NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Afinitor 2.5 mg tablets

Afinitor 5 mg tablets

Afinitor 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Afinitor is everolimus.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to slightly yellow, elongated tablets with a bevelled edge and no score.

2.5 mg: The tablets are engraved with "LCL" on one side and "NVR" on the other.

5 mg: The tablets are engraved with "5" on one side and "NVR" on the other.

10 mg: The tablets are engraved with "UHE" on one side and "NVR" on the other.

Active substance

Tablets

2.5 mg: Each tablet contains 2.5 mg everolimus.

5 mg: Each tablet contains 5 mg everolimus.

10 mg: Each tablet contains 10 mg everolimus.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Afinitor is indicated for the treatment of patients with:

- Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin
- Advanced renal cell carcinoma in patients who have received prior VEGF-targeted therapy
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery. The evidence is based on change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

4.2 Posology and method of administration

Afinitor should be administered orally once daily at the same time every day, either consistently with or consistently without food (see section 5 Pharmacological properties).

Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. For patients unable to swallow tablets, Afinitor tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered (see section 5 Pharmacological properties).

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

General target population:

Adults

Dosing in advanced neuroendocrine tumours of pancreatic origin and advanced renal cell carcinoma:

Treatment with Afinitor should be initiated by a physician experienced in the use of anticancer therapies.

The recommended dose of Afinitor is 10 mg, to be taken once daily.

Management of severe and/or intolerable suspected adverse drug reactions (ADRs) may require temporary dose reduction and/or interruption of Afinitor therapy. If dose reduction is required, the suggested dose is 5 mg daily (see section 4.4 Special warnings and precautions for use).

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of Afinitor in the management of ADRs. 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 Afinitor dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[a]	Afinitor 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]; oxygen 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.

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	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%) mouthwash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
		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. hyper-glycemia, dys-lipidemia)	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] - 75,000/mm^3; <LLN[e] - 75.0 x 10^9/L)	No dose adjustment required.
	Grade 2 (<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose.
	Grade 3 (<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9/L) **OR** Grade 4 (<25,000/mm^3; <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] – 1,500/mm^3; <LLN[e] – 1.5 x 10^9/L) **OR** Grade 2 (<1,500 – 1,000/mm^3; <1.5 – 1.0 x 10^9/L)	No dose adjustment required.
	Grade 3	Temporary dose interruption until recovery to

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	(<1,000 - 500/mm^3; <1.0 - 0.5 x 10^9/L)	Grade ≤2. Re-initiate treatment at the same dose.
	Grade 4 (<500/ mm^3; <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] <1,000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than one hour.	Temporary dose interruption until recovery to Grade ≤2 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.*
[e] *Lower limit of normal (LLN)*
[f] *Absolute Neutrophil Count (ANC)*

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4/PgP inhibitors. If patients require co-administration of a moderate CYP3A4/inhibitor, reduce the Afinitor dose by approximately 50% lower. For dose reductions below the lowest available Afinitor strength, alternate day dosing should be considered. Further dose reduction to 5 mg every other day or 2.5 mg daily may be required to manage ADRs (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration of a strong CYP3A4 inducer, an Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered (based on pharmacokinetic data), using 5 mg increments. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions).

Adults and paediatrics

Dosing in TSC with subependymal giant cell astrocytoma (SEGA):

Treatment with Afinitor should be initiated by a physician 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 TSC with SEGA (see "Therapeutic Drug Monitoring" in the text below).

Titration may be required to obtain the optimal therapeutic effect. Doses that are tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus and may contribute to this variance (see section 4.5 Interactions).

Dosing is individualized based on Body Surface Area (BSA, in m^2) using the Dubois formula, where weight (W) is in kilograms and height (H) is in centimetres:

$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$

The recommended starting daily dose for Afinitor for the treatment of patients with TSC who have SEGA is 4.5 mg/m^2, rounded to the nearest strength of Afinitor Tablets. Different strengths of Afinitor Tablets can be combined to attain the desired dose.

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability. If concentrations are below 3 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability (see section 5 Pharmacological properties).

SEGA volume should be evaluated approximately 3 months after commencing Afinitor therapy, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration, and tolerability (see section 5 Pharmacological properties).

Dose modifications in TSC with SEGA

Adverse reactions: Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without dose reduction) or discontinuation of Afinitor therapy (see section 4.4 Special warnings and precautions for use). If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the Afinitor daily dose by approximately 50%. Further Afinitor dose reduction may be required to manage adverse reactions (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions). For dose reductions below the lowest available strength, alternate day dosing should be considered. Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate CYP3A4/PgP inhibitor is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the moderate CYP3A4 or PgP inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. Patients receiving concomitant strong CYP3A4 inducers (e.g., enzyme inducing antiepileptic drug) may require an increased Afinitor dose to attain trough concentrations of 3 to 15 ng/mL. If concentrations are below 3 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, checking the trough level and assessing tolerability before increasing the dose. If the strong inducer is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions).

Therapeutic drug monitoring for patients treated for TSC with SEGA

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA using a validated bioanalytical LC/MS method. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Trough concentrations should be assessed approximately 2 weeks after the initial dose, after any change

in dose, or after an initiation or change in co-administration of CYP3A4/PgP inducers and/or inhibitors (see section 4.4 Special warnings and precautions for use and section 4.5 Interactions), or after any change in hepatic (Child-Pugh) status. Dosing should be titrated with the objective of attaining everolimus trough concentrations of 3 to 15 ng/mL, subject to tolerability (see section 5 Pharmacological properties). The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

Dosing in special populations:

Paediatric population

- **Advanced neuroendocrine tumours of pancreatic origin and renal cell carcinoma:** Afinitor is not recommended for use in paediatric cancer patients.
- **SEGA:** Dosing recommendations for paediatric patients with TSC who have SEGA are consistent with those for the corresponding adult population with the exception of those patients with hepatic impairment. Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

Elderly patients (≥ 65 years)

No dosage adjustment is required (see section 5 Pharmacological properties).

Patients with renal impairment

No dosage adjustment is required (see section 5 Pharmacological properties).

Patients with hepatic impairment

Advanced neuroendocrine tumours of pancreatic origin and advanced renal cell carcinoma:

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

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

TSC with SEGA:

Patients ≥ 18 years of age

- Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B) – 25% of the dose calculated based on BSA (rounded to the nearest strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic status (Child-Pugh). Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability. If concentrations are below 3 ng/mL, the daily dose may be increased by 2.5 mg, subject to tolerability (see section 5 Pharmacological properties).

Patients < 18 years of age

Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

4.3 Contraindications

Afinitor is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see section 4.8 Undesirable effects). 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 section 4.4 Special warnings and precautions for use – 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 Afinitor 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. Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt Afinitor until resolution to less than or equal to grade 1. Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the circumstances (see section 4.2 Dose and method of administration). If toxicity recurs at grade 3, consider discontinuation of Afinitor. For cases of grade 4 non-infectious pneumonitis, Afinitor 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) may be considered.

The development of pneumonitis has also been reported at a reduced dose (see section 4.2 Dosage and method of administration).

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8 Undesirable effects). Localised and systemic infections, including pneumonia, other bacterial infections, 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 Afinitor. 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 paediatric patients (see section 4.8 Undesirable effects).

Physicians and patients should be aware of the increased risk of infection with Afinitor. Treat pre-existing infections prior to starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor.

If a diagnosis of invasive systemic fungal infection is made, discontinue Afinitor and treat with appropriate antifungal therapy.

