PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNAT-EVEROLIMUS

Everolimus
Tablets, 2.5 mg, 5 mg, 7.5 mg, and 10 mg, Oral

Protein kinase inhibitors
ATC Code: L01XE10

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Date of Initial Authorization:
August 22, 2022

Date of Revision:
January 25, 2023

Submission Control Number: 267697

RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NAT-EVEROLIMUS (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 14 CLINICAL TRIALS).

- 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 14 CLINICAL TRIALS).

- 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 14 CLINICAL TRIALS).

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

NAT-EVEROLIMUS is not indicated for the treatment of patients with functional carcinoid tumours (see 7 WARNINGS AND PRECAUTIONS and 14 CLINICAL TRIALS).

- the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell morphology, after failure of initial treatment with either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-receptor TKIs) 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 14 CLINICAL TRIALS).

- 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 14 CLINICAL TRIALS).

NAT-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.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for NAT-EVEROLIMUS for pediatric use in patients with Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer, Advanced NET, Metastatic RCC and renal angiomyolipoma associated with TSC (see 7.1.3 Pediatrics).

Pediatrics (>1 to <18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of everolimus in pediatric patients with SEGA > 1 year of age has been established. Therefore, Health Canada has authorized an indication for pediatric patients with SEGA > 1 year of age. There are limited efficacy and safety data in patients 1 to 3 years of age with everolimus in patients with SEGA (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age):

In the advanced breast cancer study, 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 7.1.4 Geriatrics and 14 CLINICAL TRIALS).

In two other randomized trials (metastatic RCC and advanced PNET), no overall differences in safety or effectiveness were observed between elderly and younger patients (see 14 CLINICAL TRIALS).

In the randomized advanced GI/Lung NET study, 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.

2 CONTRAINDICATIONS

- NAT-EVEROLIMUS (everolimus) is contraindicated in patients who are hypersensitive to the drug, to other rapamycin derivatives or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS COMPOSITION AND PACKAGING (see also 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hormone receptor-positive, HER2-negative advanced breast cancer, advanced NET and metastatic kidney cancer:

- NAT-EVEROLIMUS (everolimus) should be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy.

SEGA associated with TSC:

- Treatment with NAT-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 4 DOSAGE AND ADMINISTRATION, Therapeutic drug monitoring for patients treated for SEGA).
- The optimal duration of NAT-EVEROLIMUS therapy for patients with SEGA is not known; however, SEGA re-growth has been reported to occur once therapy is discontinued (see 4 DOSAGE AND ADMINISTRATION, SEGA volume monitoring for patients treated with NAT-EVEROLIMUS and 14 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, Pediatrics below and 16 NON-CLINICAL TOXICOLOGY).
- NAT-EVEROLIMUS and everolimus tablets for oral suspension are not interchangeable (see 4 DOSAGE AND ADMINISTRATION, Dosing Considerations).

Renal Angiomyolipoma associated with TSC:

- Treatment with NAT-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 NAT-EVEROLIMUS therapy for patients who have renal angiomyolipoma associated with TSC is not known (see 14 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 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential).

The following are clinically significant adverse events:

- Non-infectious pneumonitis, including fatalities (see 7 WARNINGS AND PRECAUTIONS, "Respiratory" section)
- Infections, including fatalities (see 7 WARNINGS AND PRECAUTIONS, Immune section)
- Renal failure, including fatalities (see 7 WARNINGS AND PRECAUTIONS, Renal section)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

NAT-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.

NAT-EVEROLIMUS (everolimus) is only available in one dosage form, tablets.

NAT-EVEROLIMUS (everolimus tablets) and everolimus tablets for oral suspension are **not** interchangeable and should not be combined to achieve the desired dose. Consistently use the same dosage form, as appropriate for the indication being treated (see 4.4 Administration).

For dosing recommendations of everolimus tablets for oral suspension for the use in SEGA associated with TSC, please see the product monograph for the tablets for oral suspension.

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

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

NAT-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 10 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 NAT-EVEROLIMUS therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered (see Table 1 and 7 WARNINGS AND PRECAUTIONS). For dose reductions below the lowest available tablet strength, alternate day dosing should be considered.

4.2 Recommended Dose and Dosage Adjustment

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

The recommended dose of NAT-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 NAT-EVEROLIMUS and exemestane should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Advanced NET and Metastatic RCC: Treatment with NAT-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 NAT-EVEROLIMUS is not known.

Geriatrics (≥ 65 years):
No dosage adjustment is required for elderly patients (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years):
Health Canada has not authorized an indication for NAT-EVEROLIMUS for pediatric use in patients with Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer, Advanced NET, Metastatic RCC and renal angiomyolipoma associated with TSC.

SEGA associated with Tuberous Sclerosis Complex

Individualise dosing based on body surface area (BSA, in m^2), calculated using the Dubois formula[1].

Titration 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 9 DRUG INTERACTIONS and Therapeutic drug monitoring for patients treated for SEGA associated with TSC).

Starting dose and target trough concentrations in SEGA associated with TSC

The recommended starting daily dose for NAT-EVEROLIMUS for the treatment of patients with SEGA associated with TSC is 4.5 mg/m^2, rounded to the nearest strength of NAT-EVEROLIMUS. Different strengths of NAT-EVEROLIMUS can be combined to attain the desired dose. NAT-EVEROLIMUS (everolimus tablets) and everolimus tablets for oral suspension are not interchangeable and should **not** be combined to achieve the desired dose. For dosing recommendations of the everolimus tablets for oral suspension, please see the product monograph for the tablets for oral suspension.

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

*Dose titration for SEGA (NAT-EVEROLIMUS)***.**

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.

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

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 or dosage form (between everolimus tablets and everolimus tablets for oral suspension), after an initiation or change in co-administration of inducers or inhibitors of CYP3A4/PgP (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS) or after any change in hepatic (Child-Pugh) status (see Recommended Dose and Dosage Adjustment, Patients with hepatic impairment below and 10 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 NAT-EVEROLIMUS

SEGA volume should be evaluated approximately 3 months after commencing NAT-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 NAT-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.

Pediatrics (< 18 years):

Dosing recommendations for pediatric patients with SEGA are consistent with those for the corresponding adult population.

Dosage Modifications for Adverse Reactions

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of NAT-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 1 NAT-EVEROLIMUS dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[a]	NAT-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 compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.
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.

Adverse Drug Reaction	Severity[a]	NAT-EVEROLIMUS Dose Adjustment[b] and Management Recommendations
		Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 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.
	Grade 3	Temporary dose interruption. Re-initiate treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment 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.

Adverse Drug Reaction	Severity[a]	NAT-EVEROLIMUS Dose Adjustment[b] and Management Recommendations
		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 a lower dose.
	Grade 4 (<25.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a 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 the same dose.
	Grade 4 (<0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at a 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 hour.	Temporary dose interruption until recovery of ANC to ≥ 1.25 x 10^9/L and no fever. Re-initiate treatment at a 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)

Dosage Modifications for Use with CYP3A4 and/or PgP Inhibitors

Moderate inhibitors of CYP3A4 and/or PgP: Use caution when administering NAT-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 NAT-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 7 WARNINGS AND PRECAUTIONS and 9 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 NAT-EVEROLIMUS dose is increased. The NAT-EVEROLIMUS dose should be returned to the dose used prior to initiation of the moderate inhibitor of CYP3A4 or PgP (see 7 WARNINGS AND PRECAUTIONS and 9 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 NAT-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 7 WARNINGS AND PRECAUTIONS and 9 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 7 WARNINGS AND PRECAUTIONS and 9 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 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Dosage Modifications for Use with CYP3A4 and/or PgP Inducers

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 NAT-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 NAT-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 NAT-EVEROLIMUS recommended dose up to 20 mg daily, using increments of 5 mg or less. This dose of NAT-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 NAT-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 NAT-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 NAT-EVEROLIMUS (see Therapeutic drug monitoring for patients treated for SEGA associated with TSC below, 7 WARNINGS AND PRECAUTIONS and 9 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 NAT-EVEROLIMUS dose. Double the daily dose of NAT-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 patients treated for SEGA associated with TSC below).

SEGA associated with TSC:
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 patients treated 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 patients treated 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 NAT-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 9 DRUG INTERACTIONS).

Dose Modification for Patients with Renal Impairment
No studies with NAT-EVEROLIMUS in patients with impaired renal function have been carried out. However, given that renal metabolism and clearance of NAT-EVEROLIMUS is minimal (< 5% of total), no dosage adjustment is recommended (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency)

Dose Modification for Patients with Hepatic Impairment

Table 2 Patients with Hormone receptor-positive, HER-2 negative advanced breast cancer, advanced NET, metastatic renal cell carcinoma and renal angiomyolipoma associated with TSC.

Patients with hepatic impairment	Recommended dose
Mild hepatic impairment (Child-Pugh A)	7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated
Moderate hepatic impairment (Child-Pugh B)	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.

Table 3 Patients with SEGA associated with TSC, ≥18 years of age

Patients with hepatic impairment	Recommended dose
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

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

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

4.3 Reconstitution

Not Applicable.

4.4 Administration

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

4.5 Missed Dose

NAT-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, NAT-EVEROLIMUS should be taken at its usual time. Double doses should not be taken to make up for the one that was missed.

5 OVERDOSAGE

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 NAT-EVEROLIMUS overdose and general supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
NAT-EVEROLIMUS		
Oral	Tablet 2.5 mg, 5 mg, 7.5 mg, and 10 mg	Anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, magnesium stearate.

Tablets
NAT-EVEROLIMUS (everolimus) tablets are white to off white in colour, oval and flat shaped.
NAT-EVEROLIMUS tablets are available in four strengths: 2.5 mg, 5 mg, 7.5 mg, and 10 mg.

2.5 mg:
The tablets are debossed with "EVR" on one side and "2.5" on the other.

5 mg:
The tablets are debossed with "EVR" on one side and "5" on the other.

7.5 mg:
The tablets are debossed with "EVR" on one side and "7.5" on the other.

10 mg:
The tablets are debossed with "EVR" on one side and "NAT" on the other.

NAT-EVEROLIMUS 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are supplied in blister packs of 30 tablets (10 tablets/blister, 3 blisters/carton).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Drug-Drug Interactions
Co-administration with strong inhibitors of CYP3A4 and/or PgP should be avoided (see 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS).

Use caution when administered in combination with moderate inhibitors of CYP3A4 and/or PgP. If NAT-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 4 DOSAGE AND ADMINISTRATION and 9 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 NAT-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 NAT-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 4 DOSAGE AND ADMINISTRATION and 9 DRUG INTERACTIONS).

Exercise caution when NAT-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 NAT-EVEROLIMUS and non-orally administered CYP3A4 substrates has not been studied (see 9 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.

Endocrine and Metabolism

***Hyperlipidaemia*:** Hypercholesterolaemia and hypertriglyceridaemia have been reported in patients taking everolimus (see 8 ADVERSE REACTIONS). Monitoring of fasting lipid profile is recommended prior to the start of NAT-EVEROLIMUS therapy and periodically thereafter. Consider dose reduction, dose interruption or discontinuation, as well as management with appropriate medical therapy (see 4 DOSAGE AND ADMINISTRATION, Dosing Considerations, Table 1).

***Hyperglycaemia*:** Hyperglycaemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of NAT-EVEROLIMUS therapy and periodically thereafter (see Monitoring and Laboratory Tests below).
More frequent monitoring is recommended when NAT-EVEROLIMUS is co-administered with other drugs that may induce hyperglycaemia. Optimal glycaemic control should be achieved before starting a patient on NAT-EVEROLIMUS. New onset type 2 diabetes has occurred with everolimus treatment (see 8 ADVERSE REACTIONS).

