Attachment 1: Product information for AusPAR Afinitor Novartis Pharmaceuticals Australia Pty Ltd PM-2012-00337-3-4 Final 22 August 2013. This Product Information was approved at the time this AusPAR was published.

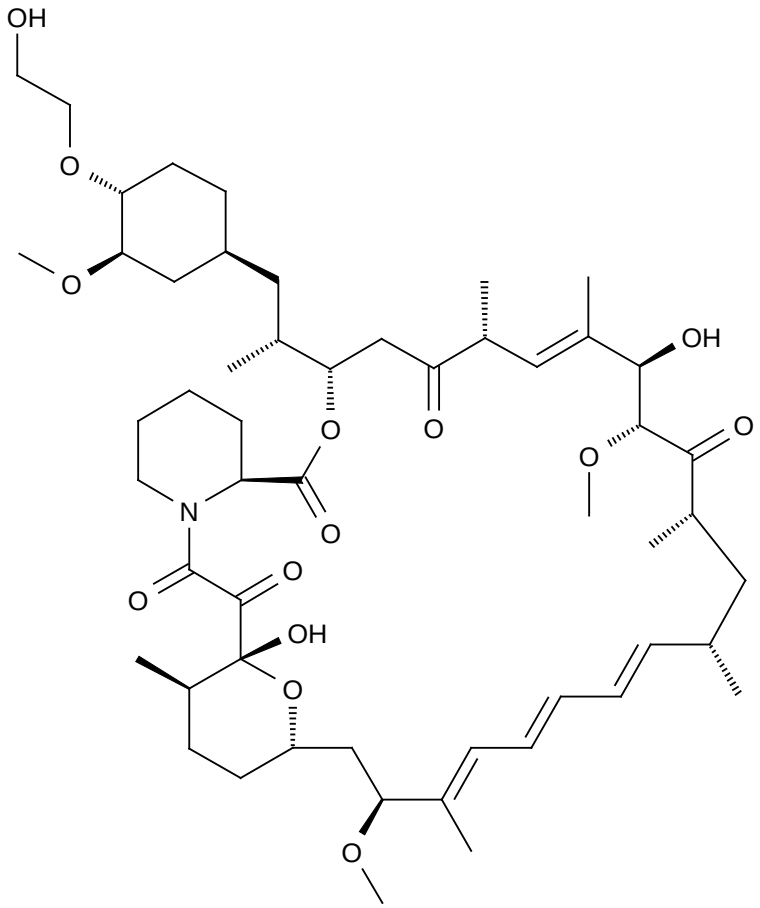
AFINITOR®
(everolimus)

NAME OF THE MEDICINE

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.

The structural formula of everolimus is:



DESCRIPTION

Everolimus is a white to faintly yellow powder practically insoluble in water but soluble in organic solvents such as ethanol and methanol.

CAS number: 159351-69-6

Excipients: (Tablets) Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.

PHARMACOLOGY

Pharmacodynamics

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.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *In vitro* studies show that oestrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination of everolimus with Akt, HER2, or aromatase inhibitors synergistically enhances the anti-tumour effect of everolimus.

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 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 an inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells.

In a mouse neuronal model of TS in which TSC1 is ablated in most neurons during cortical development, everolimus was shown to markedly improve survival and neurological function following repeated intraperitoneal administration.

Pharmacokinetics

Absorption

In patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg. AUC shows dose-proportionality over the 5 to 70 mg dose range.

Effects of Food

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

Distribution

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

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

Metabolism

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

Excretion

No specific excretion studies have been undertaken in cancer patients; however, data are available from the transplant setting. Following the administration of a single dose of radiolabeled everolimus in conjunction with cyclosporin, 80% of the radioactivity was

recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in the urine or faeces.

Steady-state pharmacokinetics

After daily administration of everolimus in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on the daily regimen. Mean elimination half-life is approximately 30 hours.

Hepatic impairment

The average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh Class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The impact of severe hepatic impairment (Child-Pugh Class C) has not been assessed (see Dosage and Administration and Precautions).

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.

Paediatrics

There is no relevant indication for use of Afinitor in the paediatric cancer population (see Dosage and Administration). In patients with SEGA, intra-patient steady-state trough concentrations were dose-proportional at daily doses of 1.5 to 14.6 mg/m2 (see Dosage and Administration).

Elderly

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

Ethnicity

Asian patients with neuroendocrine tumours (NETs) showed a consistent pattern of reduced clearance, and higher AUC values, with higher C_{min} values compared to non-Asian patients (see Precautions).

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 SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, as responses have been observed at trough concentrations as low as 2 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary (see Dosage and Administration).

CLINICAL TRIALS

Hormone receptor-positive advanced breast cancer

BOLERO-2 (Study CRAD001Y2301) a randomized, double-blind, multicentre phase III study of Afinitor + exemestane versus placebo + exemestane was conducted in postmenopausal women with oestrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer (ABC) with recurrence[1] or progression[2] following prior therapy with letrozole or anastrozole. A total of 724 patients were randomized in a 2:1 ratio to receive either Afinitor (10 mg daily) plus exemestane (25 mg daily) (n=485) or placebo plus exemestane (25 mg daily) (n=239). 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), based on the investigators (local radiology) assessment. Supportive PFS analyses were based on an independent central radiology review.