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.

Impaired Wound Healing

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

Radiation therapy complications

Severe radiation reactions (including radiation esophagitis, radiation pneumonitis and radiation skin injury) have been reported when everolimus was used during, or shortly after radiation therapy. Caution should therefore be exercised for patients using everolimus in close temporal relationship with radiation therapy.

Additionally, radiation recall syndrome has been reported in patients on everolimus who have received prior radiotherapy.

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 section 4.3 Contraindications).

Angioedema with concomitant 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).

Stomatitis

Stomatitis, including mouth ulceration, and oral mucositis is the most commonly reported adverse drug reaction in patients treated with Afinitor (see section 4.8 Undesirable effects). Stomatitis mostly occurs within the first 8 weeks of treatment. If stomatitis occurs, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products should be avoided as they may exacerbate the condition (see section 4.2 Dose and method of administration, Table 1). Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5 Interactions).

Haemorrhage

Serious cases of haemorrhage, some with a fatal outcome, have been reported in patients treated with everolimus in the oncology setting. No serious cases of renal haemorrhage were reported in the TSC setting.

Caution is advised in patients taking Afinitor, particularly during concomitant use with active substances known to affect platelet function or that can increase the risk of haemorrhage as well as in patients with a history of bleeding disorders. Healthcare professionals and patients should be vigilant for signs and symptoms of bleeding throughout the treatment period, especially if risk factors for haemorrhage are combined.

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function. (see Laboratory tests and monitoring and section 4.8 Undesirable effects).

Laboratory tests and monitoring

Renal function

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking Afinitor (see section 4.8 Undesirable effects). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter.

Blood glucose

Hyperglycaemia has been reported in patients taking Afinitor (see section 4.8 Undesirable effects). Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. More frequent monitoring is recommended when Afinitor is co-administered with other drugs that may induce hyperglycemia. Optimal glycaemic control should be achieved before starting a patient on Afinitor.

Blood lipids

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking Afinitor. Monitoring of blood cholesterol and triglycerides prior to the start of Afinitor therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Haematological parameters

Decreased haemoglobin, lymphocytes, platelets and neutrophils have been reported in patients treated with Afinitor (see section 4.8 Undesirable effects). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

Drug-drug interactions

Co-administration with strong CYP3A4/PgP inhibitors should be avoided (see section 4.5 Interactions with other medicines).

Use caution when administered in combination with moderate CYP3A4/PgP inhibitors. If Afinitor must be co-administered with a moderate CYP3A4/PgP inhibitor, the patient should be carefully monitored for adverse effects and the dose reduced if necessary (see section 4.2 Dose and administration and section 4.5 Interactions with other medicines).

Co-administration with strong CYP3A4/PgP inducers should be avoided (see section 4.5 Interactions with other medicines). If Afinitor must be co-administered with a strong CYP3A4/PgP inducer, the patient should be carefully monitored for clinical response. Consider a dose increase of Afinitor when co-administered with strong CYP3A4/PgP inducers if alternative treatment is not possible (see section 4.2 Dose and administration and ection 4.5 Interactions with other medicines).

Exercise caution when Afinitor is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Afinitor is taken with orally administered CYP3A4 substrates with a narrow therapeutic index, the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section 4.5 Interactions with other medicines).

Hepatic impairment

Exposure to everolimus was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment (see section 5 Pharmacological properties).

Everolimus is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) for the treatment of advanced neuroendocrine tumours of pancreatic origin, or advanced renal cell carcinoma unless the potential benefit outweighs the risk (see sections 4.2 Dose and method of administration and 5 Pharmacological properties).

Afinitor is not recommended for use in patients <18 years of age with TSC who have SEGA and concomitant hepatic impairment, (Child-Pugh A, B or C) or in patients ≥18 years of age with severe hepatic impairment (Child-Pugh C) (see sections 4.2 Dose and method of administration and 5 Pharmacological properties).

Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor (see section 4.5 Interaction with other medicines). For paediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines.

4.5 Interaction with other medicines and other forms of interaction

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

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

Agents that may increase everolimus blood concentrations:

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

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

Concurrent treatment with strong CYP3A4/PgP inhibitors (including but not limited to ketoconazole, itraconazole, ritonavir, clarithromycin and telithromycin) should be avoided.

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

Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, ciclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and PgP inhibitors requires caution. Reduce the Afinitor dose if co-administered with moderate CYP3A4/PgP inhibitors (see section 4.2 Dose and method of administration and section 4.4 Special warnings and precautions for use).

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

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

Other moderate inhibitors of CYP3A4 and PgP that may increase everolimus blood concentrations include certain antifungal agents (e.g. fluconazole) and calcium channel blockers (e.g. diltiazem).

There have been reports of increased blood levels of everolimus during concomitant use with cannabidiol. Caution should be exercised when cannabidiol and everolimus are co-administered. Close monitoring of everolimus blood levels as well as for adverse events suggestive to everolimus toxicity are recommended.

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

Agents that may decrease everolimus blood concentrations:

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

Concurrent treatment with strong CYP3A4/PgP inducers should be avoided. If Afinitor must be co-administered with a strong CYP3A4/PgP inducer (e.g. rifampicin and rifabutin), it may be necessary to adjust the Afinitor dose (see section 4.2 Dose and method of administration and section 4.4 Special warnings and precautions for use).

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

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

Agents whose plasma concentration may be altered by everolimus:

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between Afinitor and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of Afinitor.

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

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$, whereas the metabolic $AUC_{(0\text{-}inf)}$ ratio (1-hydroxy-midazolam/midazolam) and the terminal $t_{1/2}$ of midazolam were not affected. This suggests that increased exposure to midazolam is due to effects of everolimus in the gastrointestinal system when both drugs are taken at the same time. Therefore, everolimus may affect the bioavailability of orally co-administered drugs which are CYP3A4 substrates. Everolimus is unlikely to affect the exposure of other CYP3A4 substrate drugs which are administered by non-oral routes such as intravenous, subcutaneous, and transdermal administrations (see section 4.4 Special warnings and precautions for use).

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) which was unlikely to have clinically significant effects on the efficacy response to everolimus in patients with advanced neuroendocrine tumours.

Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with Afinitor may therefore be less effective. The use of live vaccines should be avoided during treatment with Afinitor (see section 4.4 Special warnings and precautions for use). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Afinitor in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity (see section 5.3 Preclinical safety data). The potential risk for humans is unknown. Afinitor should not be given to pregnant women

unless the potential benefit outweighs the potential risk to the foetus. Male patients taking Afinitor should not be prohibited from attempting to father children.

Women of childbearing potential should be advised to use an effective method of contraception while receiving Afinitor, and for up to 8 weeks after ending treatment.

Lactation

It is not known whether everolimus is transferred in human breast milk. There are no reported cases of exposure to everolimus during breast-feeding in humans. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking Afinitor should therefore not breast-feed during treatment and for 2 weeks after the last dose.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed.

Based on non-clinical findings, male and female fertility may be compromised by treatment with Afinitor. (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include fatigue, asthenia and insomnia which could affect the ability to drive or use machines (see section 4.8 Undesirable effects).

4.8 Undesirable effects

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

Oncology- Summary of the safety profile

Adverse drug reaction (ADR, suspected to be related to treatment by the investigator) information is based on pooled safety data in patients receiving Afinitor (N=2470) in clinical studies including randomized, double-blind, placebo-or active comparator controlled phase III and phase-II studies related to the approved indications in oncology.