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 NAT-EVEROLIMUS in patients with functional carcinoid tumours is not recommended outside an investigational study.

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 8 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 4 DOSAGE AND ADMINISTRATION, Table 1 and 9 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.

Hematologic

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in patients taking everolimus (see 8 ADVERSE REACTIONS). Monitoring of complete blood count is recommended prior to the start of NAT-EVEROLIMUS therapy and periodically thereafter.

Hemorrhage

Clinical trials in patients with advanced cancers treated with everolimus have reported all grades of hemorrhage. In the RCC trial, gastrointestinal (GI) hemorrhage, retinal hemorrhage, vaginal hemorrhage, pulmonary alveolar hemorrhage, melaena and hematuria were reported as adverse

events. In the hormone receptor-positive, HER2-negative advanced breast cancer trial, a single case of tumour hemorrhage was reported as a fatal adverse drug reaction. Post-marketing surveillance reported GI, tumour, pulmonary and cerebral hemorrhage as adverse events. Some cases were fatal (GI hemorrhage and cerebral hemorrhage). In the renal angiomyolipoma with TSC trial, low grade epistaxis, vaginal haemorrhage and menorrhagia were reported (see 8 ADVERSE REACTIONS).

Caution is advised in patients taking NAT-EVEROLIMUS during concomitant use with active substances known to affect platelet function or that can increase the risk of hemorrhage 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 hemorrhage 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 2 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 8 ADVERSE REACTIONS). Localised 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 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Physicians and patients should be aware of the increased risk of infection with NAT-EVEROLIMUS. Pre-existing infections should be treated and fully resolved prior to starting treatment with NAT-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 NAT-EVEROLIMUS.

If a diagnosis of invasive systemic fungal infection is made, discontinue NAT-EVEROLIMUS and treat with appropriate antifungal therapy (see 4 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 NAT-EVEROLIMUS (see 9 DRUG INTERACTIONS). 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 according to local treatment guidelines (e.g. updated Canadian Immunization Guide).

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 NAT-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 pediatric patients (see Special Populations, Pediatrics).

Musculoskeletal

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 NAT-EVEROLIMUS therapy, patients should be monitored for the possible development of rhabdomyolysis especially if they are prescribed a concomitant statin. Patients on treatment with NAT-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 NAT-EVEROLIMUS (see 9 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 NAT-EVEROLIMUS in the peri-surgical period.

Radiation Sensitization and Radiation Recall

Severe cases of radiation sensitization and radiation recall involving cutaneous and visceral organs (including radiation esophagitis and radiation pneumonitis) have been reported in patients treated with radiation prior to, during, or following everolimus treatment. Caution should therefore be exercised for patients using NAT-EVEROLIMUS in close temporal relationship with radiation therapy (see 8.5 Post-Market Adverse Reactions).

Renal

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus (see 8 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 NAT-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).

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus (see 8 ADVERSE REACTIONS).

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

If amenorrhoea develops in a woman of childbearing potential who is receiving NAT-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 8 ADVERSE REACTIONS).

- **Fertility**

Both female and male fertility may be compromised by treatment with NAT-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 16 NON-CLINICAL TOXICOLOGY).

Respiratory

Non-infectious pneumonitis: Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Cases of non-infectious pneumonitis (including interstitial lung disease) were reported in up to 19% of patients treated with everolimus (see 8 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 non-specific 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 NAT-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. NAT-EVEROLIMUS may be reintroduced at a daily dose approximately 50% lower than the dose previously administered (see 4 DOSAGE AND ADMINISTRATION, Table 1).

For cases of Grade 3 non-infectious pneumonitis, interrupt NAT-EVEROLIMUS until resolution to less than or equal to Grade 1. NAT-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 NAT-EVEROLIMUS. For cases of Grade 4 non-infectious pneumonitis, NAT-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 4 DOSAGE AND ADMINISTRATION, Table 1).

Sporadic lymphangioleiomyomatosis (LAM)

The safety and effectiveness of NAT-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 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

Foetal harm may occur when administered to pregnant women. Apprise women of potential harm to the foetus. Animal studies have shown post-implantation loss in rats and rabbits as well as foetal toxicity at below clinical exposures (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is unknowns if everolimus is excreted in breast milk. Precaution should be exercised because many drugs can be excreted in human milk. In animal studies everolimus and/or its metabolitesreadily passed into the milk of lactating rats. Women taking NAT-EVEROLIMUS should therefore not breastfeed during treatment and for 2 weeks after the last dose.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for NAT-EVEROLIMUS for pediatric cancer patients use withHormone Receptor-Positive, HER2-Negative Advanced Breast Cancer, Advanced NET, Metastatic RCC and renal angiomyolipoma associated with TSC.

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

The optimal duration of NAT-EVEROLIMUS therapy for patients with SEGA is not known; however, SEGA re-growth has been reported to occur once therapy is discontinued (see 4 DOSAGE AND ADMINISTRATION, SEGA volume monitoring for patients treated with NAT-EVEROLIMUS and 14 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 16 NON-CLINICAL 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 NAT-EVEROLIMUS on neurological development is unknown, NAT-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 pediatric patients. Therapy should be individualized for the patient and clinical situation.

NAT-EVEROLIMUS is not recommended for use in pediatric patients with renal angiomyolipoma associated with TSC.

The pooled safety data from clinical trials in the TSC setting included 3 randomized double-blind placebo-controlled trials and one prospective open label single arm trial to evaluate the safety and efficacy of everolimus for treatment of TSC and its related indication. 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.

No data are available in a pediatric population with hepatic impairment. Everolimus clearance, normalised 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 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics). NAT-EVEROLIMUS is not recommended for use in patients < 18 years of age with SEGA and concomitant hepatic impairment (Child-Pugh A, B or C). (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

7.1.4 Geriatrics

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 4 DOSAGE AND ADMINISTRATION).

Other reported clinical experience has not identified differences in response between the elderly and younger patients (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

In a randomized, placebo-controlled phase III study (BOLERO-2) in patients with Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer, the most common treatment-emergent adverse events irrespective of causality (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhea 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, dyspnea 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%). 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 hemorrhage, 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%), dyspnea (1.9%), fatigue (1.9%), decreased appetite (1.7%), anemia (1.7%) and rash (1.5%). The incidence of 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%).

Adverse Events in Advanced Pancreatic Neuroendocrine Tumours

In a randomized, controlled trial of everolimus (n=204) versus placebo (n=203) in patients with advanced pancreatic neuroendocrine tumours (PNET), the most common adverse reactions (incidence ≥ 30%) were stomatitis, rash, diarrhea, fatigue, oedema, abdominal pain, nausea, fever and headache. The most common grade 3/4 adverse reactions (incidence ≥ 5%) were stomatitis and diarrhea.
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, diarrhea and peripheral oedema.

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

In a randomized, controlled phase III study (RADIANT-4) in patients with advanced non-functional NET of GI or lung origin, 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 anemia, 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.

Adverse Events in Metastatic RCC

In a randomized phase III study for the treatment of metastatic renal cell carcinoma, the most common treatment-emergent adverse events irrespective of causality (incidence ≥ 30%) were stomatitis, anemia, infections, asthenia, fatigue, cough and diarrhea. The most common grade 3-4 adverse events (incidence ≥ 3%) were anemia, infections, dyspnea, 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.

Adverse Events in Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

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 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. 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.

Adverse Events in SEGA associated with Tuberous Sclerosis Complex

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 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.

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

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 oestrogen 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). Table 5 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 5 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 5 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
Diarrhea	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

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

	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**
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
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
Dyspnea	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

Advanced Pancreatic Neuroendocrine Tumours

In a randomised, 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.

Table 6 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 6 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
Diarrhea[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

	Everolimus N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
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
Dyspnea/dyspnea 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 (wks)	**37**			**16**		

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 diarrhea, enteritis, enterocolitis, colitis, defecation urgency and steatorrhoea.

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

Advanced Non-Functional Neuroendocrine Tumours of Gastrointestinal or Lung Origin

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.

Table 7 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.

Table 7 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						
Anemia	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
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
Hyperglycemia	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
Dyspnea	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.

Metastatic RCC

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomised 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.

Table 8 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 8 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 8 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**
Gastrointestinal Disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0

	Everolimus 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
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
Dyspnea	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 hemorrhage, pulmonary toxicity and alveolitis.

Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

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.

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						
Anemia	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
Diarrhea	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

	Everolimus 10 mg/day N=79			Placebo N=39		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Metabolism and Nutrition Disorders						
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.

Amenorrhea (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 hemorrhage (8%), menstruation delayed (2%) and oligomenorrhoea (2%).

Further long-term follow-up with a median duration of exposure of 47 months resulted in the following additional 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).

SEGA associated with Tuberous Sclerosis Complex

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.

Table 10 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 10 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 10 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
Diarrhea	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%).

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%).

8.3 Less Common Clinical Trial Adverse Reactions

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

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%), hemoptysis (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 hemorrhage (0.8%), rectal hemorrhage (0.8%), hemorrhoidal hemorrhage (0.6%), intra-abdominal haematoma (0.6%), deep vein thrombosis (1%)

Advanced Pancreatic Neuroendocrine Tumours

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

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

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

Hematologic disorders: Pure red cell aplasia (0.5%)

Metabolism and nutrition disorders: Dehydration (6%)

Psychiatric disorders: Depression (6%)

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

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

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

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

Advanced Non-Functional Neuroendocrine Tumours of Gastrointestinal or Lung Origin

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%)

Metastatic RCC

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

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

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

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

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dyspepsia (4%), dysphagia (4%), anal hemorrhage (<1%), hematochezia (<1%), melaena (<1%) and rectal hemorrhage (<1%)

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

Investigations: Blood creatinine increased (9%)

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%)

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

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

Psychiatric disorders: Insomnia (9%)

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

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

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

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

Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

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%)

SEGA associated with Tuberous Sclerosis Complex

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

Blood and Lymphatic Disorders: Neutropenia (6 %), anemia (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%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

Clinically relevant laboratory abnormalities are presented in Table 11.

Table 11 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
	%	%	%	%	%	%
Hematology[a]						
Hemoglobin 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-glutamyltransferase 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 anemia, leukopenia, lymphopenia, neutropenia and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency

Advanced Pancreatic Neuroendocrine Tumours

Clinically relevant laboratory abnormalities are presented in Table 12.

Table 12 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
	%	%	%	%
Hematology				
Hemoglobin 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

Advanced Non-Functional Neuroendocrine Tumours of Gastrointestinal or Lung Origin

Clinically relevant laboratory abnormalities are presented in Table 13.

Table 13 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						

Metastatic RCC

Clinically relevant laboratory abnormalities are presented in Table 14.

Table 14 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
	%	%	%	%	%	%
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1

Laboratory parameter	Everolimus 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
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 anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia

Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

Clinically relevant laboratory abnormalities are presented in Table 15 below.

Table 15 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 %
Hematology						
Hemoglobin 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%).

SEGA associated with Tuberous Sclerosis Complex

Key laboratory abnormalities reported more frequently with everolimus than placebo are presented in Table 16.

Table 16 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 %
Hematology						
Elevated partial thromboplastin time	72	3	0	44	5	0
Neutrophils decreased	46	9	0	41	3	0
Hemoglobin 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

8.5 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 NAT-EVEROLIMUS exposure.