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Clinical Benefit Rate (CBR), Safety, change in Quality of Life (QoL) and time to ECOG PS deterioration. Additional endpoints included changes in bone turnover markers at 6 and 12 weeks.

The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics and history of prior anti-neoplastic usages. The median age of patients was 61 years (range 28 to 93) and 75% were Caucasian.

The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 months and 3.2 months in the Afinitor and placebo arms, respectively.

[1] Recurrence while on or within 12 months of end of adjuvant treatment with letrozole or anastrozole.

[2] Progression while on or within one month of the end of letrozole or anastrozole treatment for ABC.

Patients in the placebo+exemestane arm did not cross-over to Afinitor at the time of progression. The median duration of treatment was 29.5 weeks (range 1.0-123.3 weeks) for patients receiving Afinitor + exemestane and 14.1 weeks (range 1.0-101.0 weeks) for the placebo + exemestane group.

The study demonstrated a statistically significant increase in PFS with Afinitor + exemestane compared with placebo + exemestane based on the investigator assessment (Table 1 and Figure 1). The independent assessment was supportive.

Table 1 BOLERO-2 – efficacy results

Analysis	**Afinitor[a] N = 485**	**Placebo[a] N = 239**	**Hazard ratio**	**P-value**
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38 (0.31 to 0.48)	<0.0001
Best overall response (%, 95% CI)				
Objective response rate (ORR)[b]	12.6 (9.8 to 15.9)	1.7 (0.5 to 4.2)	n/a[d]	<0.0001[e]
Clinical benefit rate (CBR)[c]	51.3 (46.8 to 55.9)	26.4 (20.9 to 32.4)	n/a[d]	<0.0001[e]

a Plus exemestane

b Objective response rate = proportion of patients with CR or PR

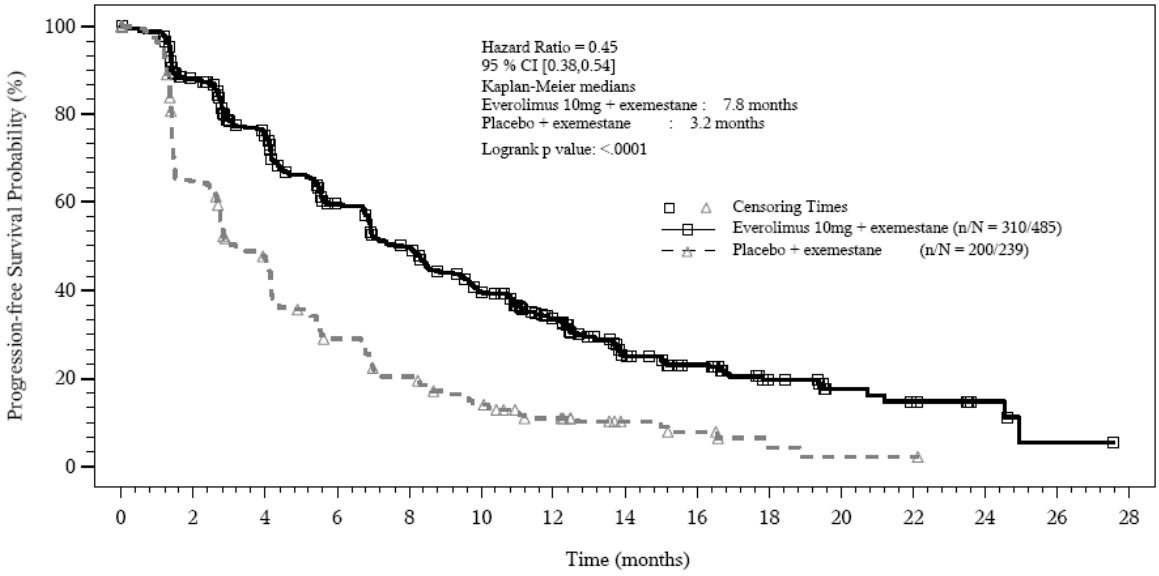
c Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

d not applicable

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

Overall Survival (OS) data are not mature at the time of the interim analysis and no statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)].

