage	10m, 10f	0, 0.15, 0.5, 1.5, 5, 15	• ≥ 0.15 mg/kg: higher incidence of swollen spleen • ≥ 0.5 mg/kg: reduced testes and epididymides weight, depletion of germ cells and vacuolation of the germinal epithelium of testis, reduced sperm content and germ cells in tubular lumina of epididymides (m), skin lesions (f), increased microvesiculation of zona glomerulosa and/or zona fasciculate of the adrenals (m), thymic atrophy • ≥ 1.5 mg/kg: higher liver weight (m), slightly higher cholesterol (m), skin lesions (+m), foamy alveolar macrophages (f), reduced ovarian follicular development and atrophy of uterus (f) • ≥ 5 mg/kg: lower body weight gain (m), higher incidence of skin abrasions (m), higher cholesterol (+f), reduced uterus weight (f), renal tubular degeneration with karyomegaly and interstitial inflammation (m), foamy alveolar macrophages (+m) • 15 mg/kg: high incidence of skin abrasions (+f), higher creatinine concentrations (m), lower albumin and A/G ratio (m), reduced thymus weight and higher spleen weight (m), higher liver weight (+f), renal tubular degeneration with karyomegaly and interstitial inflammation (+f) • NTEL=0.15 (m), and 0.5 (f)
Rat	2 weeks	Oral, gavage	4m, 4f	0, 2.5, 10, 40 (everolimus), 40 (rapamycin)	• ≥ 2.5 mg/kg: reduced body weight gain, food intake (m); decrease in lymphocytes, platelets and albumin; thymic atrophy; lymphoid depletion of spleen and lymph nodes; atrophy/decreased secretion of prostate and seminal vesicles; increased focal myocardiac degeneration; decreased extramedullary splenic haemopoiesis; increase in alveolar macrophages in lungs • ≥ 10 mg/kg: reduced body weight gain, food intake (+f); increased cholesterol (m); skin lesions; bone marrow depletion

Species (strain)	Duration	Route	No./group	Dose (mg/kg)	Major Findings
					(m) • 40 mg/kg: increased WBC/neutrophils; degenerative changes in testes; increased incidence of dioestrus stage. No major differences in toxicity profile compared with rapamycin • NTEL < 2.5 mg/kg
Rat	2 weeks	Oral, gavage	10m, 10f	0, 1.5, 15 (in microemulsion), 0, 1.5, 15 (in solid dispersion)	• No relevant differences in toxicity profile and exposure between microemulsion and solid dispersion
Rat	4 weeks (with 2 week recovery)	Oral, gavage	10m, 10f, additional 6m, 6f in recovery	0, 0.5, 1.5, 5, 15, Recovery: 0, 15	• ≥ 0.5 mg/kg: reduced body weight gain, food intake (m); haemo-concentration; low platelets; increased cholesterol (m); chronic myocarditis (m) • ≥ 1.5 mg/kg: reduced body weight gain, food intake (+f); increased triglycerides (f); chronic myocarditis (+f); medullary atrophy of thymus; foamy alveolar macrophages; loss of germ cells in testes; atrophy/reduced secretion of seminal vesicles; interstitial cell hypertrophy of ovaries; depletion of secretory granules in salivary glands • ≥ 5 mg/kg: Increased neutrophils; increased cholesterol (+f); low albumin; anterior suture line opacities in lens; swelling/disruption of anterior cortical lens fibres; atrophy/reduced secretion of prostate; uterus atrophy; thinning of cortical bone • 15 mg/kg: Reduced sperm counts in testes; reduced contents in epididymides. Recovery of changes except for lungs, heart, eyes and testes • NTEL approx. 0.5 mg/kg
Rat	4 weeks (with 2 week recovery)	Oral, gavage	10m, 10f, additional 6m, 6f in recovery	0, 0.1, 0.25, 0.5, 1.5 Recovery: 0, 15	• ≥ 0.5 mg/kg: Medullary atrophy of thymus • 1.5 mg/kg: Reduced body weight gain, food intake; anterior suture line opacities in lens; haemo-concentration; decreased platelets; increased cholesterol (m); chronic myocarditis; increased alveolar macrophages; interstitial cell hyperplasia of ovaries; uterus atrophy; depletion of secretory granules in