Table 17 Adverse Drug Reactions Reported in the Post Marketing Setting

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)
Injury, poisoning and procedural complications	Radiation sensitization and radiation recall
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
Vascular disorders	lymphoedema

9 DRUG INTERACTIONS

9.2 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.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 18 Established or Potential Drug-Drug Interactions

Proper/Common name/ Drug class	Source of Evidence	Effect	Clinical comment
Strong CYP3A4 inhibitor /Pgp (including but not limited to ketoconazole, itraconazole, voriconazole, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone, clarithromycin and telithromycin)	CT	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.	Concurrent treatment should be avoided
Moderate inhibitors of CYP3A4 (including, but not limited to erythromycin, verapamil, cyclosporine, fluconazole, diltiazem, amprenavir, fosamprenavir or aprepitant) and moderate PgP inhibitors	CT	Increase in exposure to everolimus in healthy subjects when everolimus was co-administered with: • erythromycin; C_{max} and AUC increased by 2.0- and 4.4-fold, respectively. • verapamil; C_{max} and AUC increased by 2.3- and 3.5-fold, respectively. • Cyclosporine (a CYP3A4 substrate and inhibitor of PgP); C_{max} and AUC increased by 1.8- and 2.7-fold, respectively.	Requires caution. Reduce the NAT-EVEROLIMUS dose if co-administered with moderate inhibitors of CYP3A4 and/or PgP (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

Inducers of CYP3A4 and/or PgP (including, but not limited to rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, efavirenz, nevirapine).	CT	Pre-treatment of healthy subjects with multiple doses of rifampin 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%.	Concurrent treatment with strong inducers of CYP3A4 and/or PgP should be avoided. If NAT-EVEROLIMUS must be co-administered with a strong inducer of CYP3A4 and/or PgP, it may be necessary to adjust the NAT-EVEROLIMUS dose (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).
HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate), simvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate)	CT	No clinically significant pharmacokinetic interactions.	Caution should be exercised if a statin is prescribed for hyperlipidaemia, since the risk of developing rhabdomyolysis may be increased with statin use (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).
CYP3A4 Substrates (midazolam)	CT	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.	Interaction between everolimus and non-orally administered CYP3A4 substrates has not been studied (see 7 WARNINGS AND PRECAUTIONS).
Depot octreotide		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).	
Exemestane		Co-administration of NAT-EVEROLIMUS and exemestane (a drug which is metabolized in part by CYP3A4) increased	No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-

		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.	negative advanced breast cancer receiving the combination.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Effect of Everolimus on Antiepileptic drugs (AEDs):
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. Everolimus had no impact on pre-dose concentrations of AEDs that are substrates of CYP3A4 (clonazepam, diazepam, felbamate and zonisamide) or other AEDs, including valproic acid, topiramate, oxcarbazepine, phenobarbital, phenytoin and primidone.

Effects of Combination Use of Angiotensin Converting Enzyme (ACE) Inhibitors:
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 7 WARNINGS AND PRECAUTIONS, General, Drug-Drug Interactions).

Vaccinations:
Immunosuppressants may affect the response to vaccination and vaccination during treatment with NAT-EVEROLIMUS may therefore be less effective. The use of live vaccines should be avoided during treatment with NAT-EVEROLIMUS (see 7 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.

9.5 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.

9.6 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.

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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 signalling 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 16 NON-CLINICAL TOXICOLOGY).

10.2 Pharmacodynamics

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 eIF-4G was complete at all C_{min} values after the 10 mg daily dose.

Cardiac Electrophysiology: Everolimus was studied in a randomised, 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.

10.3 Pharmacokinetics

Table 19 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-τ (ng.h/mL)	CL/F (L/h)	CL/F (L/h/m²)
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%)

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.

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.

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 faeces, while 5% was excreted in the urine over 10 days. The parent substance was not detected in urine or faeces.

Special Populations and Conditions

- **Pediatrics:** In patients who have SEGA associated with TSC receiving everolimus, the geometric mean C_{min} values normalized to mg/m² 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 4.2 Recommended Dose and Dosage Adjustment, SEGA associated with Tuberous Sclerosis Complex, Therapeutic drug monitoring for SEGA).

- **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.

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

- **Ethnic Origin:** 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 Insufficiency:** 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 (4 DOSAGE AND ADMINISTRATION).

- **Renal Insufficiency:** 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 – 30 °C). Store in the original package to protect from light and moisture.

Keep in a safe place out of the reach of children and pets.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Everolimus

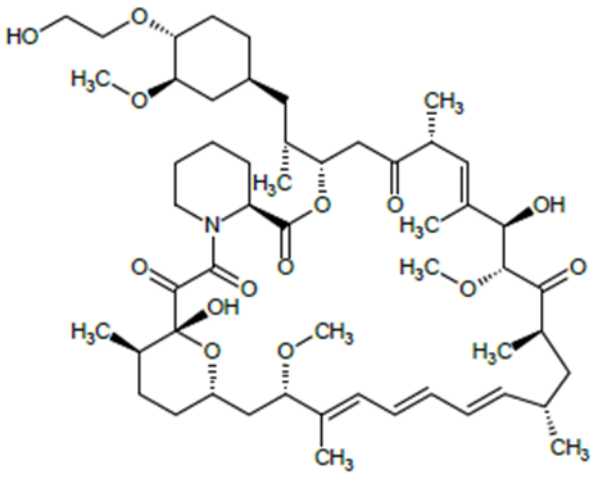
Chemical name:

(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: 958.22 g/mol

Structural formula:



Physicochemical properties:

Physical description:	White to light yellow coloured powder. Solubility: The drug substance is practically insoluble in water, but it is soluble in organic solvents.
pH:	7.15 (1% suspension in water)
pKa:	7.3
Partition Coefficient:	6.74
Melting Point:	Not applicable since the drug substance is amorphous.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

Study Y2301 (BOLERO-2)

Table 20 Summary of patient demographics for clinical trial in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

Study	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
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 was required, but letrozole or anastrozole did not have to be the last line of therapy.	Everolimus 10 mg tablet, oral. The median duration of blinded treatment was 24 weeks for patients receiving everolimus plus exemestane and 13.4 weeks for those receiving placebo plus exemestane.	n = 724 Everolimus plus exemestane (n = 485) and placebo plus exemestane (n = 239). **Race (n [%]):** Caucasian - 547 (75.6%) Asian – 143 (19.8%) Black – 16 (2.2%) Other – 18 (2.5%)	**Median Age:** 61 years (range 28 years to 93 years) **Age category (years) (n [%]):** < 65 years: 449 (62%) ≥ 65 years to <75 years: 181 (25%) ≥ 75 years: 94 (13%)	Females (100%)

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.

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 20 and Table 21). Overall, 84% of patients were considered to be sensitive to prior endocrine therapy. Patients in the placebo plus exemestane arm did not cross-over to everolimus at the time of progression.

Table 21 Disease Characteristics (Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer)

Disease characteristic	Everolimus plus exemestane N=485 n (%)	Placebo plus exemestane N=239 n (%)	All patients N=724 n (%)
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 22 and Figure 1).

The analysis of PFS based on independent central radiological assessment was supportive (see Table 22).

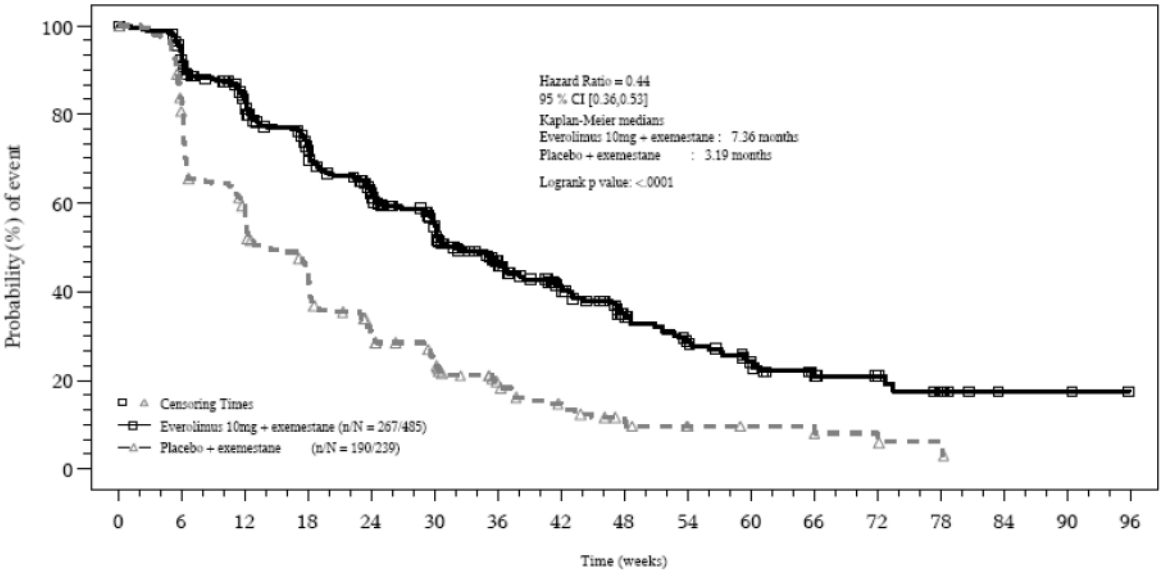
No clinically or statistically significant differences were observed between the two treatment arms in terms of time to deterioration of ECOG PS (≥ 1 point) and median times to deterioration (≥ 5%) of QLQ-C30 domain scores.
OS data were not mature at the time of a second interim analysis (additional 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 22 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