The most common ADRs (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, edema peripheral, hyperglycemia, asthenia, pruritus, weight decreased, hypercholesterolemia, epistaxis, cough and headache.

The most common grade 3 to 4 ADRs (incidence ≥1/100 to <1/10and suspected to be related to treatment by the investigator) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, pneumonia and diabetes mellitus.

Tabulated summary of adverse drug reactions from clinical trials in oncology

Table 2 presents the frequency category of ADRs reported in the pooled safety analysis. ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to

<1/1,000); very rare (<1/10,000).

Table 2 Adverse drug reactions from oncology trials

Infections and infestations	
Very common	Infections[a]
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia
Uncommon	Pancytopenia
Rare	Pure red cell aplasia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage[b], hypertension, lymphoedema[g]
Uncommon	Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis[c], epistaxis, cough
Common	Dyspnoea
Uncommon	Haemoptysis, pulmonary embolism
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis[d], diarrhoea, nausea

Common	Vomiting, dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, acne, erythema, hand-foot syndrome[e]
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria, renal failure
Uncommon	Increased daytime urination, acute renal failure
Reproductive system and breast disorders	
Common	Menstruation irregular[f]
Uncommon	Amenorrhoea[f]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, oedema peripheral
Common	Pyrexia, mucosal inflammation
Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood creatinine increased

[a]*Includes all reactions within the 'infections and infestations' system organ class including common: pneumonia, urinary tract infection; uncommon: bronchitis, herpes zoster, sepsis, abscess and isolated cases of opportunistic infections (e.g. aspergillosis, candidiasis, and hepatitis B) and rare: viral myocarditis.*

[b]*Includes different bleeding events from different sites not listed individually*

[c]*Includes common: pneumonitis, interstitial lung disease, lung infiltration; and rare: alveolitis, pulmonary alveolar hemorrhage, and pulmonary toxicity*

[d]*Includes very common: stomatitis; common: aphthous stomatitis, mouth and tongue ulceration; uncommon: glossitis, glossodynia*

[e]*reported as palmar-plantar erythrodysaesthesia syndrome*

[f]*frequency is based upon number of women age 10 to 55 yrs of age in the safety pool*

[g]*ADR was determined based on postmarketing reports. Frequency was determined based on oncology trials safety pool.*

Clinically relevant laboratory abnormalities

In the pooled double-blind phase III safety database, the following new or worsening clinically relevant laboratory abnormalities were reported with an incidence of ≥1/10 (very common, listed in decreasing

frequency):

- Haematology: haemoglobin decreased, lymphocytes decreased, white blood cells decreased, platelets decreased, and neutrophils decreased (or collectively as pancytopenia);
- Clinical chemistry: glucose (fasting) increased, cholesterol increased, triglycerides increased, AST increased, phosphate decreased, ALT increased, creatinine increased, potassium decreased and albumin decreased.

Most of the observed abnormalities (≥1/100) were mild (grade 1) or moderate (grade 2). Grade 3/4 haematology and chemistry abnormalities include:

- Haematology: lymphocytes decreased, hemoglobin decreased (very common); neutrophils decreased, platelet count decreased, white blood cells decreased (all common).
- Clinical chemistry: glucose (fasting) increased (very common); phosphate decreased, potassium decreased, AST increased, ALT increased, creatinine increased cholesterol (total) increased, triglycerides increased, albumin decreased (all common).

Tuberous sclerosis complex (TSC) – Summary of the safety profile

Adverse drug reaction (ADR, suspected to be related to treatment by the investigator) information is based on pooled data from patients with TSC receiving Afinitor (N=251) in three randomized, double-blind, placebo-controlled, phase III studies including blinded and open label treatment periods, and one non-randomized, open-label, single-arm phase II study which serve as the basis for the listed indications (see Table 3 and Indications):

Table 3 Afinitor TSC studies in the pooled safety data

Study name Indication	CRAD001C2485[a] TSC-SEGA	EXIST-1 (M2301) TSC-SEGA	EXIST-2 (M2302) TSC-renal angiomyolipoma (not an approved indication)	EXIST-3 (M2304) TSC-Seizures (not an approved indication)
Total number of patients receiving everolimus	28	111[b]	112[b]	361[c]
Median duration of exposure, months (range)	67.8 (4.7 to 83.2)	47.1(1.9 to 58.3)	46.9 (0.5 to 63.9)	30.4 (0.5 to 48.8)
Exposure in Patient-Years	146	391	391	833

[a] *Open label single arm trial, no comparator or control arm*

[b] *Total number of patients receiving everolimus during the double blind and open label extension phases including patients from the placebo arm who crossed over to everolimus treatment*

[c] *Total number of patients receiving everolimus during the core, extension and post-extension phases, including patients from placebo arm who crossed over to everolimus treatment.*

The most frequent ADRs (incidence ≥1/10) from the pooled safety database are (in decreasing order): stomatitis, pyrexia, nasopharyngitis, diarrhoea, upper respiratory tract infection, vomiting, cough, rash, headache, amenorrhoea, acne, pneumonia, urinary tract infection, sinusitis, menstruation irregular, pharyngitis, decreased appetite, fatigue, hypercholesterolemia and hypertension.

The most frequent grade 3/4 ADRs (incidence ≥1/100 to <1/10) were pneumonia, stomatitis, amenorrhea, neutropenia, pyrexia, menstruation irregular, hypophosphataemia, diarrhoea and cellulitis,

Tabulated summary of adverse reactions from clinical trials in TSC

Table 4 shows the incidence of ADRs based on pooled data in patients receiving everolimus in the TSC studies (including both the double-blind and open-label study and extension periods) covering a median duration of exposure of up to 36.8 months.ADRs are listed according to MedDRA system organ class.

Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

Table 4 Adverse drug reactions from clinical trials in TSC

Infections and infestations	
Very common	Nasopharyngitis, upper respiratory tract infection, pneumonia, urinary tract infection, sinusitis, pharyngitis,
Common	Otitis media, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis
Uncommon	Herpes zoster, sepsis, bronchitis viral
Blood and lymphatic system disorders	
Common	Anaemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypercholesterolaemia,
Common	Hypertriglyceridaemia, hyperlipidaemia, hypophosphataemia, hyperglycaemia
Psychiatric disorders	
Common	Insomnia, aggression, irritability
Nervous system disorders	
Very common	Headache
Uncommon	Dysgeusia
Vascular disorders	
Very common	Hypertension
Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Epistaxis, pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis[a], diarrhoea, vomiting
Common	Constipation, nausea, abdominal pain, flatulence, oral pain, gastritis
Skin and subcutaneous tissue disorders	

Very common	Rash[b], acne,
Common	Dry skin, dermatitis acneiform
Uncommon	Angioedema
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very common	Amenorrhoea[c], menstruation irregular[c]
Common	Menorrhagia, ovarian cyst, vaginal haemorrhage
Uncommon	Menstruation delayed[c]
General disorders and administration site conditions	
Very common	Pyrexia, fatigue
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased
Uncommon	Blood follicle stimulating hormone increased
[a]*Includes very common: stomatitis, mouth ulceration, aphthous ulcer; common: tongue ulceration, lip ulceration; uncommon: gingival pain, glossitis.* [b]*Includes very common: rash; common: rash erythematous, erythema,; uncommon: rash generalised, rash maculo-papular, rash macular.* [C]*frequency is based upon number of women 10 to 55 yrs of age while on treatment in the safety pool*	

Clinically relevant laboratory abnormalities

In the pooled TSC safety database the following new or worsening clinically relevant laboratory abnormalities reported with an incidence of ≥ 1/10 (very common, listed in decreasing frequency):

- Haematology: partial thromboplastin time increased, neutrophils decreased, haemoglobin decreased, white blood cells decreased, platelet count decreased and lymphocytes decreased.
- Clinical chemistry: cholesterol increased, triglycerides increased, AST increased, ALT increased, phosphate decreased, alkaline phosphatase increased and glucose (fasting) increased.