Species (strain)	Duration	Route	No./group	Dose (mg/kg)	Major Findings
					salivary glands. Recovery of changes except for heart • EM: Alveolar macrophages in lungs with vacuoles and multi-lamellar bodies • NTEL = 0.5 mg/kg
Rat	26 weeks (with 4 weeks recovery)	Oral, gavage	20m, 20f, additional 5m, 5f in recovery	0, 0.05, 0.1, 0.15, 0.5, 1.5 Recovery: 0, 1.5	• ≥ 0.15 mg/kg: reduced body weight gain (f); medullary atrophy of thymus (f) • ≥ 0.5 mg/kg: haemo-concentration (m); low platelets (m); increased amylase (m); medullary atrophy of thymus (+m); lymphoid atrophy of LN; pigment (lipofuscin) in renal tubular epithelial cells; increased hydronephrosis (m); increased alveolar macrophages and perivascular lymph. infiltration; mucus cell hypertrophy/plasia of stomach; follicular cell hypertrophy/vacuolation of thyroids (m) • 1.5 mg/kg: reduced body weight gain (+m), food intake; hemo-concentration (+f); low platelets (+f); increased neutrophils; increased cholesterol (m) and amylase (+f), decreased albumin (m) and iron; interstitial pneumonitis (m); splenic haemosiderosis; depletion of germ cells, tubular vacuolation and spermatid giant cells in testes. Recovery of changes except for lungs or testes • Special investigations on the liver drug metabolizing enzyme levels and on the overall metabolism: Minor increase in total metabolite formation and reduction of P450 2B1/2 • NTEL = 0.15 mg/kg
Monkey	24 days	Oral, gavage	1m, 1f	1 (4d), 2 (3d), 4 (4d), 10 (3d), 20 (4d), 40 (3d) 60 (3d) 5-7 d washout after each dose of 10 and above	• ≥ 2 mg/kg: quietness (f) • ≥ 20 mg/kg: increased WBC • ≥ 40 mg/kg: quietness (m), piloerection and huddled posture (f) • 60 mg/kg: piloerection and huddled posture (+m); reduced lymphoid activity in thymus, spleen, LN
Monkey	2 weeks	Oral, gavage	1m, 1f	0, 5, 15, 45	• ≥ 5 mg/kg: piloerection, rash on chest; increased fibrinogen (m), activated partial thromboplastin time; decreased lymphoid

Species (strain)	Duration	Route	No./group	Dose (mg/kg)	Major Findings
					activity in thymus, spleen and LN; subendocardial/ interstitial haemorrhage in heart; reduced cellularity of bone marrow (f) • ≥ 15 mg/kg: quietness; increased fibrinogen (+f); subendocard./interstitial haemorrhage in heart (m) • 45 mg/kg: rough coat, huddled posture (f); body weight loss and reduced food intake; increased glucose and cholesterol (m); decreased phosphorus (m); increased globulins; sub-endocardial/ interstitial haemorrhage in heart (f); reduced cellularity of bone marrow (f) • NTEL < 5 mg/kg
Monkey	4 weeks (with 2 week recovery)	Oral, gavage	3m, 3f additional 2m, 2f in recovery	0, 1.5, 5, 15 Recovery: 0, 15	• ≥ 1.5 mg/kg: reduced food intake (f); increased fibrinogen; decreased phosphorus; splenic lymphoid atrophy • ≥ 5 mg/kg: increase in skin lesions; reduced food intake (+m); reduced RBC parameters; increased α2/β globulins, decreased albumin and Alb/Glob ratio (m); thymic medullary atrophy; increased histiocytosis in small intestine (f) • 15 mg/kg: pilo-erection, reddening of abdomen (m); increased WBC, neutrophils, monocytes; increased alanine and aspartate aminotransferases; increased α2/β globulins and decreased albumin and Alb/Glob ratio (+f); reduced urine sodium; increased histiocytosis in small intestine (+m) • NTEL = 1.5 mg/kg
Monkey	26 weeks	Oral, gavage	4m, 4f, additional 4m, 4f in control and 2m, 2f at high-dose	0, 0.1, 0.5, 1.5, 5	• ≥ 0.5 mg/kg: increased skin lesions (m); reduced body weight gain; splenic lymphoid atrophy; lymphoid depletion in LN; macrophage aggregation in small intestine • ≥ 1.5 mg/kg: early sacrifice (2m) in weeks 14/25 due to poor health condit.; increased skin lesions (+f); reduced food intake; reduced RBC parameters; increased neutrophils/monocytes, fibrinogen; decreased phosphorus; increased cholesterol; thymic cortical and medullary atrophy; myocardial degeneration/necrosis (1m); degranulation of pancreat. exocrine cells (m); reduced follicular development and atresia of ovaries • 5 mg/kg: early termination in weeks 9/10 due to skin lesions,

Species (strain)	Duration	Route	No./group	Dose (mg/kg)	Major Findings
					poor health, body weight loss; in-creased α2/β globulins and decreased albumin and Alb/Glob ratio; increased triglycerides, increased mucosal inflammation of large intestine; myocardial degeneration/necrosis (m); degranulation of pancreatic exocrine cells and increased islet cell degeneration; vacuolation of adrenals • Virology: coxsackie virus in plasma (including pretest) and heart tissue • NTEL = 0.5 mg/kg
Monkey	39/52 weeks	Oral, gavage	4m, 4f	0, 0.1, 0.3, 0.9	• ≥ 0.3 mg/kg: diarrhoea/soft feces (m); reduced body weight/food intake (2m); increased neutrophils (f); inflammatory changes in GI tract; atrophy of testes • 0.9 mg/kg: termination after 39 weeks; 1m and 2f sacrificed early due to poor health condition consequent to diarrhoea/soft feces and inflammation/ ulceration of large intestine; body weight loss and reduced food intake; increased fibrinogen (f) • NOAEL = 0.1 mg/kg
Minipig	2 weeks	Oral, gavage	1m, 1f	0, 0.5, 1.5, 5	• ≥ 0.5 mg/kg: decreased platelets and lymphocytes; increased creatinine (f); increased seminiferous tubular atrophy in testes; thymic cortical lymphocytolysis; decreased germinal centre activity in LN • ≥ 1.5 mg/kg: decreased albumin, γ- globulins and Alb/Glob ratio; increase in ß1 globulins • 5 mg/kg: early sacrifice (f) due to pneumonitis; increased creatinine (m)
Minipig	4 weeks (with 4 week recovery)	Oral, gavage	3m, 3f additional 2m, 2f in recovery	0, 1.5, 5, 15 Recovery: 15	• ≥ 1.5 mg/kg: diarrhoea related to increased coccidial infestation of intestine (m); reduced body weight gain and food intake (m); increased fibrinogen and neutrophils (m); decreased albumin and alb/glob ratio (m); decreased phosphorus, alkaline phosphatase and γ-globulins; increased α2 and β1 globulins; increased percent. of β-lipoproteins and decreased percent of chylomicrons (m); thymic atrophy; atrophy/decreased lymphoid