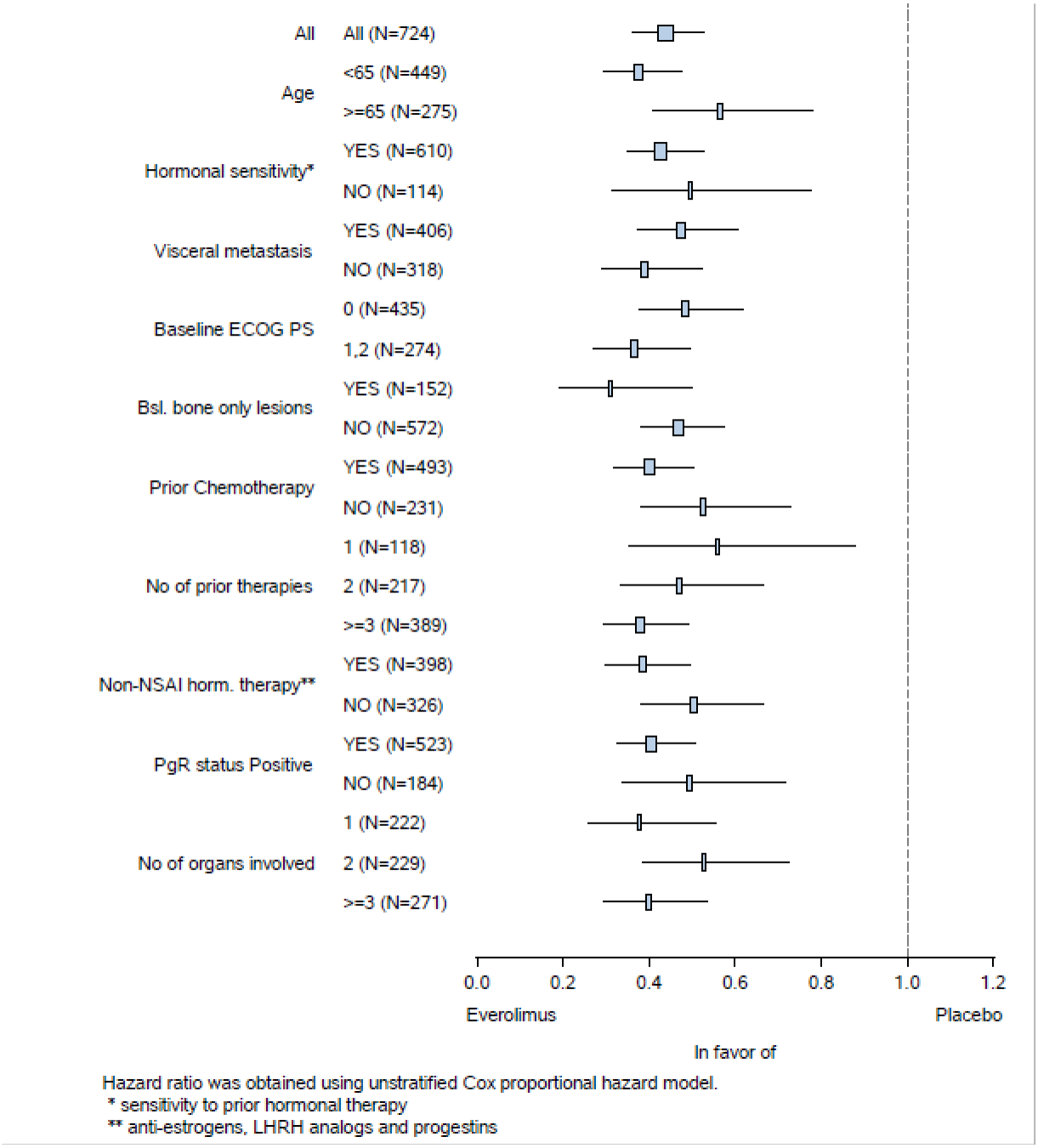


Number of Patients still at Risk

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 analysed (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)

Table 23 Summary of patient demographics for clinical trial in Pancreatic Neuroendocrine Tumours (PNET)

Study	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex (%)
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.	Everolimus 10mg/day tablet, oral. Patients were treated with study medication until objective tumor progression was documented per RECIST criteria (as per the local investigator), unacceptable toxicity, or until treatment discontinuation because of any other reason.	n=410 Everolimus 10mg/day (n=207) or placebo (n=203). **Race (n[%])** Caucasian – 322 (78.5%) Asian – 74 (18.0%) Black – 11 (2.7%) Other - 3 (0.7%)	**Mean age:** 56.5 years **Range** 20 to 87 years **Age (n [%])** < 65 years 299 (72.9%) ≥ 65 years 111 (27.1%)	Male 55.4% Female 44.6%

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 24 Disease Characteristics (PNET)

Disease characteristic	Everolimus N=207 n (%)	Placebo N=203 n (%)	Total N-410 N (%)
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 25 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 25.

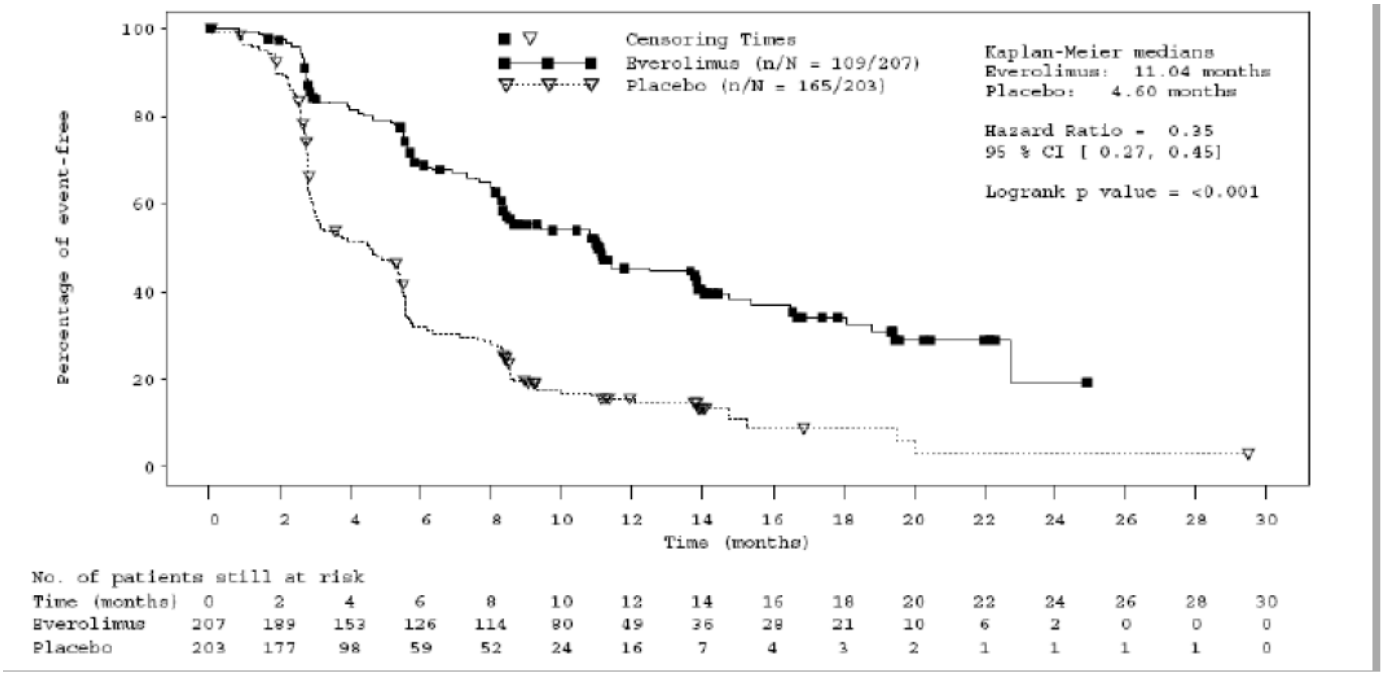
Table 25 Progression Free Survival Results (PNET)

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

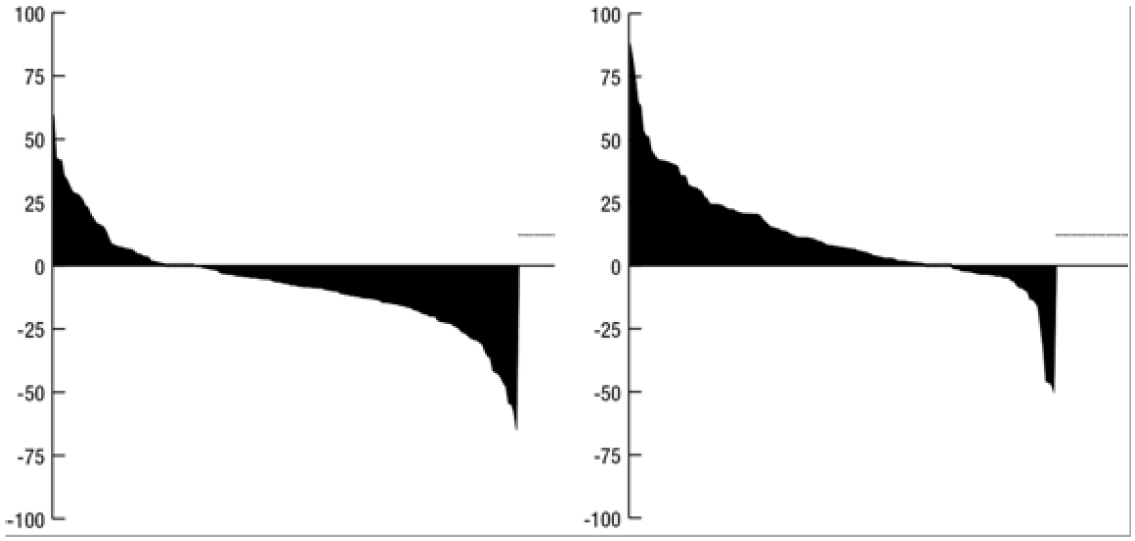
[b] one-sided p-value from a stratified log-rank test

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



	Everolimus n (%)	Placebo 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)

Table 26 Summary of patient demographics for clinical trial in Neuroendocrine tumours (PNET)

Study	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex (n [%])
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.	Everolimus 10 mg/day, tablet, oral. The median duration of blinded treatment was 40.4 weeks for patients receiving Everolimus and 19.6 weeks for those receiving placebo.	n = 302 Everolimus (10 mg daily) (n = 205), placebo (n = 97).	Median age 63 years Range 22 to 86 years **Age (n [%])** <65 years: 159 (52.6%) ≥ 65 years: 143 (47.4%)	Male: 142 (47%) Female: 160 (53.0%)

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. Patients in the placebo arm did not cross-over to everolimus at the time of progression.

Table 27 Disease Characteristics (GI or lung NET)

Disease Characteristics	Everolimus N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
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)
Previous treatments			
Any prior antineoplastic therapy[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)

Disease Characteristics	Everolimus N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
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.

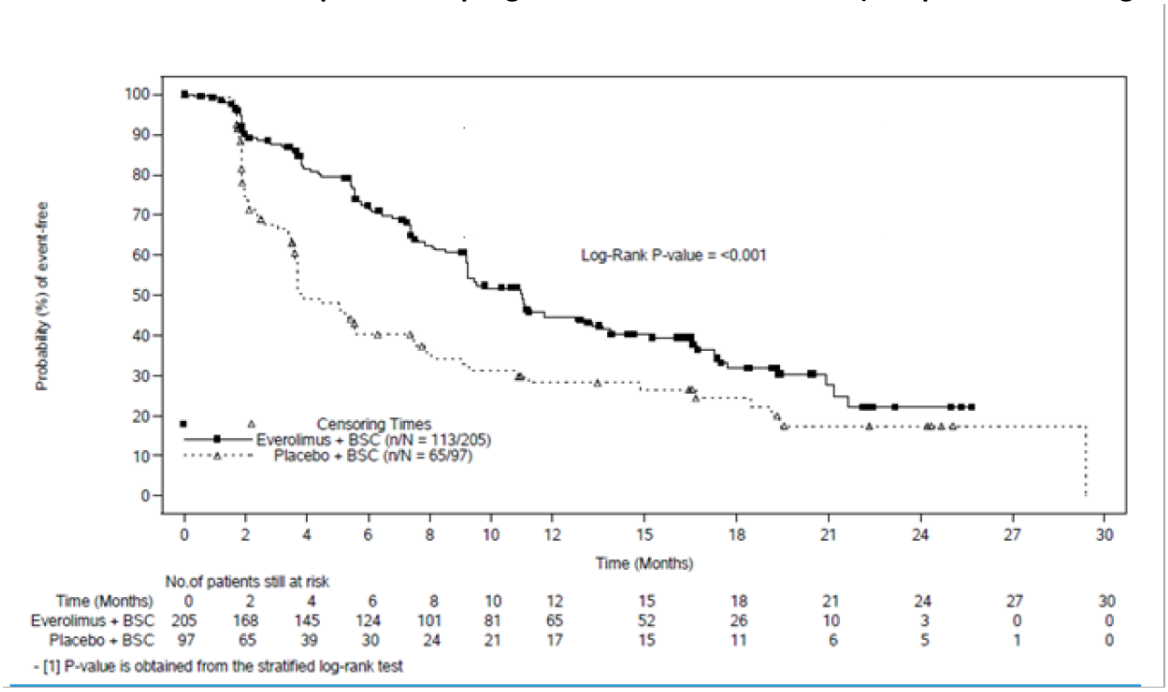
The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 52% risk reduction of progression or death (HR 0.48; 95% CI: 0.35, 0.67; one-sided stratified log-rank test p-value <0.001) per independent assessment (see Table 28 and Figure 5). The analysis of PFS based on local investigator assessment was supportive.