Most of the laboratory abnormalities were mild (grade 1) or moderate (grade 2). Grade 3/4 haematology and chemistry abnormalities included:

- Haematology: neutrophils decreased, partial thromboplastin time increased, haemoglobin decreased (common); lymphocytes decreased, platelet count decreased, and white blood cells decreased (uncommon).
- Clinical chemistry: phosphate decreased, triglycerides increased, alkaline phosphatase increased ALT increased, AST increased, cholesterol increased (common);, and glucose (fasting) increased (uncommon).

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse reactions have been derived from post-marketing experience with Afinitor via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate frequency and is therefore categorised as not known.

Injury, poisoning and procedural complications: radiation recall syndrome.

Description of selected adverse reactions

In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression.

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome) and proteinuria. Monitoring of renal function is recommended (see section 4.4 Special warnings and precautions for use).

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhea (including secondary amenorrhea).

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with pneumocystis jirovecii pneumonia (PJP), some with fatal outcome (see Warnings and precautions).

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors (see Warnings and precautions).

Special populations

Paediatrics

Paediatric use of Afinitor is recommended for patients with TSC who have SEGA and do not require immediate surgery. The safety and effectiveness of Afinitor have not been established in paediatric cancer patients.

The safety of Afinitor in paediatric patients with SEGA was demonstrated in two clinical trials.

The overall type, frequency and severity of ADRs across the age groups evaluated were similar, with the exception of infections, which were reported at a higher frequency and severity in patients below the age of 6 years. Two fatal cases due to infection were reported in patients <18 years receiving everolimus.

In Study CRAD001C2485, the frequency of ADRs across the age groups was generally similar. The long term effects of Afinitor on growth and pubertal development are unknown.

Everolimus clearance normalized to body surface area was higher in paediatric patients than in adults with SEGA (see Clinical Pharmacology). The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 3 to 15 ng/mL are the same for adult and paediatric patients with SEGA (see section 4.2 Dose and method of administration).

Geriatrics

In the pooled oncology safety database, 37% of the Afinitor-treated patients were ≥ 65 years of age.

The number of oncology patients with an ADR leading to discontinuation of Afinitor was higher in patients ≥ 65 years of age (20% vs. 13%). The most common ADRs (≥1/100) leading to discontinuation were pneumonitis (including interstitial lung disease), stomatitis, fatigue, and dyspnea.

4.9 Overdose

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2,000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Protein kinase inhibitors, ATC code: L01XE10.

Mechanism of action

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

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

Pharmacodynamic properties

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor, specifically targeting the mTOR-raptor signal transduction complex (mTORC1). mTOR is a key serine-threonine kinase in the PI3K /AKT signalling cascade, a pathway known to be dysregulated in the majority of human cancers. Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signalling capacity. mTORC1 signalling is effected through modulation of the phosphorylation of downstream effectors, the best characterised of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumour growth and expression of hypoxia-inducible factors (e.g. HIF-1 transcription factors); the latter resulting in reduced expression of factors involved in the potentiation of tumour angiogenic processes (e.g. the vascular endothelial growth factor VEGF). Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells. Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumour cell proliferation, glycolysis and angiogenesis in solid tumours *in vivo*, and thus provides two independent mechanisms for inhibiting tumour growth: direct antitumour cell activity and inhibition of the tumour stromal compartment.

In a mouse neuronal model of TSC in which TSC1is ablated in most neurons during cortical development, everolimus improved median survival from 33 days to more than 100 days, and behaviour, phenotype, and weight gain all also markedly improved. There was brain penetration, with accumulation over time with repetitive treatment, and effective reduction of levels of phospho-S6, a downstream marker of mTORC1. Neurofilament abnormalities, myelination, and cell enlargement were all improved by the treatment, although dysplastic neuronal features persisted, and there were only modest changes in dendritic spine density and length. Mice treated with everolimus for 23 days only (postnatal days 7–30) displayed a persistent improvement in phenotype, with median survival of 78 days. In summary, everolimus is a highly active in this neuronal model of TSC, with benefit apparently attributable to

effects on mTORC1 and Akt signaling and, consequently, cell size and myelination.

Clinical efficacy and safety

Advanced neuroendocrine tumours of pancreatic origin

RADIANT-3 (Study CRAD001C2324), a randomised, double-blind, multicentre phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with progressive, unresectable or metastatic, well or moderately differentiated pancreatic neuroendocrine tumours (pNET), demonstrated a statistically significant clinical benefit of Afinitor over placebo by a 2.4-fold prolongation in median progression-free-survival PFS (11.04 months versus 4.6 months), resulting in a 65% risk reduction in PFS (HR 0.35; 95%CI: 0.27, 0.45; one sided p<0.0001) (see Table 5 and Figure 1).

RADIANT-3 enrolled patients with advanced pNET whose disease had progressed within the prior 12 months, was well or moderately differentiated, and unresectable or metastatic. Patients were stratified by prior cytotoxic chemotherapy (yes/no) and by WHO performance status (0 vs. 1 and 2). Treatment with somatostatin analogs 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 radiological review. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label Afinitor.

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

In total, 410 patients were randomised 1:1 to receive either Afinitor 10mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55.4% male, 78.5% Caucasian).

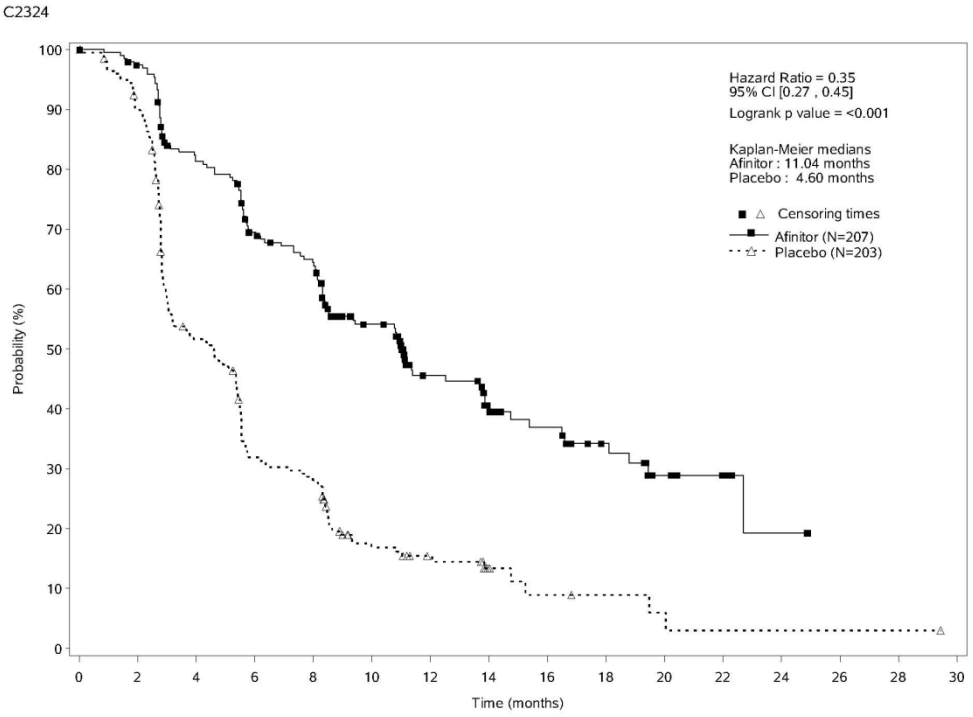
Table 5 RADIANT-3 – Progression Free Survival results