Species (strain)	Duration	Route	No./group	Dose (mg/kg)	Major Findings
					activity in LN; myelitis and focal encephalitis (m); increased dermatitis; increased testicular tubular atrophy and oligospermia in epididymides • ≥ 5 mg/kg: lymphoid depletion of spleen (1f); necrotic follicles in uterus; microvacuolation of adrenals • 15 mg/kg: diarrhoea with one death (m)/early sacrifices (3m/1f) due to intestinal erosion with coccidial infestation; reduced body weight gain and food intake; decreased platelets (m); increased urea and creatinine (2f); decreased cholinesterase; increased LDL (LDL-3 to LDL-6) and decreased HDL-2a; lymphoid depletion of spleen (m); vacuolation of exocrine pancreatic cells with necrosis (m); atrophy of vagina and uterus. • Recovery of all changes except for the testes. • NTEL < 1.5 mg/kg

Abbreviations: NTEL = no toxic effect level
NOAEL = no observed adverse effect level
m = males, f = females, + m = (f+m), + f = (m+f)
EM = electronic microscopy
d = day
LN=lymph node

In summary, the major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Everolimus appeared to spontaneously exacerbate background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution.

Genotoxicity and Carcinogenicity Studies

Genotoxicity studies covering relevant genotoxicity endpoints 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 3.9 and 0.2 times the estimated clinical exposure from a 10 mg daily dose.

Fertility, Embryofoetal Development, and Pre- and Post-natal Development Studies

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure (52 ng.hr/mL and 414 ng.hr/mL respectively compared to 560 ng.hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/foeto-toxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions. The effects of everolimus on the pre- and post-natal development or rats were limited to slightly affected body weight and survival in the F1-generation at ≥ 0.1 mg/kg, and did not indicate a specific toxic potential.

Study in Juvenile Animals

In a rat oral juvenile development study, the administration of everolimus at 0.15, 0.5 and 1.5 mg/kg on post-partum days 7 to 70 with 13- and 26-week recovery periods resulted in systemic toxicity at all doses, including decreased absolute body weight gain, food consumption, delayed attainment of some developmental landmarks, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding (where young animals

appeared to be more susceptible), it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse effects of everolimus as compared to adult animals. In juvenile monkeys (approximately 1 year old), the oral treatment with everolimus at dosages up to 0.5 mg/kg for 4 weeks did not cause relevant toxicity.

REFERENCES

1. Amato RJ, Jac J, Giessinger S, Saxena S, Willis JP (2009) A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. Cancer; 115: 2438-46.

2. Amato RJ, Misellati A, Khan M, Chiang S (2006). A phase II trial of RAD001 in patients (Pts) with metastatic renal cell carcinoma (MRCC). J Clin Oncol; 24(18 Suppl): abstract 4530.

3. Baselga J, Campone M, Piccart M, et al (2012). Everolimus in Postmenopausal Hormone-Receptor Positive Advanced Breast Cancer. N Engl J Med; 366(6): 520-529

4. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberget BA, et al (2012). Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. www.thelancet.com Published online January 11, 2013 http://dx.doi.org/10.1016/S0140-6736(12)61767-X.

5. Bissler JJ, Kingswood JC, Radzikowska E, et al (2015). Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial. Nephrol Dial Transplant; 0:1-9.

6. Boulay A, Zumstein-Mecker S, Stephan C, et al (2004). Antitumor efficacy of intermittent treatment schedules with the rapamycin derivative RAD001 correlates with prolonged inactivation of ribosomal protein S6 kinase 1 in peripheral blood mononuclear cells. Cancer Res; 64: 252-61.

7. Ellard SL, Clemons M, Gelmon KA, et al (2009) Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163. J Clin Oncol; 27: 4536-41.

8. Escudier B, Ravaud A, Oudard S, et al (2008) Phase-3 randomised trial of everolimus (RAD001) vs placebo in metastatic renal cell carcinoma. Ann Oncol 2008; 19(Suppl 8): viii45 (Abstract 72O). Available at: http://www.esmo.org/fileadmin/media/presentations/977/937/2240%20Escudier%20ESMO%202008%20Final.pptx.pdf (last accessed 12-Nov-2009).