Table 28 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 favored 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)

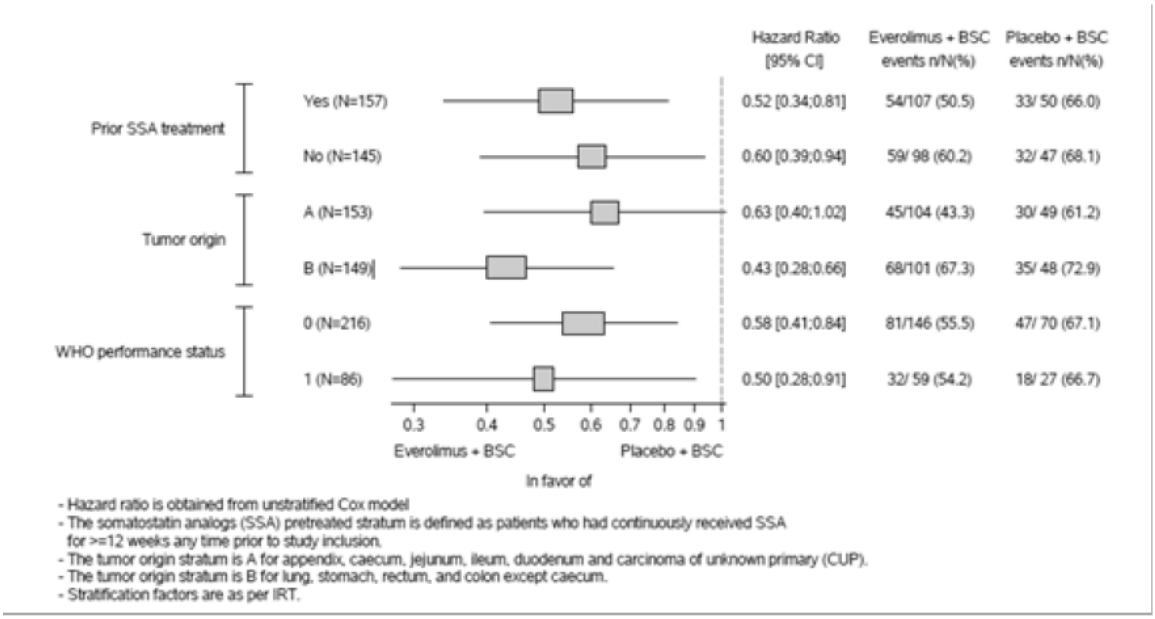
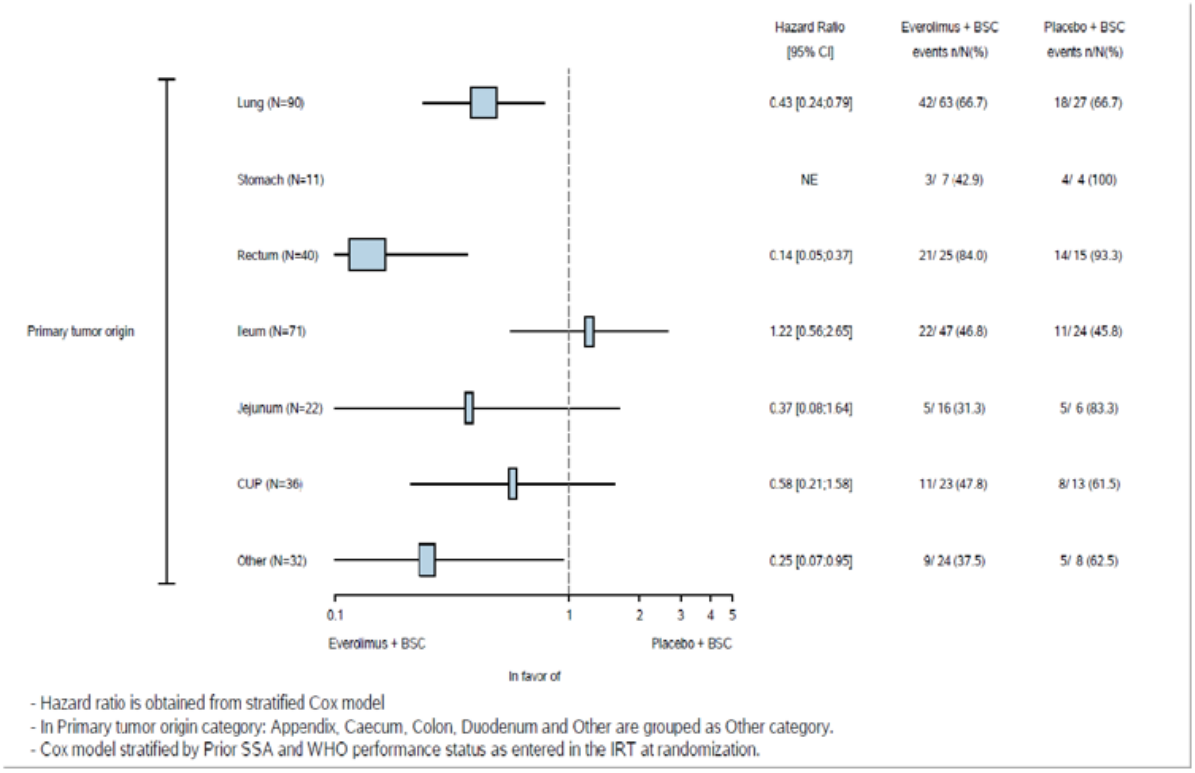


Figure 7 Forest plot of stratified hazard ratio for PFS treatment effect for patient subgroups (independent radiological review)



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).

Metastatic Renal Cell Carcinoma (mRCC)

Study C2240 (RECORD-1)

Table 29 Summary of patient demographics for clinical trial in Metastatic Renal Cell Carcinoma (mRCC)

Study	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex (n (%))
C2240 (RECORD – 1)	A phase III, international, multi-centre, randomised, double-blind study comparing	Everolimus 10 mg/day, tablet, oral. The blinded treatment	n=416 Everolimus n=277 Placebo	**Median age**: 61 years **Range:** 27 to 85 years	Male 106 (76.3 %) Female

	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.	continued until the occurrence of tumour progression or unacceptable toxicity.	n=139 **Race (n[%])** **Everolimus:** Caucasian: 246 (88.8%) Asian: 16 (5.8%) Black: 2 (0.7%) Native American: 1 (0.4%) Other/Missing: 9/4 (2.9%/1.4%) **Race (n[%]) Placebo:** Caucasian: 121 (87.1%) Asian: 11 (7.9%) Black: 3 (2.2%) Native American: 0 (0%) Other/Missing: 3/1 (2.2%/0.7%)	**Age (n [%])** **<65 years:** Everolimus: 165 (59.6%) Placebo: 98 (70.5%) **≥ 65 years:** Everolimus: 112 (40.4%) Placebo: 41 (29.5%)	33 (23.7%)

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 randomised 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.

Table 30 Disease Characteristics (mRCC)

Disease characteristic	Everolimus N=277	Placebo N=139
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)

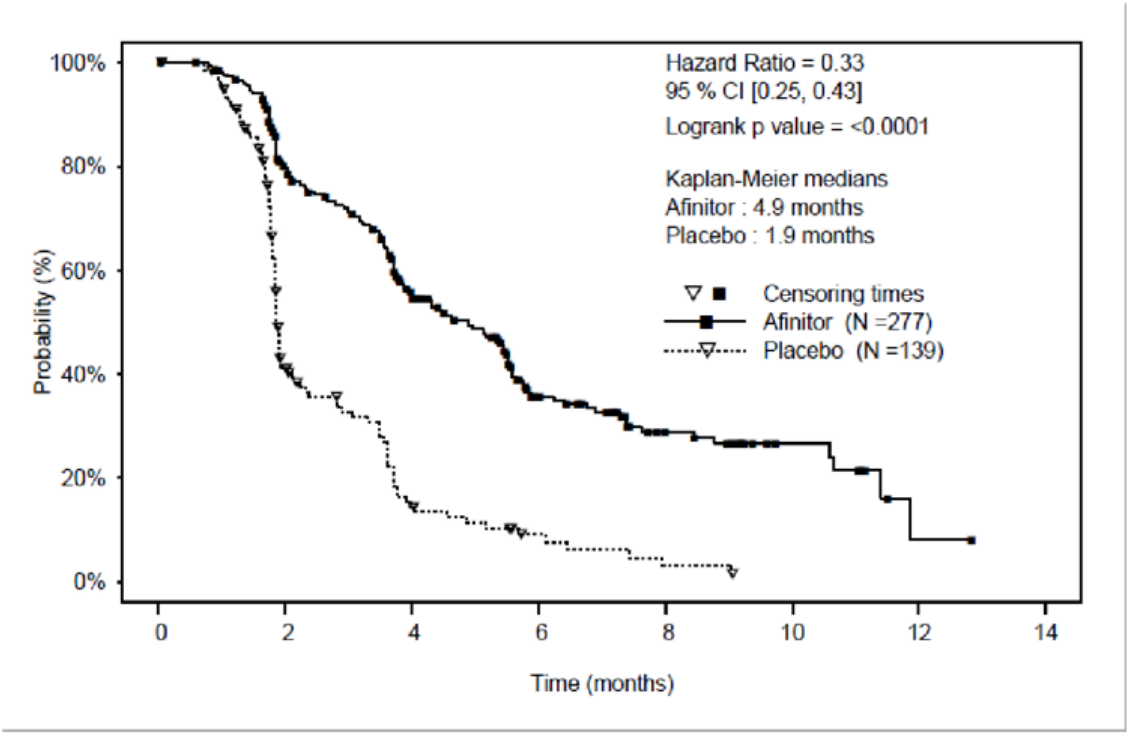
Results from a planned interim analysis showed that everolimus was superior to placebo for the primary endpoint of progression-free survival (PFS), with a statistically significant 67% reduction in the risk of progression or death. At 6 months, PFS rates were 36% for everolimus therapy compared with 9% for placebo (see Table 31 and Figure 8).