Analysis	N	Afinitor N=207	Placebo N=203	Hazard Ratio (95%CI)	p-value[b]
	410	Median progression-free survival (months) (95% CI)			
Investigator radiological review		11.04 (8.41 to 13.86)	4.60 (3.06 to 5.39)	0.35 (0.27 to 0.45)	<0.0001
Independent radiological review[a]		11.40 (10.84 to 14.75)	5.39 (4.34 to 5.55)	0.34 (0.26 to 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 1 RADIANT-3 – Kaplan-Meier progression-free survival curves (investigator radiological review)



Eighteen-months PFS rates were 34.2% for Afinitor therapy compared to 8.9% for placebo.

The overall survival results are not yet mature and no statistically significant difference in OS was noted (HR=0.99 (95% CI 0.68 to 1.43) in an updated analysis). Crossover of >74% of patients from placebo to open-label Afinitor following disease progression likely confounded the detection of any treatment-related difference in OS.

Advanced neuroendocrine tumours of non-pancreatic origin

RADIANT-2 (Study CRAD001C2325), a randomised, double-blind, multicentre phase III study of Afinitor plus depot octreotide (Sandostatin LAR®) versus placebo plus depot octreotide in patients with advanced neuroendocrine tumours (carcinoid tumour) primarily of gastrointestinal or lung origin showed evidence of borderline clinical efficacy of Afinitor over placebo by a 5.1-month prolongation in median PFS (16.43 months versus 11.33 months; HR 0.77; 95%CI: 0.59 to 1.00; one sided p=0.026), resulting in a 23% risk reduction in primary PFS (see Table 6 and Figure 2). The efficacy data shown are insufficient in the context of the product's safety profile and lack of evidence of overall survival benefit in RADIANT-2 to support approval in patients with non-pancreatic advanced neuroendocrine tumours.

RADIANT-2 enrolled patients with advanced neuroendocrine tumours (carcinoid tumour) primarily of gastrointestinal or lung origin whose disease had progressed within the prior 12 months and had a history of secretory symptoms. 80.1% of the patients in the Afinitor group received somatostatin analog therapy prior to study entry compared to 77.9% in the placebo group.

The primary endpoint is PFS evaluated by RECIST (version 1.0) as per Independent radiological review. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label Afinitor.

Secondary endpoints include safety, objective response, response duration, and overall survival.

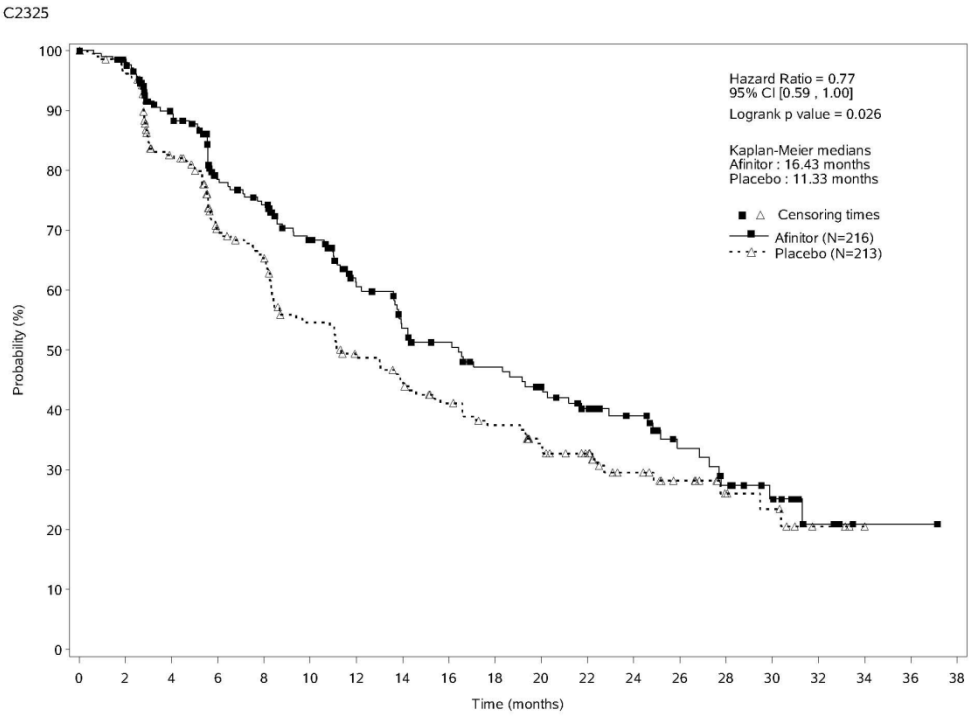
In total, 429 patients were randomised 1:1 to receive either Afinitor 10mg/day (n=216) or placebo (n=213), in addition to depot octreotide (Sandostatin LAR®, administered intramuscularly) 30 mg every 28 days. Notable imbalances were evident for several important baseline prognostic factors, mainly in favour of the placebo group.

Table 6 RADIANT-2 – Progression Free Survival results

Analysis	N	Afinitor[a] N=216	Placebo[a] **N=213**	**Hazard Ratio (95%CI)**	**p-value[c]**
	429	Median progression-free survival (months) (95% CI)			
Independent radiological review[b]		16.43 (13.67 to 21.19)	11.33 (8.44 to 14.59)	0.77 (0.59 to 1.00)	0.026
Investigator radiological review		11.99 (10.61 to 16.13)	8.61 (8.08 to 11.14)	0.78 (0.62 to 0.98)	0.018

[a] Plus depot octreotide (Sandostatin LAR®)
[b]Includes adjudication for discrepant assessments between investigator radiological review and central radiological review
[c]One-sided p-value from stratified log-rank test

Figure 2 RADIANT-2 – Kaplan-Meier progression-free survival curves (independent radiologic review)



Eighteen-months PFS rates were 47.2% for Afinitor therapy plus depot octreotide (Sandostatin LAR®) compared with 37.4% for placebo plus depot octreotide (Sandostatin LAR®).

The overall survival results are not yet mature and no statistically significant difference in OS was noted (HR for pre-specified adjusted analysis =1.05 (95% CI 0.79 to 1.39) in an updated analysis). Crossover

of >58% of patients from placebo to open-label Afinitor following disease progression likely confounded the detection of any treatment-related difference in OS.

Advanced renal Cell Carcinoma

RECORD-1 (CRAD001C2240), a phase III, international, multicentre, randomised, double-blind study comparing Afinitor 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and 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 VEGFR-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 Afinitor 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were randomised 2:1 to receive Afinitor (n=277) or placebo (n=139). Demographics were well balanced (pooled median age 61 years [range 27 to 85], 77% male, 88% Caucasian, 74% one prior VEGFR-TKI therapy).

Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 7 and Figure 3).