9. Franz DN, Belousova E, Sparagana S, et al (2014) Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. Lancet Oncol;15: 1513-20

10. Franz DN, Belousova E, Sparagana S, et al (2013) Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet; 381:125-32

11. Jac J, Amato RJ, Giessinger S, Saxena S, Willis JP (2008). A phase II study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic renal cell carcinoma which has progressed on tyrosine kinase inhibition therapy. J Clin Oncol; 26(Suppl): abstract 5113.

12. Jac J, Giessinger S, Khan M, et al (2007). A phase II trial of RAD001C in patients (Pts) with metastatic renal cell carcinoma. J Clin Oncol; 25(18 Suppl): 261s (abstract 5107).

13. Knox J, (2008). Progression-fee survival as endpoint in metastatic RCC? Lancet; 372: 427-9.

14. Krueger DA, Care M., Holland K, et al (2010). Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis. N Engl J Med; 363: 1801-1811.

15. Motzer RJ, Escudier B, Oudard S, et al (2008). RAD001 vs placebo in patients with metastatic renal cell carcinoma (RCC) after progression on VEGFr-TKI therapy: results from a randomized, double-blind multicenter Phase-3 study. J Clin Oncol; 26(Suppl): abstract LBA5026.

16. Motzer RJ, Escudier B, Oudard S, et al (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet; 372: 449-56.

17. O'Donnell A, Faivre S, Burris HA, et al (2008). Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. J Clin Oncol; 26: 1588-95.

18. Porter LL, Burris A, Jones SF, et al (2006). Summary of results in patients with metastatic renal cell cancer (RCC) for phase I studies of RAD001 (everolimus). J Clin Oncol; 24(18 Suppl): abstract 14599.

19. Rugo HS, Seneviratne L, Beck T, et al (2016). Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017. Published: 14 March 2017.

20. Tabernero J, Rojo F, Calvo E, et al (2008). Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol; 26: 1603-10.

21. Tanaka C, O'Reilly T, Kovarik JM, et al (2008). Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol; 26: 1596-602.

22. Yao J, Shah M, Tetsuhide I, et al (2011). Everolimus for Advanced Pancreatic Neuroendocrine Tumors. N Engl J Med; 364: 514-523

23. Yao J, Fazio N, Singh S, et al (2016). Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet; 5;387(10022):968-77.

24. Everolimus in advanced non-functional neuroendocrine tumors (NET) of lung or gastrointestinal (GI) origin: Efficacy and safety results from the placebo-controlled, double-blind, multicenter, Phase 3 RADIANT-4 study. Abstract ECC 2015

25. Pavel ME, Hainsworth JD, Baudin E, et al (2011). Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. www.thelancet.com Published online November 25, 2011 DOI:10.1016/S0140-6736(11)61742-X.

26. AFINITOR® Product Monograph, Novartis Pharmaceuticals Canada Inc., Submission Control No. 200814, Date of Revision: November 16, 2017

PART III: CONSUMER INFORMATION

[Pr]TEVA-EVEROLIMUS
everolimus tablets
2.5 mg, 5 mg, 7.5 mg and 10 mg

This leaflet is part III of a three-part "Product Monograph" published when TEVA-EVEROLIMUS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-EVEROLIMUS. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet. You may need to read it again. This medicine has been prescribed only for you. Do not give it to anybody else or use it for any other illnesses.

ABOUT THIS MEDICATION

What this medication is used for:
TEVA-EVEROLIMUS is used in the treatment of:
- hormone receptor-positive, HER2-negative advanced breast cancer in postmenopausal women in whom certain other medicines (letrozole or anastrozole) no longer keep the disease under control. It is given together with a medicine called exemestane. It is not known whether TEVA-EVEROLIMUS prolongs overall survival or improves the quality of life of patients with advanced breast cancer
- a type of pancreatic cancer known as pancreatic neuroendocrine tumour (PNET), that has progressed and cannot be treated with surgery.
- a type of cancer known as neuroendocrine tumour (NET) of gastrointestinal or lung origin that has progressed and cannot be treated with surgery.
- metastatic kidney cancer (when cancer cells have spread from the kidney to other parts of the body) after failure of treatment with sunitinib or sorafenib. It is not known whether TEVA-EVEROLIMUS prolongs overall survival or improves the quality of life of patients with kidney cancer.
- adult patients with a genetic condition called tuberous sclerosis complex (TSC) who have angiomyolipoma of the kidney (a kidney tumour) and do not require immediate surgery.
- patients with subependymal giant cell astrocytoma (SEGA), a brain tumour seen with a genetic condition called tuberous sclerosis complex (TSC), who are not suitable for surgery.

What it does:
Everolimus in TEVA-EVEROLIMUS works by blocking a specific enzyme that is involved in tumour cell growth and division. This may help to slow down the growth and spread of kidney cancer cells and of pancreatic neuroendocrine cells and may reduce the size of brain tumours (SEGA) and of kidney tumours (angiomyolipomas) that are associated with a genetic disorder called tuberous sclerosis complex (TSC). When given together with exemestane, everolimus in TEVA-EVEROLIMUS may slow down the growth and spread of breast cancer cells.

When it should not be used:
If you are allergic (hypersensitive) to everolimus, or sirolimus (RAPAMUNE®), temsirolimus (TORISEL®), or any of the other ingredients in TEVA-EVEROLIMUS listed below in the **What the nonmedicinal ingredients are** section.