Figure 1 BOLERO-2 - Kaplan-Meier progression-free survival curves (investigator radiological review)



No. of patients still at risk

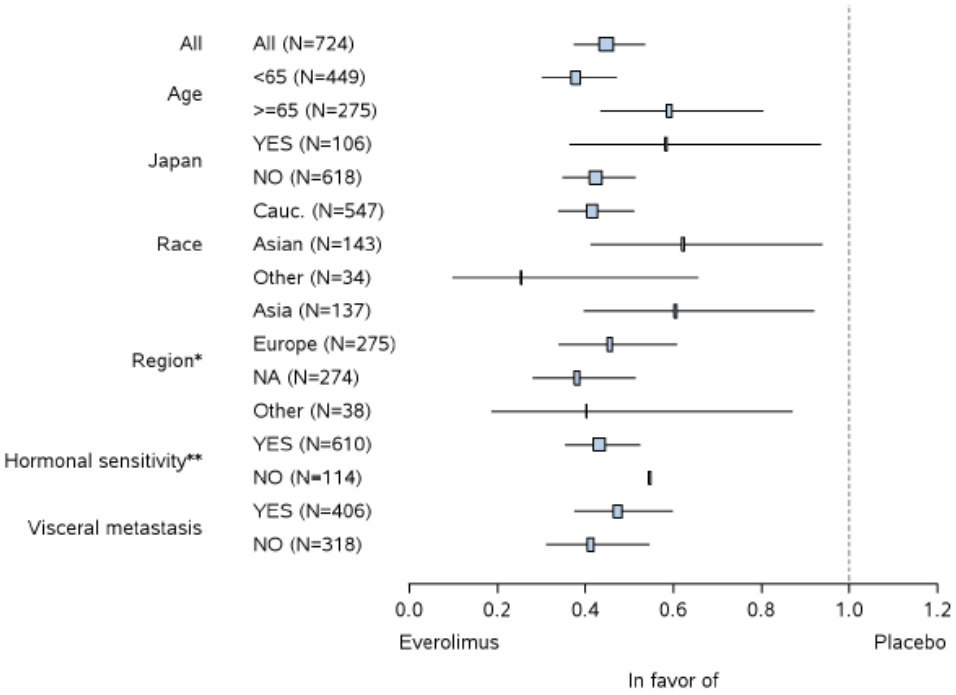
Time (wks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Everolimus	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
Placebo	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

-One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.

Nine-month PFS rates were 44% of patients receiving Afinitor + exemestane compared with 16% in the placebo + exemestane arm at a median follow-up of 17.7 months.

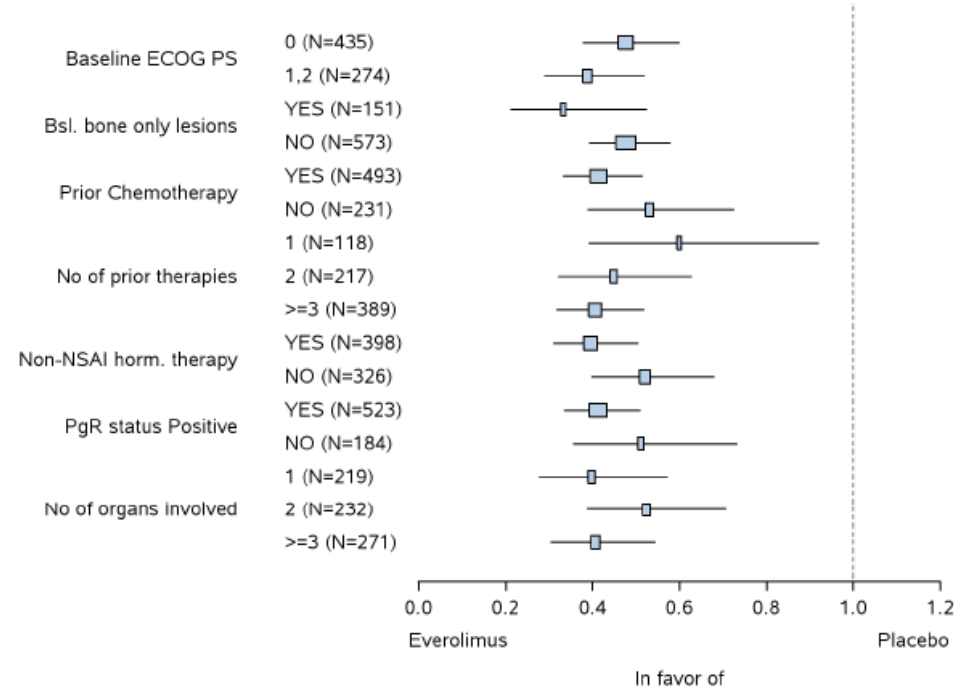
The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analysed subgroups, a positive treatment effect was seen with Afinitor + exemestane with an estimated hazard ratio vs. placebo + exemestane ranging from 0.25 to 0.62 (see Figure 2 and Figure 3). Subgroup analyses demonstrated a homogeneous and consistent treatment effect irrespective of sensitivity to prior hormonal therapy and presence of visceral metastasis, and across major demographic and prognostic subgroups.

Figure 2 Forest plot of PFS as per investigator by subgroup (1)



Hazard ratio was obtained using unstratified Cox proportional hazard model.
* NA: North America
** sensitivity to prior hormonal therapy

Figure 3 Forest plot of PFS as per investigator by subgroup (2)



Hazard ratio was obtained using unstratified Cox proportional hazard model.
* NA: North America
** sensitivity to prior hormonal therapy

Clinically or statistically significant differences were not 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.

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 2 and Figure 4).

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).