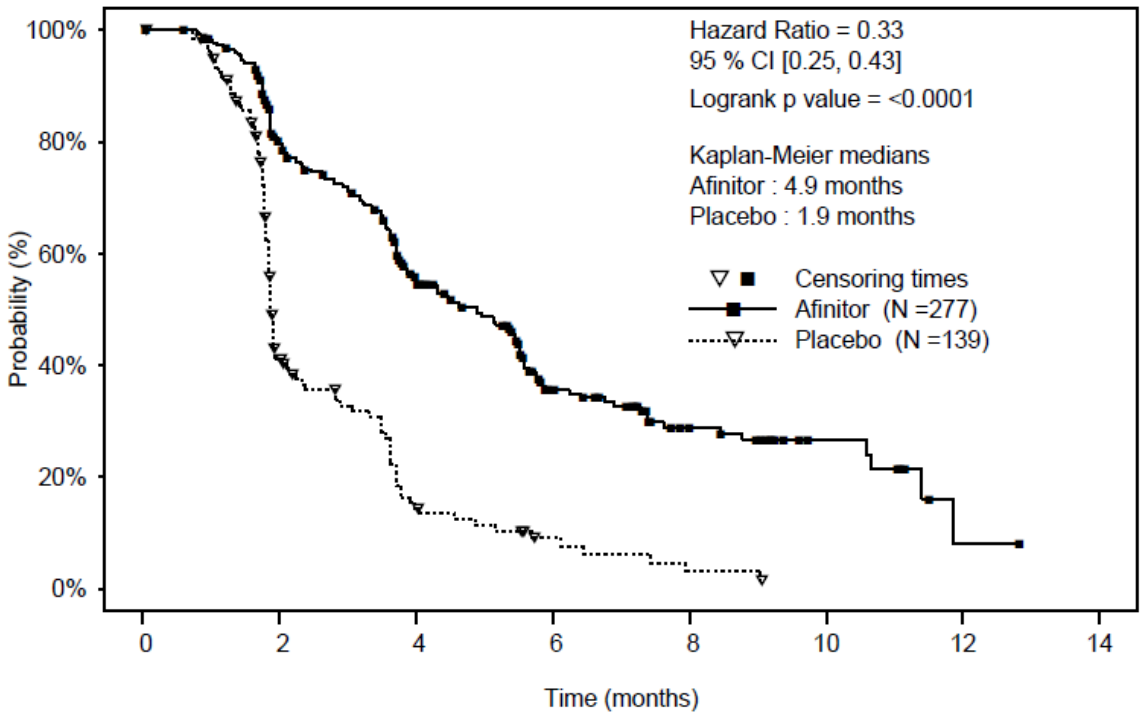
Table 7 RECORD-1- Progression Free Survival results

Population	**N**	**Afinitor N=277**	**Placebo N=139**	**Hazard Ratio (95%CI)**	**p-value**
		Median progression-free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 [a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6 to 5.8)	1.9 (1.8 to 2.2)	0.32 (0.25 to 0.41)	<0.001 [a]
MSKCC prognostic score					
Favourable risk	120	5.8 (4.0 to 7.4)	1.9 (1.9 to 2.8)	0.31 (0.19 to 0.50)	<0.001 [b]
Intermediate risk	235	4.5 (3.8 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.001 [b]
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.007 [b]
Prior VEGFR-TKI therapy					
Sunitinib only	184	3.9 (3.6 to 5.6)	1.8 (1.8 to 1.9)	0.34 (0.23 to 0.51)	<0.001 [b]

Population	N	Afinitor N=277	Placebo N=139	Hazard Ratio (95% CI)	p-value
Sorafenib only	124	5.9 (4.9 to 11.4)	2.8 (1.9 to 3.6)	0.25 (0.16 to 0.42)	<0.001 [b]
Sunitinib and sorafenib	108	4.0 (3.6 to 5.4)	1.8 (1.8 to 2.0)	0.32 (0.19 to 0.54)	<0.001 [b]

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

Figure 3 RECORD-1- Kaplan-Meier progression-free survival curves



Six-month PFS rates were 36% for Afinitor therapy compared with 9% for placebo.

Confirmed objective tumour responses were observed in 5 patients (2%) receiving Afinitor while none were observed in patients receiving placebo. The progression-free survival advantage therefore primarily reflects the population with disease stabilisation (corresponding to 67% of the Afinitor treatment group).

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

A strong trend is evident supporting better quality of life among patients receiving Afinitor as measured by disease-related symptoms (HR 0.75; 95% CI: 0.53 to 1.06; p=0.053).

Tuberous sclerosis complex (TSC) with Subependymal giant cell astrocytoma (SEGA)

Phase III trial in patients with TSC who have SEGA

EXIST-1 (Study CRAD001M2301), a randomised, double-blind, multicentre phase III study of Afinitor

versus placebo was conducted in patients with TSC who have SEGA, irrespective of age. Patients were randomised in a 2:1 ratio to receive either Afinitor or matching placebo. Presence of at least one SEGA lesion ≥ 1.0 cm in longest diameter using MRI (based on local radiology assessment) was required for entry. In addition, serial radiological evidence of SEGA growth, presence of a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus was required for entry.

The primary efficacy endpoint was SEGA response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomisation (yes/no).

Key secondary endpoints in hierarchal order of testing included the absolute change in frequency of total seizure events per 24-hour EEG from baseline to Week 24, time to SEGA progression, and skin lesion response rate.

A total of 117 patients were randomised, 78 to Afinitor and 39 to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies. Median age was 9.5 years (range: 0.8 to 26.6; 69.2% were 3 to < 18 years at enrolment; 17.1% were < 3 years at enrolment), 57.3% were male, and 93.2% were Caucasian. Of the enrolled patients, 79.5% had bilateral SEGAs, 42.7% had ≥ 2 target SEGA lesions, 25.6% had inferior growth, 9.4% had evidence of deep parenchymal invasion, 6.8% had radiographic evidence of hydrocephalus, and 6.8% had undergone prior SEGA-related surgery; 94.0% had skin lesions at baseline and 37.6% had target renal angiomyolipomas (at least one angiomyolipoma ≥ 1 cm in longest diameter). The median duration of blinded study treatment was 9.6 months (range: 5.5 to 18.1) for patients receiving Afinitor and 8.3 months (range: 3.2 to 18.3) for those receiving placebo.

Results showed that Afinitor was superior to placebo for the primary endpoint of best overall SEGA response (p<0.0001). Response rates were 34.6% (95% CI: 24.2, 46.2) for the Afinitor arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (Table 8). In addition, all 8 patients on the Afinitor arm who had radiographic evidence of hydrocephalus at baseline had a decrease in ventricular volume and no patient required surgical intervention during the course of this study.