What the medicinal ingredient is:
Everolimus

What the nonmedicinal ingredients are:
Butylhydroxytoluene, crospovidone, hypromellose, lactose anhydrous, lactose monohydrate and magnesium stearate

What dosage forms it comes in:
TEVA-EVEROLIMUS tablets are supplied as 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets that are white, oblong, with a bevelled edge and no score.

- Each 2.5 mg tablet contains 2.5 mg everolimus and is engraved with "EV" on one side and "2.5" on the other side.
- Each 5 mg tablet contains 5 mg everolimus and is engraved with "EV" on one side and "5" on the other side.
- Each 7.5 mg tablet contains 7.5 mg everolimus and is engraved with "EV" on one side and "7.5" on the other side.
- Each 10 mg tablet contains 10 mg everolimus and is engraved with "EV" on one side and "10" on the other side.

Each blister pack contains 10 tablets and there are 3 blister packs in a carton.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hormone receptor-positive, HER2-negative advanced breast cancer, advanced NET and metastatic kidney cancer: TEVA-EVEROLIMUS should be prescribed and managed only by a doctor experienced in anticancer drugs.

Angiomyolipoma of the kidney associated with TSC:
TEVA-EVEROLIMUS tablets should be prescribed and managed only by a doctor experienced in treating patients with tuberous sclerosis complex.

The best possible duration of treatment with TEVA-EVEROLIMUS for patients with angiomyolipoma of the kidney associated with TSC is not known. Absence of menstrual periods in females who previously had periods (secondary amenorrhoea) has been observed in some female patients receiving TEVA-EVEROLIMUS and is a potential risk.

SEGA associated with TSC: TEVA-EVEROLIMUS should be prescribed and managed only by a doctor experienced in treating patients with tuberous sclerosis complex.

The best possible duration of treatment with TEVA-

EVEROLIMUS for patients with SEGA is not known; however, SEGA re-growth has been seen once therapy is stopped.

TEVA-EVEROLIMUS is not to be used in children and adolescents (below 18 years of age) who have liver problems.

Information available from studies in animals suggests that there is a risk of delayed development in patients taking everolimus.

Serious side effects which have been reported with the use of everolimus include:
- Non-infectious pneumonitis (including interstitial lung disease)
- Infections
- Kidney failure

BEFORE you use TEVA-EVEROLIMUS talk to your doctor or pharmacist if you:
- have any problems with your liver or have previously had any liver disease
- have any infections. TEVA-EVEROILIMUS can make you more likely to get an infection. Some infections have resulted in death in both adults and children.
- have had hepatitis B, because it may be reactivated during your treatment with TEVA-EVEROLIMUS
- have diabetes (high level of sugar in the blood)
- have high cholesterol or triglyceride levels
- have low blood cell count
- are going to have surgery, if you had a recent surgery or if you still have an unhealed wound following surgery. TEVA-EVEROLIMUS might affect the way your wound heals.
- are pregnant, think you may be pregnant, or are planning to become pregnant**.** TEVA-EVEROLIMUS is not recommended during pregnancy, as it could harm an unborn baby.
- are breastfeeding. Do not breastfeed during treatment with TEVA-EVEROLIMUS and for two weeks after the last dose of TEVA-EVEROLIMUS, as it could harm a breastfed baby.
- need to receive a vaccine or come in contact with those who have received a live vaccine. For pediatric patients with TSC, consider completing the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines.
- have kidney problems as kidney failure has been reported in some patients taking everolimus
- are taking medication that has an effect on blood clotting or may increase the risk of bleeding, or if you have a history of bleeding disorder. Taking TEVA-EVEROLIMUS might make your bleeding worse.
- are allergic to or suspect you are allergic to any ingredient in TEVA-EVEROLIMUS that could result in swelling of the airways and tongue and/or difficulty in breathing.
- are taking other medicines.

Hormone receptor-positive, HER2-negative advanced breast cancer, advanced NET and metastatic kidney cancer: TEVA-EVEROLIMUS is not to be used in children or adolescents under 18 years of age.

Angiomyolipoma of the kidney associated with TSC: TEVA-EVEROLIMUS is not to be used in children or adolescents under 18 years of age with angiomyolipoma of the kidney associated with TSC.

SEGA associated with TSC: TEVA-EVEROLIMUS can be used in children and adolescents (below 18 years of age) who have normal liver function.

What you should know during TEVA-EVEROLIMUS treatment:

Women of child-bearing potential: TEVA-EVEROLIMUS could harm an unborn baby or a breast-fed baby. You should use a highly effective contraceptive method during treatment with TEVA-EVEROLIMUS and for 8 weeks after treatment has stopped, even if you have not yet had a first menstrual period. Absence of periods (amenorrhoea) may develop during treatment with TEVA-EVEROLIMUS, but pregnancy may still occur and use of a highly effective contraceptive method should continue. If you think you may have become pregnant, ask your doctor for advice. If you experience irregular or delayed periods or absence of periods (amenorrhoea) ask your doctor for advice.

Fertility: TEVA-EVEROLIMUS may affect your ability to become pregnant or father a child (fertility). Absence of menstrual periods in females who had periods (secondary amenorrhoea) has been observed in some female patients receiving everolimus. Abnormal levels of reproductive hormones required for the development of sperm and absence of sperm were observed in male patients.