Table 31 Progression Free Survival results (mRCC)

Population	N	Everolimus N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value [a]
		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 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.013[b]

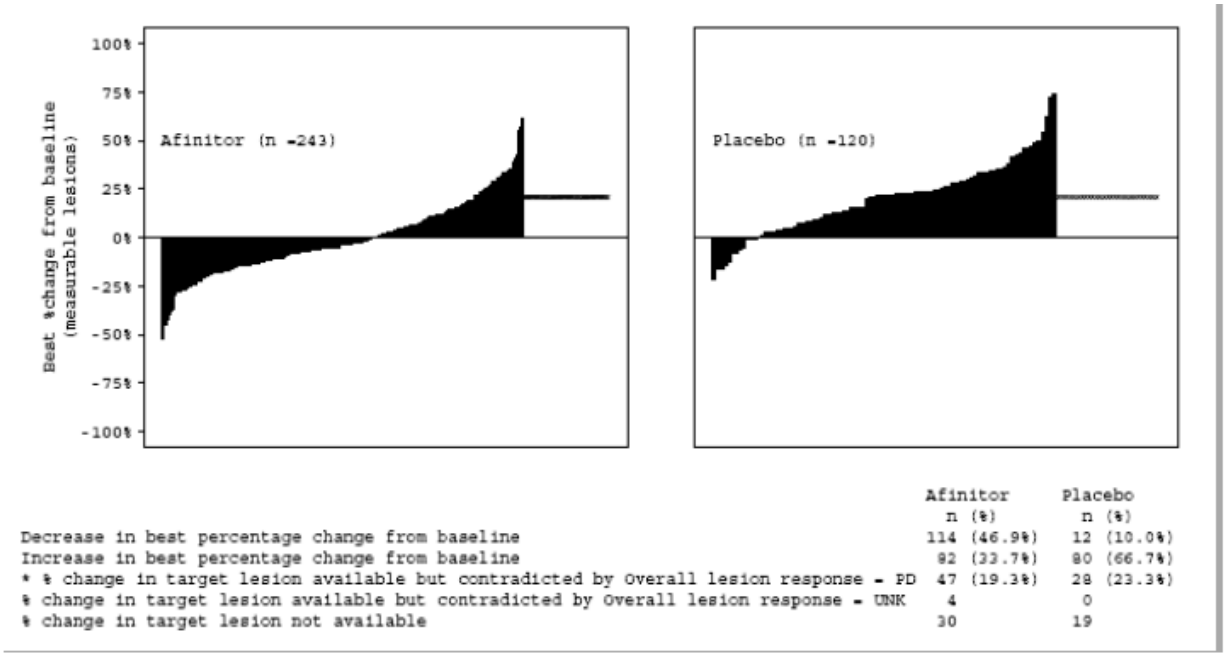
[a] Log-rank test stratified by prognostic score
[b] Unstratified, two-sided log-rank test

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 stabilisation (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



	Afinitor 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

M2302 (EXIST-2)

Table 32 Summary of patient demographics for clinical trial in Renal Angiomyolipoma associated with Tuberous Sclerosis Complex (TSC)

Study	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex (M/F)
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.	Everolimus 10 mg/day, tablet oral, until disease progression or unacceptable toxicity or discontinuation for any other reason.	n =118 Everolimus 10 mg daily (n=79) or matching placebo (n=39) **Race (n [%])** **Everolimus:** Caucasian: 71 (89.9%) Asian: 7 (8.9%) Other: 1 (1.3%) **Placebo:** Caucasian: 34 (87.2%) Asian: 4 (10.3.%) Other: 1 (2.6%)	**Mean age** Everolimus: 32.5 years Placebo: 31 years. Range: 18 to 61 years.	**Male (n [%])** Everolimus: 27 (34.2%), Placebo: 13 (33.3%) **Female (n [%])** Everolimus: 52 (65.8%), Placebo: 26 (66.7%)

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 randomisation (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).

Demographic and baseline disease characteristics and history of prior anti-angiomyolipoma therapies were generally well balanced.

Table 33 Disease Characteristics (Full Analysis Set) (Renal Angiomyolipoma associated with TSC)

Disease characteristic	**Everolimus N=79**	**Placebo N=39**
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)
< 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)		

Disease characteristic	Everolimus N=79	Placebo N=39
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

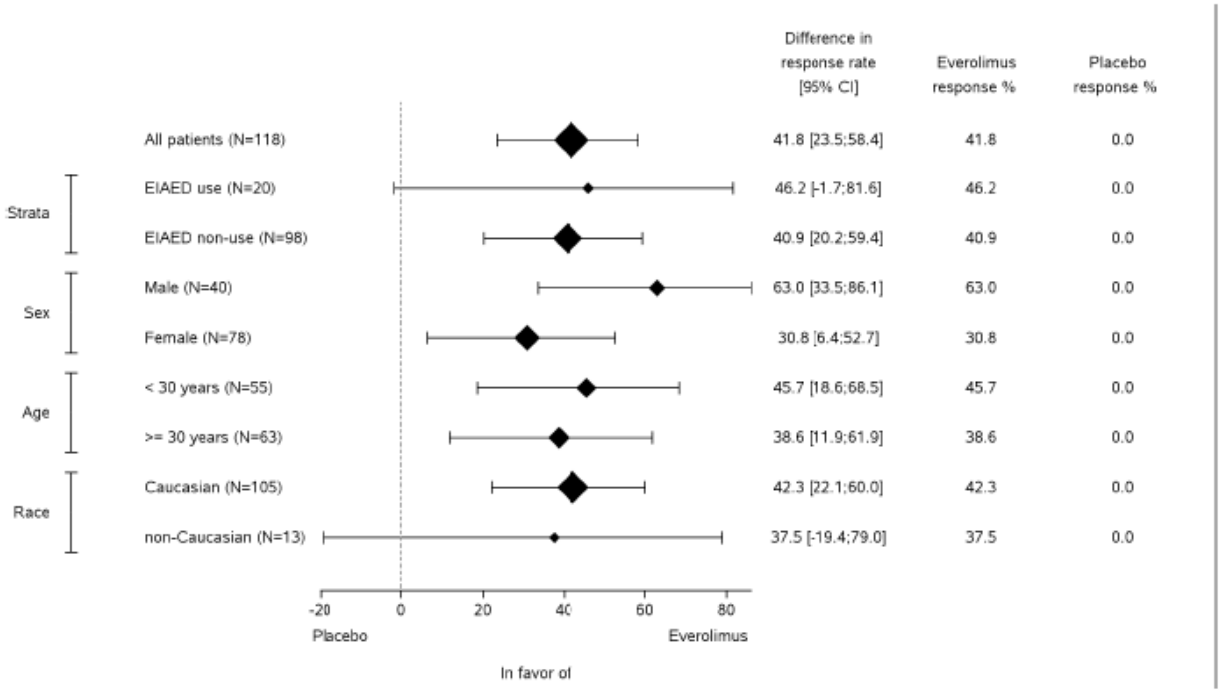
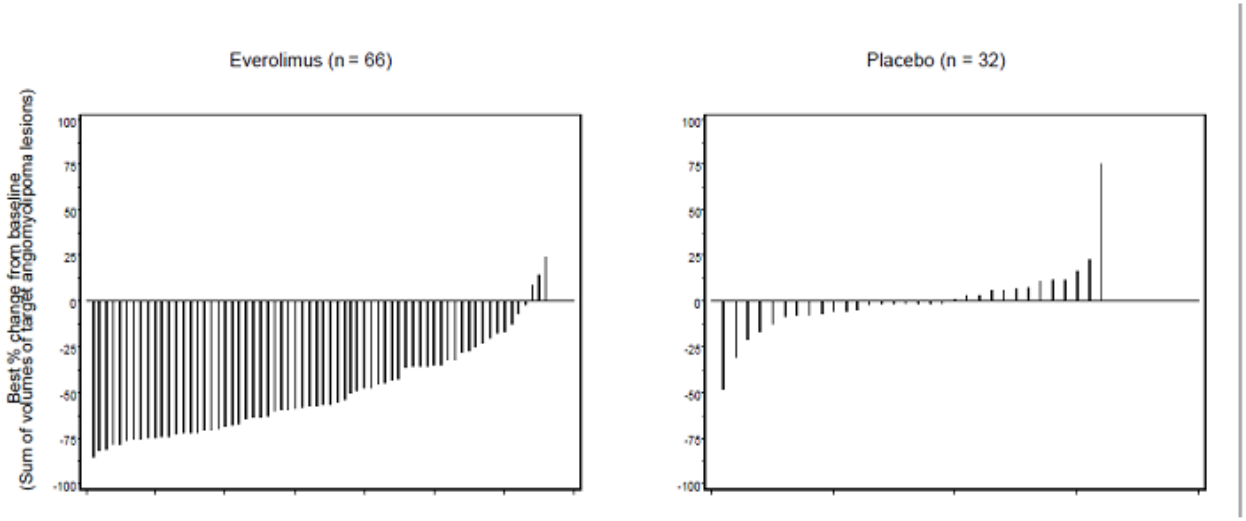


Table 34 Angiomyolipoma Response

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

SEGA associated with Tuberous Sclerosis Complex

Study M2301 (EXIST-1)

Table 35 Summary of patient demographics for clinical trial in SEGA associated with Tuberous Sclerosis Complex (TSC)

Study	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex (n [%])
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 randomised in a 2:1 ratio to receive either everolimus or placebo.	Patients randomized to the treatment arm received everolimus at a starting dose of 4.5 mg/m^2 daily orally, with subsequent dose adjustments as needed, to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL, as tolerated. 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.	n = 117 Everolimus (n=78), Placebo (n=39) **Race (n [%])** Caucasian: 109 (93.2%) Black: 4 (3.4%) Other: 3 (2.6%)	**Mean Age** Everolimus: 10.1 years Placebo: 10.3 years Range 0.8 to 26.6 years	Male 67 (57.3%) Female 50 (42.7%)

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.

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 randomised. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomisation (yes/no).

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

The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies.

Table 36 Demographic and Disease Characteristics

Disease characteristic	Everolimus N=78 n (%)	Placebo N=39 n (%)	Total N=117 n (%)
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 31). 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 31).

Table 37 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 radiology review

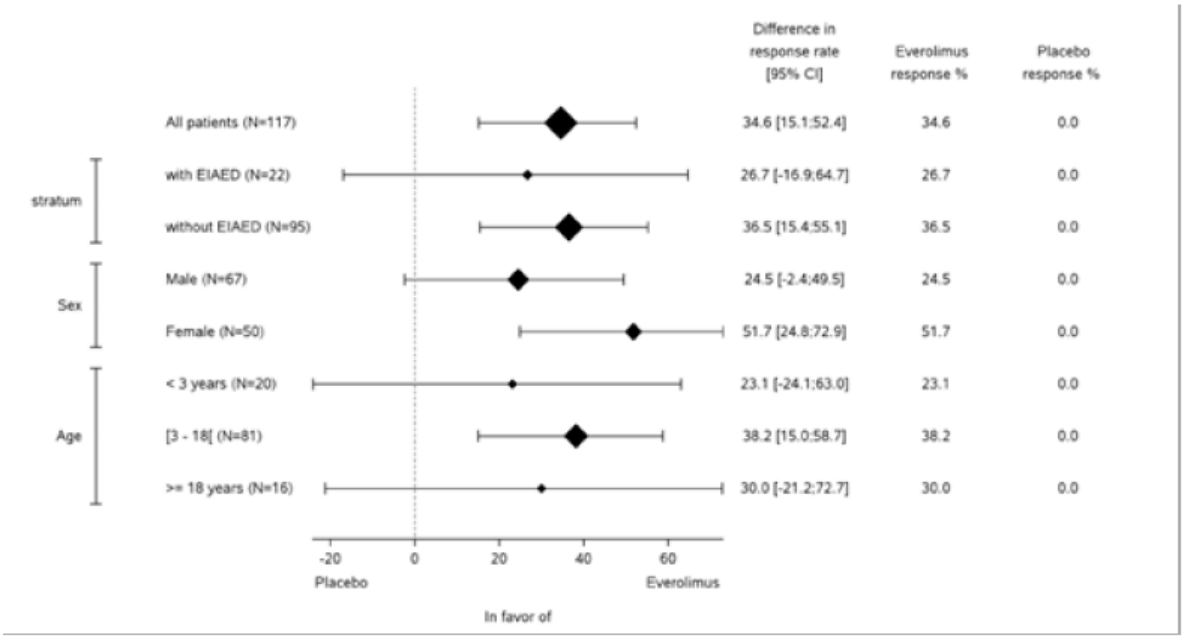
[2] SEGA responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of SEGA volume relative to baseline, plus no unequivocal worsening of non-target SEGA lesions, plus absence of new SEGA ≥ 1 cm in longest diameter, plus no new or worsening hydrocephalus.