Table 8 EXIST-1 – SEGA response

	AFINITOR N=78	**Placebo N=39**	**p-value**
Primary analysis			
SEGA response rate1,2 - (%)	34.6	0	<0.0001
95% CI	24.2, 46.2	0.0, 9.0	
Best overall SEGA response - (%)			
Response	34.6	0	
Stable disease	62.8	92.3	
Progression	0	7.7	
Not evaluable	2.6	0	

[1] Per independent central radiology review

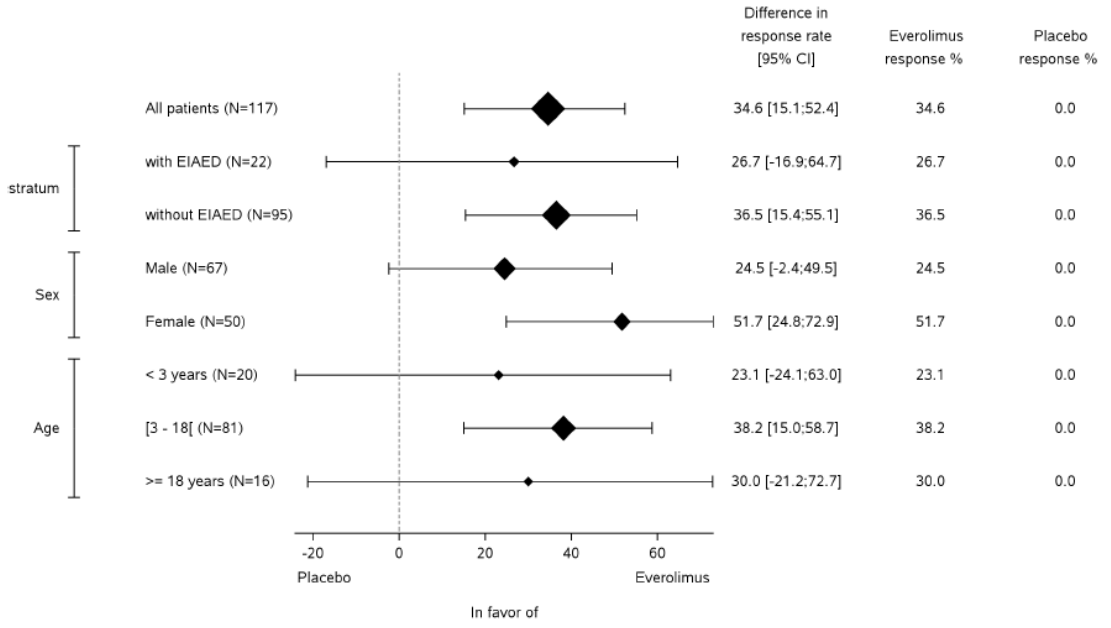
[2] SEGA responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of SEGA volume relative to baseline, plus no unequivocal worsening of non-target SEGA lesions, plus absence of new SEGA ≥ 1 cm in longest diameter, plus no new or worsening hydrocephalus

Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, and age) (Table 9, Figure 4).

Table 9 EXIST-1 - SEGA response by subgroup

Subgroup	Afinitor		Placebo		Difference in response rates (95% CI)
	N	Responders %	N	Responders %	
All patients	78	34.6	39	0	34.6 (15.1, 52.4)
Modified strata					
EIAED use	15	26.7	7	0	26.7 (-16.9, 64.7)
No EIAED use	63	36.5	32	0	36.5 (15.4, 55.1)
Sex					
Male	49	24.5	18	0	24.5 (-2.4, 49.5)
Female	29	51.7	21	0	51.7 (24.8, 72.9)
Age					
<3 years	13	23.1	7	0	23.1 (-24.1, 63.0)
3-<18 years	55	38.2	26	0	38.2 (15.0, 58.7)
≥18 years	10	30.0	6	0	30.0 (-21.2, 72.7)

Figure 4 EXIST-1 - Forest plot of SEGA response by subgroup

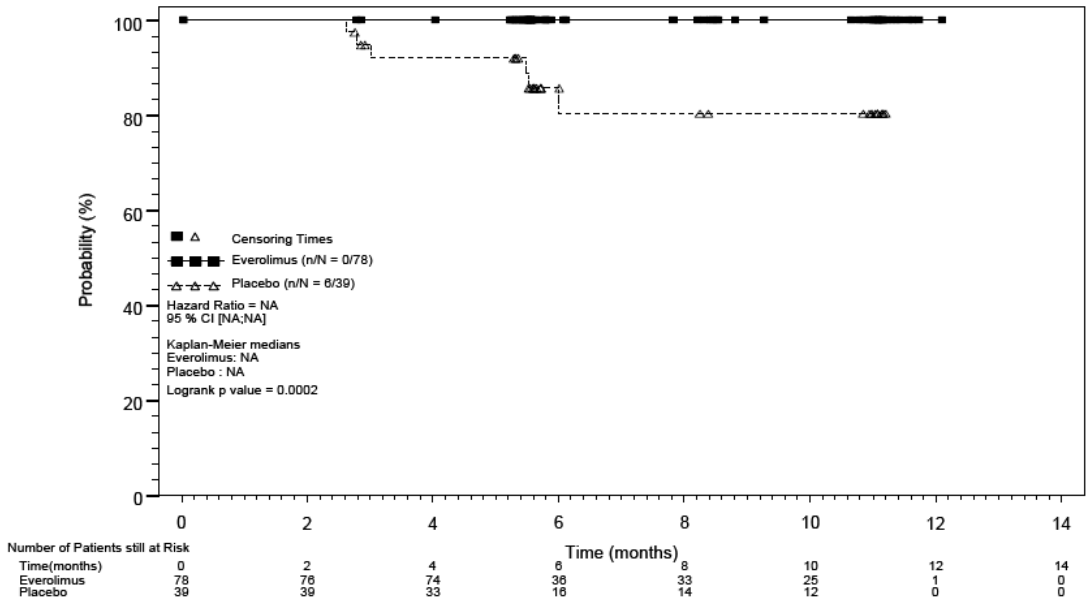


SEGA shrinkage was evident within the initial 12 weeks of treatment with Afinitor: 73.0% of patients had ≥ 30% reductions and 29.7% had ≥ 50% reductions at the time of the first radiological evaluation (Week 12). Sustained reductions were evident at subsequent timepoints; at Week 24, 78.4% of patients had ≥ 30% reductions and 41.9% had ≥ 50% reductions.

Analysis of the first key secondary endpoint, change in seizure frequency, was inconclusive.

Median time to SEGA progression based on central radiology review was not reached in either treatment arm. Progressions were only observed in the placebo arm (15.4%; unadjusted p=0.0002) (Figure 5). Estimated progression-free rates at 6 months were 100% for the Afinitor arm and 85.7% for the placebo arm.

Figure 5 EXIST-1 - Kaplan-Meier plot of time to SEGA progression1,2



[1] Per independent central radiology review

[2] SEGA progression was defined as: ≥ 25% increase in the sum of SEGA volume relative to baseline, or unequivocal worsening of non-target SEGA lesions, or appearance of new SEGA ≥ 1.0 cm in longest diameter, or new or worsening hydrocephalus

Afinitor demonstrated clinically meaningful improvements in skin lesion response (unadjusted p=0.0004), with response rates of 41.7% (95% CI: 30.2, 53.9) for the Afinitor arm and 10.5% (95% CI: 2.9, 24.8) for the placebo arm (Table 10).

Table 10 EXIST-1 - best overall skin lesion response

	Afinitor N=72	**Placebo N=38**	**p-value**
Skin lesion response rate[1,2,3,4] - %	41.7	10.5	0.0004
95% CI	(30.2, 53.9)	(2.9, 24.8)	
Best overall skin lesion response - %			
Complete clinical response	0	0	
Partial response	41.7	10.5	
Stable disease	58.3	86.8	
Progression	0	0	
Not evaluable	0	2.6	

[1] Complete clinical response or partial response
[2] Per investigator
[3] Skin lesion response was determined for the 110 patients with ≥ 1 skin lesion at baseline.
[4] Skin lesion response was defined as ≥ 50% improvement in appearance of skin lesions by Physician's Global Assessment of Clinical Condition.

Phase II trial in patients with TSC who have SEGA

A prospective, open-label, phase II study was conducted to evaluate the safety and efficacy of Afinitor in patients with SEGA. Serial radiological evidence of SEGA growth was required for entry.