Monitoring during your treatment with TEVA-EVEROLIMUS:

You will have regular blood tests during treatment. These will monitor the amount of blood cells (white blood cells, red blood cells and platelets) in your body, your kidney function (levels of creatinine, blood urea nitrogen or urinary protein), liver function (level of liver enzymes) as well as your cholesterol, triglyceride and blood sugar levels.

If you receive TEVA-EVEROLIMUS for the treatment of SEGA, regular blood tests are necessary to measure how much everolimus is in your blood since this will help your doctor decide how much TEVA-EVEROLIMUS you need to take.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist before taking TEVA-EVEROLIMUS if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes in particular:

- drugs to treat infections (antifungals like ketoconazole, itraconazole; voriconazole or fluconazole; antibiotics like clarithromycin, telithromycin or erythromycin)
- drugs to treat tuberculosis, such as rifampicin or rifabutin
- St. John's wort (also known as *Hypericum perforatum)*
- drugs to stop seizures or fits (anticonvulsants like phenytoin, carbamazepine, oxcarbazepine or phenobarbital)
- drugs to treat AIDS/HIV like ritonavir, amprenavir, fosamprenavir, efavirenz, or nevirapine
- drugs to treat heart conditions or high blood pressure (such as verapamil or diltiazem)
- angiotensin-converting enzyme (ACE) inhibitors, medicines used to treat high blood pressure or other cardiovascular problems
- a class of medications called "statins" (like atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin) to treat high levels of lipids or cholesterol in the blood
- cyclosporine, a medicine to stop the body from rejecting organ transplants
- aprepitant, a medicine to prevent nausea and vomiting
- midazolam, a medicine used to treat acute seizures, or used as a sedative before or during surgery or a medical procedure
- drugs containing pimozide, quinidine or ergotamine, as the concentration of these drugs in your blood may be affected if these drugs are taken together with TEVA-EVEROLIMUS

For patients with SEGA who are taking anti-seizure medications, a change in anti-seizure medication dose (up or down) may require a change in TEVA-EVEROLIMUS dose.

While you are taking TEVA-EVEROLIMUS you should never start a new medicine without checking first with the doctor who prescribed **TEVA-EVEROLIMUS**. This includes prescribed medicines, over the counter medicines and herbal or alternative medicines.

PROPER USE OF THIS MEDICATION

Your doctor will tell you exactly how many tablets of TEVA-EVEROLIMUS to take. Follow your doctor's instructions carefully.

TEVA-EVEROLIMUS should be taken at about the same time each day (preferably in the morning), either consistently on an empty stomach or consistently with food.

TEVA-EVEROLIMUS tablets should be taken by mouth, once daily. Swallow the tablets whole, with a glass of water. Do not chew or crush the tablets.

Do not drink grapefruit juice or eat grapefruit, star fruit or Seville oranges. It may increase the amount of TEVA-EVEROLIMUS in the blood, possibly to a harmful level.

Continue taking TEVA-EVEROLIMUS as long as your doctor tells you.

Usual dose:

Hormone receptor-positive, HER2-negative advanced breast cancer, NET, metastatic kidney cancer and angiomyolipoma of the kidney associated with TSC: The usual dose is 10 mg, to be taken by mouth once daily, at about the same time each day (preferably in the morning). TEVA-EVEROLIMUS should be taken either consistently with food or consistently without food.

A higher or lower dose may be recommended by your doctor based on your individual treatment needs (e.g. if you have liver problems or if you are taking certain additional medicines).

SEGA associated with TSC: Your doctor will determine the starting dose of TEVA-EVEROLIMUS you need to take depending on your body size, the health of your liver and other medicines you are taking. Blood tests are necessary during treatment with TEVA-EVEROLIMUS to measure the amount of everolimus in your blood and find the best daily dose for you.

Your doctor might need to reduce your dose of TEVA-EVEROLIMUS, or to interrupt or discontinue your treatment with TEVA-EVEROLIMUS (e.g., if you have lung or breathing problems, mouth ulcers).

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take TEVA-EVEROLIMUS, you may still take it up to 6 hours after the time you normally take it.

If you remember more than 6 hours after you normally take your TEVA-EVEROLIMUS skip the dose for that day. The next day, take TEVA-EVEROLIMUS at your usual time. Do not take a double dose to make up for the one that you missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TEVA-EVEROLIMUS can cause side effects.