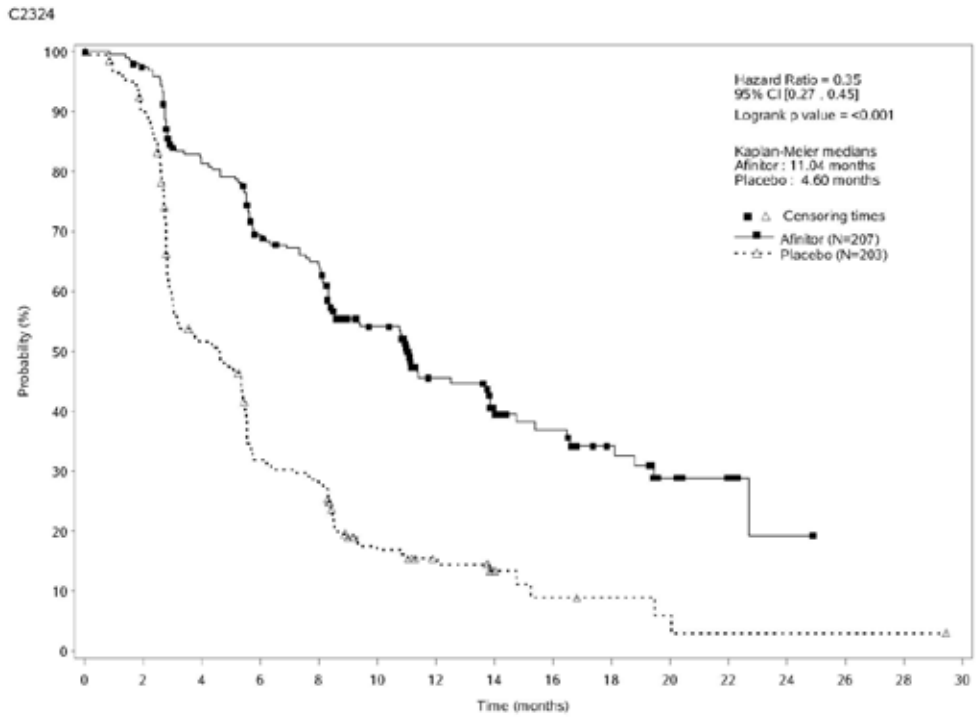
Table 2 RADIANT-3 – Progression Free Survival results

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 4 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 3 and Figure 5). 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 3 RADIANT-2 – Progression Free Survival results

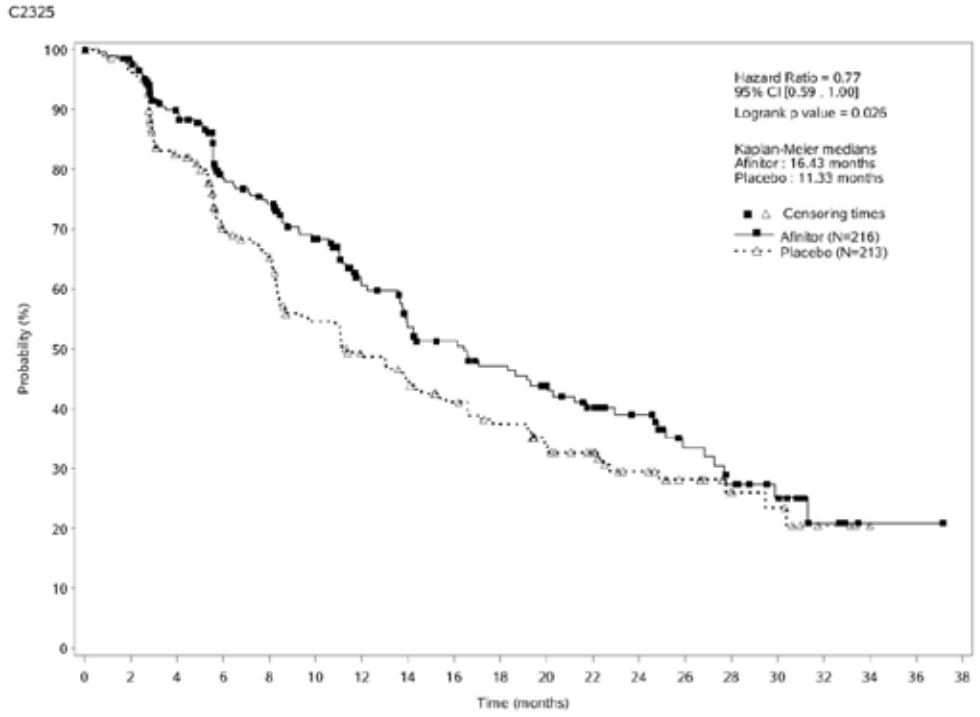
Analysis	N	Afinitor[a] N=216	Placebo[a] **N=213**	**Hazard Ratio (95%CI)**	**p-value**[c]
	429	Median progression-free survival (months) (95% CI)			
Independent radiological review[b]		16.43 (13.67 to 21.19)	11.33 (8.44 to 14.59)	0.77 (0.59 to 1.00)	0.026
Investigator radiological review		11.99 (10.61 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 5 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, cytokines and chemotherapy 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.