[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 in 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.

14.3 Comparative Bioavailability Studies

A double blind, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence study comparing NAT-EVEROLIMUS 10 mg tablets (Natco Pharma (Canada) Inc.) to AFINITOR® (everolimus) 10 mg tablets (Novartis Pharmaceuticals Canada Inc.) was conducted in 72 healthy, adult human subjects under **fasting** conditions. The results from the 71 subjects who completed the study are summarized in the table below.

Everolimus (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_{0-72}[3] (ng.h/mL)	634.98 656.87 (25.78)	636.84 664.13 (29.35)	99.7	95.2 – 104.4
AUC_I[3] (ng.h/mL)	753.71 775.25 (24.28)	767.20 793.71 (26.89)	98.2	94.2 – 102.5
C_{max} (ng/mL)	95.82 97.96 (20.48)	93.09 96.64 (27.15)	102.9	98.0 – 108.1
T_{max}[4] (h)	0.75 (0.50 - 2.33)	0.75 (0.50 - 2.33)		
$T_{1/2}$[3,5] (h)	28.89 (20.12)	30.66 (23.53)		

[1] NAT-EVEROLIMUS (everolimus) 10 mg tablets (Natco Pharma (Canada) Inc.).
[2] AFINITOR® (everolimus) 10 mg tablets (Novartis Pharmaceuticals Canada Inc.), were purchased in Canada.
[3] n=67 subjects
[4] Expressed as median (range).
[5] Expressed as arithmetic mean (CV% only).

A double blind, balanced, randomized, two treatment, two sequence, two period, single dose, cross over, bioequivalence study comparing NAT-EVEROLIMUS 10 mg tablets (Natco Pharma (Canada) Inc.) to AFINITOR® (everolimus) 10 mg tablets (Novartis Pharmaceuticals Canada Inc.) was conducted in 96 healthy, adult, male subjects under **fed** conditions. The results from the 90 subjects who completed the study are summarized in the table below.

Everolimus (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_{0-72}[3] (ng.h/mL)	757.92 776.08 (22.29)	800.19 823.18 (24.97)	94.7	91.7 - 97.9
AUC_I[3] (ng.h/mL)	911.28 937.21 (24.72)	948.44 978.57 (25.82)	96.1	93.1 - 99.1

Everolimus (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**Confidence Interval**
C_{max} (ng/mL)	511.09 542.11 (33.78)	557.72 592.97 (36.31)	91.6	85.4 - 98.3
T_{max}[4] (h)	2.67 (1.00 - 16.00)	2.84 (0.75 - 10.00)		
$T_{1/2}$[3,5] (h)	30.87 (27.47)	29.34 (13.42)		

[1] NAT-EVEROLIMUS (everolimus) 10 mg tablets (Natco Pharma (Canada) Inc.).
[2] AFINITOR® (everolimus) 10 mg tablets (Novartis Pharmaceuticals Canada Inc.), were purchased in Canada.
[3] n=84 subjects
[4] Expressed as median (range).
[5] Expressed as arithmetic mean (CV% only).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 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.

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.

Carcinogenicity:

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.

Genotoxicity:

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity.

Reproductive and Developmental Toxicology:

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/foetotoxicity 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 of 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.

Juvenile Toxicity:

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 (exposure below the therapeutic exposure, based on AUC), 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 (exposure equivalent to the therapeutic exposure, based on AUC) for 4 weeks did not cause relevant toxicity.

17 SUPPORTING PRODUCT MONOGRAPHS

1. AFINITOR® (tablets, 2.5 mg, 5 mg, and 10 mg), submission control number (255457), Product Monograph, Novartis Pharmaceuticals Canada Inc., (November 30, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrNAT-EVEROLIMUS
Everolimus tablets

Read this carefully before you start taking **NAT-EVEROLIMUS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NAT-EVEROLIMUS**.

Serious Warnings and Precautions

- NAT-EVEROLIMUS should only be prescribed and managed by healthcare professionals who are experienced in:
  - Anticancer medicines.
  - Treating patients with Tuberous Sclerosis Complex (TSC).
- If you are taking NAT-EVEROLIMUS for the treatment of Subependymal Giant Cell Astrocytoma (SEGA) associated with TSC:
  - Your healthcare professional will monitor the level of everolimus in your blood during treatment.
  - The ideal length of treatment is not known.
  - Your condition may reappear once you stop taking NAT-EVEROLIMUS.
  - There is a risk for developmental delays and delayed puberty in patients taking everolimus.
  - NAT-EVEROLIMUS is not to be used in children and adolescents (below 18 years of age) who have liver problems.
  - **Risk of Medication Errors**: NAT-EVEROLIMUS and everolimus tablets for oral suspension are not interchangeable. The doses and the way you should be taking these two drugs are not the same. Taking everolimus for oral suspension instead of NAT-EVEROLIMUS could lead to the medicine not working properly or to more side effects.
- If you are taking NAT-EVEROLIMUS for the treatment of angiomyolipoma of the kidney associated with TSC:
  - The ideal start and length of treatment is not known.
  - Female patients who were having periods may experience secondary amenorrhea when taking everolimus. This is when periods stop happening.
- NAT-EVEROLIMUS can cause serious side effects including:
  - **Lung problems:** NAT-EVEROLIMUS can cause:
    - **Non-infectious pneumonitis** (inflammation of the lungs)
    - **Interstitial lung disease** (inflammation or scarring of the lungs)

    These lung problems can lead to death. Tell your healthcare professional **right away** if you have any new or worsening lung problems.
  - **Infections:** NAT-EVEROLIMUS can make you more likely to get an infection. Some cases have resulted in death in both adults and children. Any infections should be treated and fully healed before starting therapy with NAT-EVEROLIMUS. Tell your healthcare professional **right away** if you experience signs of infection when taking NAT-EVEROLIMUS.

- **Kidney failure** (kidney problems)**:** Cases of kidney failure (including severe kidney failure) have been reported in patients taking everolimus. Some have resulted in death. Your healthcare professional will monitor your kidney function before you start NAT-EVEROLIMUS and regularly during treatment.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

What is NAT-EVEROLIMUS used for?

NAT-EVEROLIMUS is used to treat:

- Adult women with hormone receptor-positive, HER2-negative advanced breast cancer:
  - Who are in menopause; and
  - In whom letrozole or anastrozole no longer keep their disease under control.

  For these patients, NAT-EVEROLIMUS is given with a medicine called exemestane.

- Adults with a type of pancreatic cancer known as Pancreatic Neuroendocrine Tumour (PNET) in patients whose disease cannot be treated with surgery. For these patients their disease will:
  - Be advanced, or
  - Have spread outside the pancreas, or
  - Have worsened in the last 12 months.

- Adults with a type of cancer known as Neuroendocrine Tumour (NET) that originates from the gastrointestinal (GI) tract or lungs. For these patients, their disease:
  - Cannot be treated with surgery,
  - Will be advanced or spread outside the GI tract or lung, and
  - Will have progressed.

- Adults with metastatic kidney cancer. This means their disease has spread outside of the kidney to other parts of the body. These patients will have received previous treatment with sunitinib or sorafenib, which did not work.

- Adults with an angiomyolipoma of the kidney (a kidney tumour) that is linked to a genetic condition called Tuberous Sclerosis Complex (TSC). These patients will not need immediate surgery.

- Children (1 year of age or older) and adults with Subependymal Giant Cell Astrocytoma (SEGA), a brain tumour seen with a genetic condition called Tuberous Sclerosis Complex (TSC). For these patients, their disease will have progressed and cannot be treated with surgery. As well, they will not need immediate surgery.

How does NAT-EVEROLIMUS work?

Everolimus, the active ingredient in NAT-EVEROLIMUS, works by blocking a specific enzyme that is involved in tumour cell growth, division and survival. Taking NAT-EVEROLIMUS may help to:

- Slow down the growth and spread of:
  - Kidney cancer cells.
  - Pancreatic neuroendocrine cells.
  - Breast cancer cells when taken with exemestane.
- Reduce the size of brain tumours (SEGA) and kidney tumours (angiomyolipomas) that are associated with TSC.

What are the ingredients in NAT-EVEROLIMUS?
Medicinal ingredients: Everolimus
Non-medicinal ingredients: Anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, magnesium stearate.

NAT-EVEROLIMUS comes in the following dosage forms:
Tablets: 2.5 mg, 5 mg, 7.5 mg, and 10 mg.

Do not use NAT-EVEROLIMUS if:

- You are allergic to:
  - Everolimus or any other ingredients in NAT-EVEROLIMUS.
  - Sirolimus.
  - Temsirolimus.
- You have seizures (of any type).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NAT-EVEROLIMUS. Talk about any health conditions or problems you may have, including if you:

- Are taking other medicines.
- Have any problems with your liver or have previously had any liver disease.
- Have any infections. All infections must be treated and fully healed before starting NAT-EVEROLIMUS.
- Have had hepatitis B, because it may be reactivated during your treatment with NAT-EVEROLIMUS.
- Are going to have or have recently had surgery, or still have an unhealed wound following surgery. NAT-EVEROLIMUS might affect the way your wound heals.
- Have received or are about to receive radiation treatment.
- Have kidney problems.
- Are pregnant, think you may be pregnant, or are planning to become pregnant.

Other warnings you should know about:

NAT-EVEROLIMUS can cause serious side effects, including:

- **Diabetes, worsening of diabetes, or high blood sugar:** Everolimus, the active ingredient in NAT-EVEROLIMUS, may cause a high level of sugar in the blood, including type II diabetes. Your healthcare professional will monitor your blood sugar level before you start NAT-EVEROLIMUS and regularly during treatment. More monitoring may be required if you take other medicines. If you have diabetes, closely monitor your blood sugar while taking NAT-EVEROLIMUS.

- **Stomatitis** (mouth sores)**:** Mouth sores may appear in your mouth when taking NAT-EVEROLIMUS. Stomatitis mostly occurs within the first 8 weeks of treatment. If you experience stomatitis, you might need treatment with a mouthwash or gel. Some mouthwashes and gels can make your stomatitis worse. Do not try anything without checking with your healthcare professional first.

- **Bleeding problems**: Some patients taking everolimus have reported various types of bleeding problems, including:
  - **Hemoptysis** (coughing up blood)
  - **Hematuria** (blood in the urine)
  - **Gastrointestinal (GI) bleeding** (bleeding anywhere along the GI tract between mouth and anus)

- **Intracerebral hemorrhage** (bleeding in the brain)

Some cases have resulted in death. Your risk of experiencing bleeding problems increases if you have a history of bleeding disorders, or are taking medications that:

- Have an effect on blood clotting.
- Increase the risk of bleeding.

Stop taking NAT-EVEROLIMUS and tell your healthcare professional **right away** if you experience signs of bleeding during your treatment.

- **Rhabdomyolysis** (breakdown of damaged muscle): Some cases of rhabdomyolysis have been reported in patients taking everolimus. Your healthcare professional will monitor you for signs of rhabdomyolysis during therapy with NAT-EVEROLIMUS. Stop taking NAT-EVEROLIMUS and tell your healthcare professional **right away** if you experience symptoms of rhabdomyolysis.

- **Radiation sensitization and radiation recall** (severe reactions at sites of radiation)**:** Severe radiation reactions have been observed in some patients taking everolimus. These reactions happened during or shortly after radiation therapy. Tell your healthcare professional if you:
  - Have received radiation therapy in the past.
  - Are receiving radiation therapy at the present time.
  - Will receive radiation therapy.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Vaccinations: Patients taking NAT-EVEROLIMUS should avoid:

- Receiving live vaccines.
- Close contact with those who have received live vaccines.