Change in SEGA volume during the core 6-month treatment phase, as assessed via an independent central radiology review, was the primary efficacy endpoint. After the core treatment phase, patients could enter into the extension treatment phase where SEGA volume was assessed every 6 months.

In total, 28 patients received treatment with Afinitor; median age was 11 years (range 3 to 34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA including 12 patients with SEGA in the contralateral ventricle.

Afinitor was associated with a clinically relevant and statistically significant reduction in primary SEGA volume at 6 months relative to baseline ($p<0.001$). Tumour shrinkage was most rapid during the initial 3 months of treatment with evidence of a sustained response at subsequent timepoints (see Table 11). No patient developed new lesions, worsening hydrocephalus, increased intracranial pressure, and none required surgical resection or other therapy for SEGA.

Table 11 C2485 - Response of primary SEGA lesion to Afinitor therapy

SEGA volume (cm^3)	**Independent central review**							
	Baseline N=28	**Month 3 N=26**	**Month 6 N=27**	**Month 12 N=26**	**Month 18 N=26**	**Month 24 N=24**	**Month 30 N=17**	**Month 36 N=9**
Primary tumour volume								
Mean (standard deviation)	2.45 (2.813)	1.47 (1.646)	1.33 (1.497)	1.26 (1.526)	1.28 (1.110)	1.19 (1.042)	1.49 (1.469)	1.17 (0.796)
Median	1.74	0.84	0.93	0.84	0.81	0.94	1.05	0.97
Range	0.49 - 14.23	0.25 - 8.32	0.31 - 7.98	0.29 - 8.18	0.33 - 5.20	0.20 - 4.63	0.40 - 6.27	0.39 - 2.70
Reduction from baseline								
Mean (standard deviation)		1.08 (1.338)	1.19 (1.433)	1.07 (1.276)	1.25 (1.887)	1.25 (1.994)	1.47 (2.123)	1.73 (1.710)
Median		0.63	0.83	0.85	0.69	0.71	1.04	1.34
Range		-0.12 - 5.91	0.06 - 6.25	0.02 - 6.05	-0.24 - 9.03	-0.55 - 9.60	-0.78 - 7.96	0.15 - 4.75
Percentage reduction from baseline, n (%)								
≥ 50%		10 (38.5)	9 (33.3)	9 (34.6)	11 (42.3)	12 (50.0)	7 (41.2)	5 (55.6)
≥ 30%		17 (65.4)	21 (77.8)	20 (76.9)	18 (69.2)	19 (79.2)	11 (64.7)	7 (77.8)
> 0%		25 (96.2)	27 (100.0)	26 (100.0)	24 (92.3)	23 (95.8)	15 (88.2)	9 (100.0)
No change		0	0	0	1 (3.8)	0	0	0
Increase		1 (3.8)	0	0	1 (3.8)	1 (4.2)	2 (11.8)	0

The primary analysis was supported by the:

- Change in primary SEGA volume as per local investigator assessment ($p<0.001$), with 75% and 39% of patients experiencing reductions of ≥ 30% and ≥ 50%, respectively
- Change in total SEGA volume as per independent central review ($p<0.001$) or local investigator assessment ($p<0.001$)

One patient met the pre-specified criteria for treatment success (> 75% reduction in SEGA volume) and was temporarily taken off trial therapy; however, SEGA re-growth was evident within 3 months and treatment was restarted.

Long-term follow-up to a median duration of 34.2 months (range: 4.7 to 47.1) demonstrated sustained efficacy.

5.2 Pharmacokinetic properties

Pharmacokinetic properties

Absorption

After administration of Afinitor tablets in patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional 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.

Food effect

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

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given Afinitor 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Following intravenous administration in a rat model, everolimus was shown to cross the blood-brain barrier in a non-linear dose-dependent manner, suggesting saturation of an efflux pump at the blood-brain barrier. Brain penetration of everolimus has also been demonstrated in rats receiving oral doses of everolimus.

Biotransformation/Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, it is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself. Hence, the parent substance is considered to contribute the majority of the overall pharmacological activity of everolimus.

Elimination

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

Steady-state pharmacokinetics

After administration of Afinitor tablets in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg with a daily dosing regimen. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg daily. t_{max} occurs at 1 to 2

hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on a daily-regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Pharmacokinetics in special patient groups

Patients with hepatic impairment

The safety, tolerability and pharmacokinetics of Afinitor were evaluated in a single oral dose study of everolimus in 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1.6-fold, 3.3-fold, and 3.6-fold increase in exposure (i.e. $AUC_{(0-inf)}$) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment , respectively. Simulations of multiple dose pharmacokinetics support the dosing recommendations in hepatic impaired subjects based on their Child Pugh status. Dose adjustment is recommended for patients with hepatic impairment (see sections 4.4 Special warnings and precautions for use and section 4.2 Dose and method of administration).

Patients with renal impairment

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

Paediatric patients

- There is no indication for use of Afinitor in the paediatric cancer population (see section 4.2 Dose and method of administration).
- In patients with TSC who have SEGA receiving Afinitor tablets, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.
- In patients with TSC who have SEGA receiving Afinitor tablets, the everolimus geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10-18 years were statistically lower than those observed in adults (> 18 years of age), suggesting that everolimus clearance was higher in younger patients.

Elderly patients

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.

Ethnicity

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.

Exposure-response relationships

There was a moderate correlation between the decrease in the phosphorylation of 4E-BP1 (P4E-BP1) in tumour tissue and the average everolimus C_{min} at steady state in blood after daily administration of 5 or 10 mg everolimus. Further data suggest that the inhibition of phosphorylation of the S6 kinase is very sensitive to the mTOR inhibition by everolimus. Inhibition of phosphorylation of elF-4G was complete at all C_{min} values after the 10 mg daily dose.

In patients with TSC who have SEGA, a model based analysis indicated that a 2-fold C_{min} increase led to a 13% (95% CI: -18.2%, -7.5%) tumour size reduction from baseline, which was statistically significant at a 5% level.

5.3 Preclinical safety data

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. 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.

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 and which caused a reduction in male fertility. There was evidence of reversibility.

In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the $AUC_{0\text{-}24h}$ in patients receiving the 10 mg daily dose) resulted in increased incidence of pre-implantation loss.

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.

In juvenile rat toxicity studies at doses as low as 0.15 mg/kg/day, systemic toxicity included decreased body weight gain and food consumption, and delayed attainment of some of the developmental landmarks at all doses, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding (where young animals appeared more susceptible, it appears that there is o significant difference in the sensitivity of juvenile animals to the adverse effects of everolimus as compared to adult animals at doses of 0.5 to 5 mg/kg/day. No relevant toxicity was evident in juvenile monkeys at does up to 0.5 mg/kg/day for 4-weeks.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure from a 10 mg daily dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene (E321)
Magnesium stearate
Lactose monohydrate
Hypromellose
Crospovidone
Lactose anhydrous.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC

Store in the original package in order to protect from light and moisture.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

Blister packs containing 30, 60* and 90* tablets. Each blister strip contains 10 tablets.

*Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

The extent of absorption of everolimus through topical exposure is not known. Therefore. caregivers are advised to avoid contact with suspensions of Afinitor tablets. Wash hands thoroughly before and after preparation of either suspension.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149
Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

24 September 2009

10. DATE OF REVISION OF THE TEXT

24 October 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of change
4.5	Addition of interaction with cannabidiol

Internal document code: (afi311022iNZ.doc) based on CDS 31 May 2021.