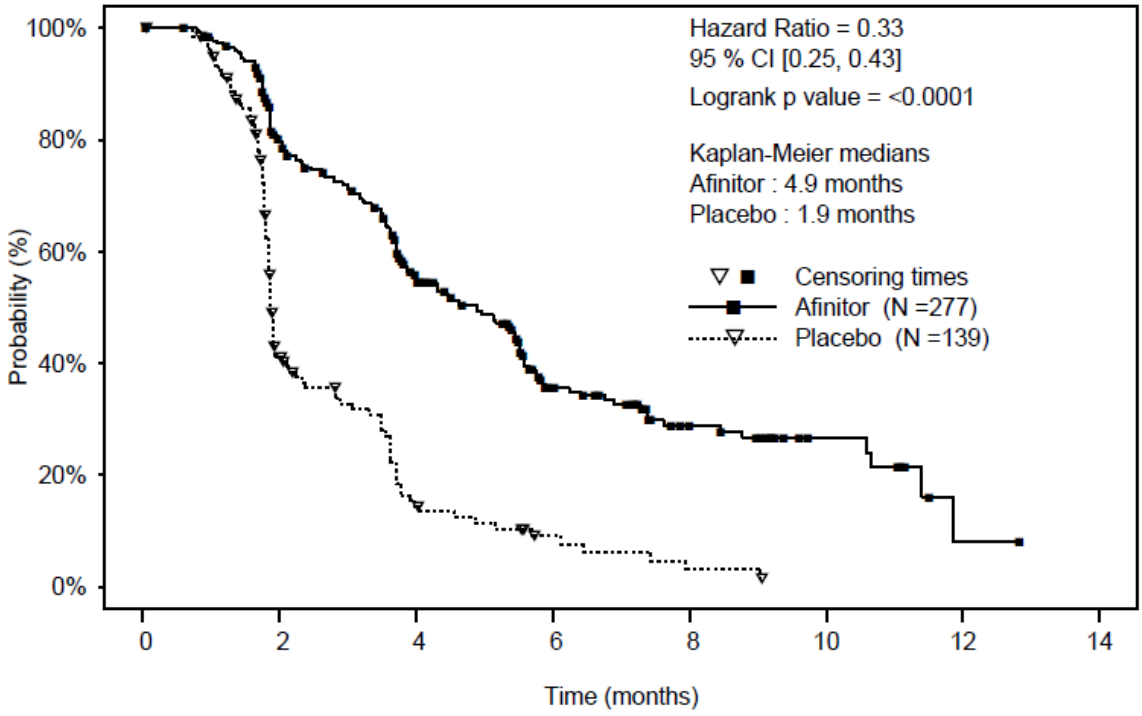
Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 4 and Figure 6).

Table 4 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]
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 6 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. Subgroup analyses by age (<65 years and ≥65 years) indicated that the Afinitor treatment effect was consistent.

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

Subependymal giant cell astrocytoma (SEGA)

The effectiveness of Afinitor is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.

An open-label, single-arm trial was conducted to evaluate the safety and efficacy of Afinitor in patients with SEGA associated with TS. Serial radiological evidence of SEGA growth was required for entry. Change in SEGA volume at the end of the core 6-month treatment phase was assessed via an independent central radiology review. In total, 28 patients received

treatment with Afinitor; median age was 11 years (range 3-34), 61% male, 86% Caucasian. Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving Afinitor treatment. After the core treatment phase, patients could continue to receive Afinitor treatment as part of an extension treatment phase where SEGA volume was assessed every 6 months. The median duration of treatment was 24.4 months (range 4.7-37.3 months).

At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumour volume of their largest SEGA lesion. Duration of response for these 9 patients ranged from 97 to 946 days with a median of 266 days. Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cut-off.

Three of 4 patients who had prior surgery experienced a ≥ 50% reduction in the tumour volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions.

INDICATIONS

For the treatment of:

- Postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.
- Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.
- Advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.

CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients (see Precautions).

PRECAUTIONS

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 Adverse 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. 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:

- In patients with hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin or advanced renal cell carcinoma, Afinitor may be reintroduced at 5 mg daily.
- In patients with SEGA, Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases where symptoms of non-infectious pneumonitis are severe (grade 3 or 4), Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. For cases of grade 3 non-infectious pneumonitis:

- In patients with hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin or advanced renal cell carcinoma, therapy with Afinitor may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.
- In patients with SEGA, therapy with Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances.

The development of pneumonitis has been reported at a reduced dose (see Dosage and Administration).

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens (see Adverse Effects). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis 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, respiratory or hepatic failure) and occasionally have had a fatal outcome. Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before 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, Afinitor should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Impaired Wound Healing

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

Hypersensitivity

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (eg swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see Contraindications).

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with Afinitor (see Adverse Effects). In such cases 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 fungal infection has been diagnosed (see Interactions with Other Medicines).