Your child should complete the recommended childhood series of live vaccinations before starting therapy with NAT-EVEROLIMUS.

Fertility: NAT-EVEROLIMUS may affect your ability to become pregnant or father a child. Absence of menstrual periods in females who previously had periods was observed in some female patients taking everolimus. Some male patients taking everolimus were reported having:

- Unusual levels of reproductive hormones required for the development of sperm.
- Absence of sperm.

Talk to your healthcare professional if you wish to have children in the future.

Pregnancy:

- NAT-EVEROLIMUS could harm an unborn baby.
- Use a highly effective birth control method during your treatment with NAT-EVEROLIMUS and for at least 8 weeks after your last dose.
- Continue using this method of birth control even if your periods have stopped. Your periods may stop during your treatment with NAT-EVEROLIMUS; however, it could still be possible for you to become pregnant.
- Patients who have not yet had their first period should also use effective birth control.
- Contact your healthcare professional if you:
  - Become pregnant.
  - Experience irregular or delayed periods.
  - Experience absence of periods.

Breastfeeding: It is possible that NAT-EVEROLIMUS will pass into breastmilk and could harm a breastfed baby. Do not breastfeed:

- During treatment with NAT-EVEROLIMUS.
- For two weeks after the last dose of NAT-EVEROLIMUS.

Talk to your healthcare professional about ways to feed your baby during this time.

Check-ups and testing: You will have blood tests before you start NAT-EVEROLIMUS and regularly during treatment. These tests will check:

- The amount of blood cells in your body.
- That your liver or kidneys are working properly.
- The level of electrolytes in your body.
- The amount of cholesterol or triglycerides (types of fat) in your blood.
- Your blood sugar level.

Depending on your blood test results, your healthcare professional may adjust your dose, stop or discontinue your therapy with NAT-EVEROLIMUS.

If your child takes NAT-EVEROLIMUS, your healthcare professional should monitor every 12 months their:

- Height and weight
- Reproductive development (puberty)

Your child's neurological development may also be monitored according to TSC guidelines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NAT-EVEROLIMUS:

- Ketoconazole, itraconazole, voriconazole, fluconazole – used to treat fungal infections.
- Clarithromycin, telithromycin, erythromycin – used to treat bacterial infections.
- Rifampicin, rifabutin – used to treat bacterial infections, primarily tuberculosis.
- St. John's Wort – an herbal remedy used mainly for depression.
- Phenytoin, carbamazepine, oxcarbazepine, phenobarbital, clobazam – used to treat seizures and epilepsy.
- Ritonavir, amprenavir, fosamprenavir, efavirenz, nevirapine, atazanavir, nelfinavir – used to treat viral infections, primarily HIV.
- Verapamil, diltiazem – used to treat heart conditions or high blood pressure.
- Angiotensin-converting enzyme (ACE) inhibitors – used to treat high blood pressure and other cardiovascular problems.
- Statins e.g. atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin – used to lower blood cholesterol levels.
- Cyclosporine – used to suppress the immune system.
- Aprepitant – used to prevent nausea and vomiting.
- Midazolam – used to produce sleepiness and drowsiness.
- Pimozide – used to treat mental disorders.
- Quinidine – used to treat certain types of irregular heartbeats.
- Ergotamine – used to treat migraines and headaches.

Do not take live vaccines or come in close contact with people who have received them while taking NAT-EVEROLIMUS. NAT-EVEROLIMUS can make you more likely to get an infection.

Do not eat or drink any product or juices containing grapefruit, star fruit or Seville oranges while taking NAT-EVEROLIMUS. They can affect the way the medicine works.

How to take NAT-EVEROLIMUS:

NAT-EVEROLIMUS and everolimus tablets for oral suspension are not interchangeable. Make sure you are using the correct tablets prescribed for you. Check with your healthcare professional if you are not sure. Do not switch use of the products without direction from your healthcare professional.

- Take NAT-EVEROLIMUS exactly as your healthcare professional tells you.
- Take your tablets at about the same time each day (preferably in the morning).
- Take with or without food. Be consistent in how you take NAT-EVEROLIMUS either always on an empty stomach or always with food.
- Place the tablet in your mouth and swallow whole with a glass of water. Do not chew or crush the tablets. This may affect how quickly the medicine gets into your body.

Usual dose:

The dose of NAT-EVEROLIMUS prescribed to you will depend on:

- The type of disease you have.
- Any other condition you have.
- Any other medications you are taking.
- Blood test results.
- Your height and weight.

Your healthcare professional will tell you how many NAT-EVEROLIMUS tablets to take each day. Continue taking NAT-EVEROLIMUS as long as your healthcare professional tells you.

Overdose:

If you think you, or a person you are caring for, have taken too much NAT-EVEROLIMUS, contact a healthcare professional, hospital emergency department, or a regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take NAT-EVEROLIMUS,

- Take the missed dose as soon as you remember if it's only been up to 6 hours after the time you usually take your dose.
- Skip the missed dose if it has been more than 6 hours after the time you usually take your dose. The next day, take NAT-EVEROLIMUS at your usual time. Do not take a double dose to make up for the one that you missed.

What are possible side effects from using NAT-EVEROLIMUS?

These are not all the possible side effects you may have when taking NAT-EVEROLIMUS. If you experience any side effects not listed here, tell your healthcare professional.

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

Side effects include:

- Dry mouth
- Swollen or bleeding gums
- Jaw pain
- Vomiting
- Difficulty swallowing
- Heartburn
- Pain in the abdomen
- Inflammation of the stomach or intestines
- Gas
- Constipation
- Diarrhea
- Fever
- Chills
- Common cold
- Sore throat
- Feeling sick
- Loss of appetite
- Slow healing of cuts and wounds
- Feeling weak or tired
- Toothache
- Problems with sinuses
- Weight loss
- Dehydration
- Back pain
- Joint pain
- Arm or leg pain
- Muscle pain or spasms
- Migraine
- Dizziness
- Change in tastes
- Headache
- Loss of taste
- Difficulty sleeping
- Changes in behaviour
- Cough
- Nose bleeds
- Runny nose
- Mouth or throat pain
- Shortness of breath
- Swelling of arms, hands, feet, ankles, face or other parts of the body
- Dry skin

- Skin redness
- Itchy skin
- Skin rash
- Acne
- Tingling or numbness of the skin
- Nail problems
- Hair loss
- Chest pain
- High blood pressure
- Hemorrhoids
- Cysts that become scaly, crusty or hard on your skin
- Abnormal or new patches of pigmented skin, lumps, bumps, sores or moles
- Hot flashes
- Hearing loss
- Pink eye
- Swelling of eyelids
- Cyst on the ovaries

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

NAT-EVEROLIMUS can cause abnormal blood test results. Your healthcare professional will perform blood tests before you take NAT-EVEROLIMUS and regularly during treatment. They will tell you if your test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia, Pure Red Cell Aplasia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale skin, shortness of breath, weakness, headache, dizziness		√	
Leukopenia, lymphopenia, neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		√	
Non-infectious Pneumonitis (inflammation of the lung tissue): shortness of breath, cough, fatigue, loss of appetite, unintentional weight loss			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Stomatitis (mouth sores, redness and swelling of the lining of the mouth)		√	
COMMON			
Acute respiratory failure: blue color on skin, lips, and fingernails; feel sleepy; irregular heartbeats; loss of consciousness; sudden worsening of shortness of breath			√
Allergic Reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√
Bronchospasm (when there is a sudden narrowing of the airway): difficulty breathing with wheezing or coughing			√
Cellulitis (skin infection): pain, tenderness, swelling, redness of the skin		√	
Convulsion: seizure, spasms, shaking or fits			√
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse			√
Diabetes, worsening of diabetes, or high blood sugar: increased thirst, frequent urination, extreme fatigue or lack of energy, dry skin, headache, blurred vision, tingling or numbness in the hands or feet			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Lymphoedema (build-up of lymph in tissues): Swelling of part or all of your arm (including fingers) or leg (including toes), feeling of heaviness, restricted movement, discomfort		√	
Ear infection: ear pain, tugging or pulling at your ear, trouble sleeping, trouble hearing, loss of balance, fever, fluid draining from the ear, headache, loss of appetite		√	
Heart Failure (heart does not pump blood as well as it should)**:** shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√
Hemoptysis: coughing up blood			√
Herpes Zoster virus (shingles): a painful skin rash of fluid-filled blisters, blisters appear along a strip of skin, itching		√	
Infection: fever and chills, nausea, vomiting, diarrhea, generally feeling unwell		√	
Interstitial lung disease (diseases that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough			√
Kidney failure (kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain		√	
Palmar-plantar erythrodysaesthesia syndrome (also called Hand-Foot syndrome)**:** red or swollen palms, thick calluses and blisters of the hands and soles of the feet, tingling or burning, tightness of the skin		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Pleural effusion (fluid around the lungs): chest pain, difficult or painful breathing, cough			√
Pneumonitis, pulmonary embolism, acute respiratory syndrome (lung or breathing problems): cough, chest pain, shortness of breath		√	
Tachycardia (abnormally fast heartbeat)			√
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness			√
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		√	
UNCOMMON			
Intestinal obstruction (partial or complete blockage of the small intestine): abdominal cramps or pain, loss of appetite, constipation, vomiting, inability to have a bowel movement or pass gas, swelling of the abdomen		√	
RARE			
Angioedema (swelling of tissue under the skin)**:** difficulty breathing; swollen face, hands and feet, genitals, tongue, throat; Swelling of the digestive tract causing diarrhea, nausea or vomiting		√	
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): swelling, pain, arm or leg may be warm to the touch and may appear red		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Gastrointestinal (GI) bleeding (bleeding anywhere along the GI tract between mouth and anus): blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness			√
Hematuria (blood in the urine): pink, red or very dark urine			√
Hepatitis B reactivation (a previous viral infection of the liver becomes active again): fever, skin rash, joint pain and inflammation as well as tiredness, loss of appetite, nausea, jaundice (yellowing of the skin or whites of eyes), pain in the upper right abdomen, pale stools and dark urine. Hepatitis B reactivation can be fatal in some cases		√	
Intracerebral hemorrhage (bleeding in the brain): sudden, severe headache; confusion; nausea and vomiting; seizures; loss of consciousness			√
Liver failure (serious disturbance of liver function, hepatic failure): yellow colour to skin, whites of the eyes (jaundice), bleeding easily, swollen abdomen, mental disorientation or confusion, sleepiness, coma			√
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			√
Sepsis and septic shock (infection of the blood): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding			√
VERY RARE			
Radiation sensitization and radiation recall (severe reactions at sites of radiation) including**:** - **Severe skin reactions**: skin rash, blistering, peeling or discoloration of the skin - **Pneumonitis** (inflammation of lung tissue): shortness of breath, which may be accompanied by a cough, fever or chills - **Esophagitis** (inflammation of the esophagus): difficulty or pain when swallowing, chest pain, heartburn or acid reflux			√
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

- Store at room temperature (15 – 30°C).
- Store in the original package to protect from light and moisture.
- Do not use after the expiry date shown on the box.
- Keep out of reach and sight of children and pets.

If you want more information about NAT-EVEROLIMUS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.natcopharma.ca, or by calling 1-800-296-9329.

This leaflet was prepared by Natco Pharma (Canada) Inc.

Last Revised: January 25, 2023