Treatment of hormone receptor-positive, HER2-negative advanced breast cancer, advanced NET and metastatic kidney cancer

Very common side effects:
These side effects may affect more than 1 in 10 patients.
- Lung or breathing problems (pneumonitis)
- Infections
- Loss of appetite

- Disturbed taste (dysgeusia)
- Dry mouth
- Headache
- Cough
- Nose bleeds (epistaxis)
- Breathlessness (dyspnoea)
- Dizziness
- Mouth ulcers: TEVA-EVEROLIMUS can cause mouth ulcers and sores. Your doctor may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide that may require a prescription. **Tell your doctor** if you have pain, discomfort, or open sores in the mouth.
- Stomach upsets like feeling sick (nausea), being sick (vomiting), diarrhea, constipation
- Hair loss
- Rash
- Dry skin
- Itching (pruritus)
- Nail disorders
- Feeling weak or tired
- Mucosal inflammation
- Swelling of arms, hands, feet, ankles, face or other part of the body (signs of edema)
- Fever
- Loss of weight
- Low red blood cell count (anemia)
- High blood glucose
- High cholesterol
- High triglycerides
- High blood pressure
- Low level of potassium in the blood (hypokalaemia)
- High level of phosphate in the blood
- Pain in arm and leg, mouth and throat, back or joints
- Trouble sleeping (insomnia)

If any of these affects you severely, **tell your doctor.**

Common side effects:
These side effects may affect between 1 and 10 in every 100 patients.
- Blockade or obstruction of a blood vessel (vein) in the legs (deep vein thrombosis). Symptoms may be swelling and/or pain in one of your legs, usually your calf, and redness or warm skin in the affected area.
- Chest pain, cough, hiccups and rapid breathing (signs of fluid collection between the layers of tissue that line the lungs and chest cavity)
- High level of sugar in the blood (diabetes)
- Worsening of diabetes
- Dehydration
- Pulmonary embolism (a condition that occurs when one or more arteries in your lungs become blocked). Symptoms may be sudden onset of shortness of breath, chest pain or coughing up blood). **Talk to your doctor right away if this occurs.**
- Coughing up blood (haemoptysis)
- Heartburn (dyspepsia)
- Difficulty in swallowing (dysphagia)
- Acne
- Rash/pain on the palms of your hands or soles of your feet (hand foot syndrome)
- Skin reddening (erythema)
- Protein in the urine
- Kidney failure
- Pain in abdomen, chest or jaw
- Low lymphocyte, platelet or white blood cell count
- Excess fluid around lung
- Haemorrhoids or bleeding
- Low blood phosphate or calcium
- Tingling sensation/feeling of numbness
- Muscle spasm
- Chills
- Swelling of eyelids
- Runny nose
- High level of liver enzymes
- Heart problems, tachycardia or rapid heartbeat, heart failure (breathlessness, difficulty breathing when lying down, swelling of the feet or legs)
- Pink eye
- Swelling of gums (gingivitis)
- Feeling depressed
- Loss of taste (ageusia)

If any of these affects you severely, **tell your doctor**.

Uncommon side effects:
These side effects may affect between 1 and 10 in every 1,000 patients.
- A type of anemia called pure red cell aplasia
- Onset of diabetes
- Abnormal wound healing
- Absence of menstrual periods (amenorrhoea)
- Loss of hearing

If any of these affects you severely, **tell your doctor**.

Treatment of angiomyolipoma of the kidney associated with TSC

Very common side effects:
These side effects may affect more than 1 in 10 patients.
- Low level of red blood cells (anemia)
- Low level of white blood cells (leukopenia)
- High level of cholesterol in the blood (hypercholesterolaemia)
- Mouth ulcers. TEVA-EVEROLIMUS can cause mouth ulcers and sores. **Tell your doctor** if you have pain, discomfort, or open sores in your mouth. You might need treatment with a mouthwash or gel. Some mouthwashes and gels can make ulcers worse, so do not try anything without checking with your doctor first.
- Middle ear infection
- Stomach upsets like feeling sick (nausea)
- Being sick (vomiting)

- Diarrhea
- Abdominal pain
- Swelling of arms, hands, feet, ankles or other parts of the body (signs of edema)
- Upper respiratory tract infection
- Acne
- Skin rash
- Itchy rash (eczema)
- High level of an enzyme, called blood lactate dehydrogenase, in the blood that gives information about the health of certain organs
- Low level of phosphate in the blood (hypophosphatemia)
- Joint pain
- Headache
- Cough
- Menstruation disorders such as absence of periods (amenorrhoea), irregular periods, heavy periods (menorrhagia)

Common side effects:
These side effects may affect between 1 and 10 in every 100 patients.
- Rash, itching, hives, difficulty breathing or swallowing, dizziness, signs of serious allergic reaction (hypersensitivity)
- Menstruation disorders such as vaginal bleeds, delayed periods, or infrequent periods (oligomenorrhoea)
- Rash with pus-filled blister
- Rash with small, fluid-filled blisters on the mouth (mouth herpes)
- Fever, coughing, difficulty breathing, wheezing, signs of inflammation of the lung (pneumonia)
- Inflammation of the sinuses and nasal passages (sinusitis). Symptoms may include headache, pressure in the eyes, nose or cheek area
- Low level of platelets (thrombocytopenia)
- A special lung functional test result decreased (carbon monoxide test)
- High level of an enzyme called blood alkaline phosphatase, in the blood that gives information about the health of certain organs
- High level of an enzyme, called blood gamma-glutamyltransferase, in the blood that gives information about the health of your liver
- High level of lipids in the blood (hyperlipidaemia)
- Decreased appetite
- Low level of iron (iron deficiency)
- Severe headache often accompanied by nausea, vomiting and sensitivity to light (migraine)
- Disturbed taste (dysgeusia)
- Loss of taste (ageusia)
- Nose bleeds (epistaxis)
- Excess amount of gas in the bowels (flatulence)
- An inflammatory condition of the skin characterized by redness, itching, and oozing liquid-filled cysts which become scaly, crusted, or hardened (dermatitis acneiform)
- Dry skin
- Fever, coughing, difficulty breathing, wheezing, signs of inflammation of the lung (pneumonitis)
- Feeling depressed
- Sudden, severe increase in blood pressure
- Inability to sleep (insomnia)
- Aggression
- Mouth pain
- Higher level of ovulation triggering hormone (blood luteinising hormone increased)
- Higher level of female reproductive hormone (blood follicle stimulating hormone increased)
- Swollen, bleeding gums, signs of gum inflammation (gingivitis)
- Bad pain in the lower abdomen and pelvic area that may be sharp, with menstrual irregularities (ovarian cyst)