Ethnicity

In Asian patients, with NETs, the reported adverse events of hypertension were 1.95 fold higher (17.6% vs. 9.0%), of pneumonitis 1.88 fold higher (13.2% vs. 7.0%), and of hyperglycaemia 1.59 fold higher (29.4% vs. 18.4%) than in Caucasian patients.

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 ADVERSE EFFECTS section, see also Laboratory tests and monitoring).

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 Dosage and Administration and Precautions).

Everolimus is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) for the treatment of hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin, and advanced renal cell carcinoma (see Dosage and Administration and Pharmacokinetics).

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 Dosage and Administration and Pharmacology).

Effects on fertility

Everolimus completely impaired male rat fertility at an everolimus dose that resulted in a drug exposure (blood AUC) that was slightly below[3] the expected maximum human value, and sperm number and motility were reduced. Testicular atrophy was observed in all animal species tested (mouse, rat, minipigs and monkey) at drug exposures similar to the expected clinical exposure (blood AUC). There was evidence for partial recovery of fertility over a period approximately equivalent to the treatment period. Female rat fertility could not be assessed at dose resulting in an adequate drug exposure (blood AUC).

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.

Use in Pregnancy (Category C)

There are no adequate data from the use of everolimus in pregnant women and the potential risk to the foetus is unknown. In a rat study in which oral treatment started before mating and continued to the end of the period of organogenesis, treatment resulted in increased pre- and post-implantation losses. There was a low incidence of foetal cleft sternum, the significance of which is uncertain because it occurred at a dose giving a high foetal resorption rate. Systemic drug exposures (blood AUC) with the doses used in this study were below the expected human value at 10 mg/day. Treatment of pregnant rabbits during the period of organogenesis slightly increased late fetal resorptions but did not otherwise affect foetal development. The highest dose used in this study gave a systemic drug exposure (blood AUC) that was below the expected human value[4] at 10 mg/day. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving Afinitor and up to 8 weeks after treatment has been stopped.

Afinitor should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

[3] At high dose (5 mg/kg/day), AUC0-24 hr=414.8 ng.hr/mL vs human AUC=560 at 10 mg/day.

[4] AUC=225.6 ng.hr/mL at high dose. Vs human AUC of 560 ng.hr/mL at 10 mg/day.

Use in Lactation

It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking Afinitor should not breast-feed.

Paediatric Use

Hormone receptor positive advanced breast cancer, PNETs and RCC: Afinitor is not recommended for use in paediatric cancer patients.

SEGA: Afinitor has not been studied in paediatric SEGA patients < 3 years of age and is currently not recommended for use in this age group (see Dosage and Administration).

Use in Elderly

In patients over 65 years, with NETs, the reported incidences of dehydration, hypomagnesaemia and pneumonitis was more than 1.4 fold higher than for patients 65 years or younger.

Genotoxicity

Everolimus did not show genotoxicity in in vitro tests for gene mutation (bacteria and mammalian cells), and in an in vitro test and an in vivo mouse micronucleus assay for clastogenic activity.

Carcinogenicity

Long-term carcinogenicity studies have been carried out in mice and rats and no oncogenic responses were observed. Drug exposures (blood AUC) were up to 4-times [5] the expected human value at 10 mg/day in mice, but were less than the expected maximum human value in rats.

Effect on laboratory tests

Renal Function

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking Afinitor (see Adverse 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.

[5] AUC0-24 hr=2231 ng.hr/mL in mice vs AUC=560 in human at 10 mg/day.

Blood glucose

Hyperglycaemia has been reported in patients taking Afinitor (see Adverse 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 hyperglycaemia. The appropriate optimal glycaemic control must be achieved before starting a patient on Afinitor.

Octreotide has been associated with a rise in blood glucose which may increase the hyperglycaemic effect of everolimus.

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, neutrophils and platelets have been reported in patients treated with Afinitor (see Adverse Effects). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

INTERACTIONS WITH OTHER MEDICINES

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.

Moderate CYP3A4 or PgP inhibitors
Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, cyclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, aprepitant, or posaconazole) and PgP requires caution. If Afinitor must be co-administered with a moderate CYP3A4 or PgP inhibitor, the patient should be carefully monitored for undesirable effects and the dose reduced if necessary (see Dosage and Administration).

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; Cmax and AUC increased by 2.0- and 4.4-fold, respectively).
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor; Cmax and AUC increased by 2.3-and 3.5-fold, respectively).
- cyclosporin (a CYP3A4 substrate and a PgP inhibitor; Cmax 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).

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.

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

There was a significant increase in exposure to everolimus (Cmax 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). An interaction with topically administered ketoconazole cannot be excluded.

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.

Strong CYP3A4 inducers
Concurrent treatment with strong inducers of CYP3A4 or PgP should be avoided (see Interactions with Other Medicines). If Afinitor must be co-administered with a strong CYP3A4 or PgP inducer (eg rifampicin and rifabutin), the patient should be carefully monitored for clinical response. Consider a dose increase of Afinitor when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment is not possible (see Dosage and Administration).

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.

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 Cmax by 58% and AUC by 63%. Other strong inducers of CYP3A4 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 cyclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus Cmax 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 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.

Co-administration of everolimus and exemestane increased exemestane C_{min} and C_{2h} by 45% and 71%, respectively. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

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. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines. For pediatric 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.

Lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicinal product.

ADVERSE EFFECTS

Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin and advanced renal cell carcinoma

Summary of the safety profile

Information about adverse drug reactions (ADRs) is mainly based on data from four randomized, double-blind, placebo-controlled phase III trials:

- BOLERO-2 (CRAD001Y2301): Afinitor in combination with exemestane in the treatment of postmenopausal women with oestrogen receptor-positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole. As of the data cut-off date of the interim analysis (11-Feb-2011), the median duration of treatment was 14.6 weeks for patients receiving Afinitor and 12.0 weeks for those receiving placebo plus exemestane.
- RADIANT-3 (CRAD001C2324): Afinitor plus best supportive care in patients with advanced pancreatic neuroendocrine tumours. Median duration of blinded study treatment was 37.8 weeks for patients receiving Afinitor and 16.1 weeks for those receiving placebo.
- RADIANT-2 (CRAD001C2325): Afinitor plus octreotide depot in patients with advanced neuroendocrine tumours (carcinoid tumours) primarily of gastrointestinal or lung origin (not an approved indication). Median duration of blinded study treatment was 37.0 weeks for patients receiving Afinitor and 36.6 weeks for those receiving placebo.
- RECORD-1 (CRAD001C2240): Afinitor plus best supportive care in patients with advanced renal cell carcinoma. Median duration of blinded study treatment was 141 days for patients receiving Afinitor and 60 days for those receiving placebo.

The most common adverse reactions (incidence ≥10% in at least one phase III trial and suspected to be related to treatment by the investigator) were (in decreasing order): stomatitis, rash, diarrhoea, fatigue, infections, asthenia, nausea, peripheral oedema, decreased appetite, headache, dysgeusia, epistaxis, mucosal inflammation, pneumonitis, weight decreased, vomiting, pruritus, cough, dyspnoea, dry skin, nail disorder, and pyrexia. The most common grade 3 - 4 ADRs (incidence ≥2% in at least one phase III trial) were stomatitis, fatigue, diarrhoea, infections, pneumonitis and diabetes mellitus.

Tabulated summary of adverse drug reactions from clinical trials

Table 5 presents the frequency category of ADRs reported with an incidence of ≥5% for patients receiving Afinitor 10 mg/day in at least one of the phase III trials; all terms included are based on the highest percentage reported in a phase III trial. Table 5 includes adverse reactions from BOLERO-2 interim analysis (11-Feb-11). See Table 6 and 9 for an updated analysis (08-Jul-2011) of adverse reactions and key laboratory abnormalities from BOLERO-2 alone.

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), including isolated reports.

Table 5 Adverse reactions reported in at least one phase III trial in at least 5% of patients and at a higher rate in the Afinitor arm than in the placebo arm

System Organ Class	Very common	Common
Infections and infestations	infections[1]	
Metabolism and nutrition disorders	decreased appetite[2]	diabetes mellitus
Vascular disorders		hypertension
Nervous system disorders	dysgeusia, headache	
Respiratory, thoracic and mediastinal disorders	cough, pneumonitis[3] epistaxis, dyspnoea	
Gastrointestinal disorders	stomatitis[4], diarrhoea, nausea, vomiting	dry mouth
Skin and subcutaneous tissue disorders	rash, dry skin, pruritus, nail disorder	acne
General disorders and administration site conditions	fatigue, asthenia, mucosal inflammation, oedema peripheral, pyrexia	
Investigations	weight decreased	

[1] Includes all those reported for the system organ class and isolated cases of opportunistic infections, including reactivation of hepatitis B (<1%),

[2] Reported as anorexia in RECORD-1 according to MedDRA v11.0

[3] Includes alveolitis, interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar haemorrhage, and pulmonary toxicity

[4] Includes aphthous stomatitis and mouth and tongue ulceration

Table 6 Adverse Reactions reported (with at least 5% incidence in either group) in patients with HR+ advanced breast cancer

	Afinitor[a] + exemestane N=482			**Placebo + exemestane[b] N=238**		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Any adverse reaction	**96.5**	**35.1**	**3.3**	**62.2**	**7.1**	**0.8**