If any of these affects you severely, **tell your doctor.**

<u>Treatment of SEGA associated with TSC</u>

Very common side effects:
These side effects may affect more than 1 in 10 patients.
- Infections, such as inflammation of the sinuses and nasal passages (sinusitis), middle or outer ear infection, gastric infection, sore throat and runny nose, skin infections, ringworm (a fungus infection of the skin), infections of the hair follicle, urinary tract infection, conjunctivitis, upper respiratory tract infection, pneumonia.
- Mouth ulcers: TEVA-EVEROLIMUS can cause mouth ulcers and sores. **Tell your doctor** if you have pain, discomfort, or open sores in the mouth. Your doctor may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- High level of cholesterol in the blood
- High levels of fats in the blood (raised triglycerides)
- Cough
- Diarrhea and constipation
- Skin problems (such as rash, acne, dry skin or scratching of the skin)
- Fever
- Low white blood cells (a type of blood cell that fights infections; your doctor will check periodically)
- Vomiting
- Stomach pain
- Seizure
- Headache
- Dizziness
- Stuffy or runny nose
- Change in personality
- Loss of appetite
- High level of sugar in the blood (hyperglycemia)
- High blood pressure (hypertension)
- Sore throat and runny nose (nasopharyngitis)

If any of these affects you severely, **tell your doctor**.

Common side effects:

These side effects may affect between 1 and 10 in every 100 patients.

- Abscess of limb
- Bronchitis viral
- Low level of red blood cells (anemia)
- Aggression
- Inability to sleep (insomnia)
- Feeling agitated
- Fits (convulsions)
- Nose bleeds
- Throat inflammation
- Inflammation of the stomach lining (gastritis)
- A pink itchy rash on your body called pityriasis rosea
- Protein in the urine
- Menstruation disorders, such as absence of periods (amenorrhoea), irregular periods
- Feeling tired
- Irritability
- Trouble walking (gait disturbance)
- Decrease antibody levels in the blood (ask your doctor)
- Increased low density lipoprotein in the blood
- Pain in the mouth or throat
- Rash of small fluid-filled blisters, appearing on reddened skin, signs of viral infection that can be potentially severe (herpes zoster)
- Higher level of ovulation triggering hormone (blood luteinising hormone increased)
- Urinary tract infection
- Swollen, bleeding gums, signs of gum inflammation (gingivitis)
- Weight loss
- Abnormal kidney function test results
- Abdominal pain
- Decrease of a special protein (fibrinogen) that helps blood clot
- Bacterial skin infections
- Absence of sperms

If any of these affects you severely, **tell your doctor**.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common			
Pain, discomfort or sores in the mouth		√	
Common			
Lung or breathing Problems (pneumonitis, Pulmonary embolism, acute respiratory syndrome) (cough, chest pain, shortness of breath)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your
Fever or chills or other signs of an infection as you might need urgent treatment		√	
Increased frequency in urination; kidney failure		√	
Rash, itching, hives, difficulty breathing or swallowing, dizziness, signs of serious allergic reaction (swelling of the face, lips, tongue or throat) (hypersensitivity)			√
Coughing up blood			√
Uncommon			
Swelling and/or pain, and redness or warm skin in your leg, usually affecting the calf (deep vein thrombosis)		√	
Blood in urine			√
Unexpected vaginal bleeding			√
Severe abdominal pain, vomiting blood, black or bloody stools, swelling of the abdomen, constipation (gastrointestinal bleeding)			√
Hepatitis B reactivation with symptoms of fever, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, yellowing of the skin, pain in the upper abdomen, pale stool or dark urine		√	
Swelling of the airways or tongue, with or without respiratory impairment (angioedema)		√	
Fever, chills, rapid breathing and heart rate, rash, and possibly confusion and disorientation (signs of serious infection, also known as sepsis)		√	
Reported from post-marketing with unknown frequency			
Severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your**
consciousness (bleeding in the brain)			
Muscle pain, tenderness and weakness that you cannot explain		√	
Brownish or discoloured urine			√

This is not a complete list of side effects. For any unexpected effects while taking TEVA-EVEROLIMUS, contact your doctor or pharmacist.

HOW TO STORE IT

Do not use after the expiry date shown on the box.

Store at room temperature (15 – 30°C).
Store in original package to protect from light and moisture.
Keep out of the reach and sight of children and pets.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice..

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada
M1B 2K9

www.tevacanada.com

Last revised: July 18, 2019