	Afinitor[a] + exemestane N=482			Placebo + exemestane[b] N=238		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
	%	**%**	**%**	**%**	**%**	**%**
Gastrointestinal disorders						
Stomatitis[c]	64.7	8.1	0	11.3	0.8	0
Diarrhoea	19.5	1.2	0.2	9.2	0.4	0
Nausea	17.6	0.2	0.2	15.1	0	0
Vomiting	7.1	0.4	0.2	4.2	0	0
Dry mouth	6.6	0	0	3.8	0	0
Constipation	5.8	0	0	5.0	0	0
General disorders and administration site conditions						
Fatigue	23.9	2.5	0.4	16.8	0	0
Asthenia	7.9	1.0	0	1.7	0	0
Oedema peripheral	7.1	0.6	0	1.7	0	0
Pyrexia	5.0	0	0	0.4	0	0
Infections and infestations[d]	15.1	2.1	0.6	2.9	0	0
Metabolism and nutrition disorders						
Decreased appetite	19.9	0.6	0	5.9	0.4	0
Hyperglycaemia	10.6	4.6	0.2	1.7	0.4	0
Hypercholesterolaemia	7.5	0.2	0	0.8	0	0
Hypertriglyceridaemia	5.0	0.2	0	1.3	0	0
Musculoskeletal and connective tissues disorders						
Arthralgia	5.4	0.2	0	6.7	0	0
Nervous system disorders						
Dysgeusia	19.1	0.2	0	4.2	0	0
Headache	9.8	0	0	5.9	0	0
Respiratory, thoracic and mediastinal disorders						
Pneumonitis	14.9	3.1	0	0	0	0
Epistaxis	11.2	0	0	0.4	0	0
Cough	8.9	0.4	0	2.9	0	0
Dyspnoea	8.9	2.3	0	2.9	0	0
Skin and subcutaneous tissue disorders						
Rash	33.8	1.2	0	4.6	0	0
Pruritus	10.0	0	0	2.9	0	0
Nail disorder	7.3	0	0	0.4	0	0
Alopecia	6.6	0	0	3.8	0	0
Dry skin	5.6	0	0	0.8	0	0
Blood and lymphatic system disorders						
Anaemia	11.4	3.1	0.4	1.7	0.4	0
Thrombocytopenia	10.4	1.9	0.2	0	0	0
Neutropenia	6.8	2.3	0	0	0	0

	Afinitor[a] + exemestane N=482			Placebo + exemestane[b] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Leukopenia	5.2	0.4	0	0.8	0	0
Vascular disorders						
Hot flush	2.7	0	0	10.9	0	0
Investigations						
Weight decreased	13.7	0.4	0	2.5	0	0
Alanine aminotransferase increased	8.9	2.7	0	2.9	1.3	0
Aspartate aminotransferase increased	8.9	2.7	0	4.2	0.4	0
Gamma-glutamyltransferase increased	5.0	1.7	1.0	5.5	2.5	0.8
Blood creatinine increased	5.0	0.4	0	0.4	0	0
Median duration of treatment (wks)		**26.6**			**14.1**	

CTCAE Version 3.0
a.Afinitor 10 mg/day
b.Exemestane 25 mg/day
c. Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration.
d. Includes all reactions within the 'infections and infestations' system organ class

Table 7 Adverse Reactions Reported ≥ 10% of Patients with Advanced pNET

	AFINITOR 10 mg/day 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
Diarrhoea[b]	50	5	0.5	25	3	0
Abdominal pain	36	4	0	32	6	1
Nausea	32	2	0	33	2	0
Vomiting	29	1	0	21	2	0
Constipation	14	0	0	13	0.5	0
Dry mouth	11	0	0	4	0	0
General disorders and administration site conditions						
Fatigue/malaise	45	3	0.5	27	2	0.5
Oedema (general and peripheral)	39	1	0.5	12	1	0
Fever	31	0.5	0.5	13	0.5	0
Asthenia	19	3	0	20	3	0

	AFINITOR 10 mg/day N=204			Placebo N=203		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Nasopharyngitis/rhinitis/ URI	25	0	0	13	0	0
Urinary tract infection	16	0	0	6	0.5	0
Investigations						
Weight decreased	28	0.5	0	11	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	18	1	0
Diabetes mellitus	10	2	0	0.5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	1	0.5	7	0.5	0
Back pain	15	1	0	11	1	0
Pain in extremity	14	0.5	0	6	1	0
Muscle spasms	10	0	0	4	0	0
Nervous system disorders						
Headache/migraine	30	0.5	0	15	1	0
Dysgeusia	19	0	0	5	0	0
Dizziness	12	0.5	0	7	0	0
Psychiatric disorders						
Insomnia	14	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough/productive cough	25	0.5	0	13	0	0
Epistaxis	22	0	0	1	0	0
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 steatorrhea.

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

Table 8 Adverse reactions reported in at least 5% of RCC patients and at a higher rate in the Afinitor arm than in the placebo arm

	Afinitor 10 mg/day N=274			Placebo N=137		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
	%	**%**	**%**	**%**	**%**	**%**
Any adverse reaction	**89**	**35**	**3.3**	**58**	**6.6**	**0**
Infections and infestations						
Infections[a]	13	2.2	2.2	2.2	0	0
Metabolism and nutrition disorders						
Anorexia	19	<1	0	5.8	0	0
Hypercholesterolemia	18	3	0	2	0	0
Hypertriglyceridemia	15	1	0	2	0	0
Hyperglycaemia	8	4	0	<1	<1	0
Nervous system disorders						
Dysgeusia	9.9	0	0	1.5	0	0
Headache	8.8	0	0	5.1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	14	0	0	4.4	0	0
Pneumonitis [b]	12	3.3	0	0	0	0
Epistaxis	12	0	0	0	0	0
Dyspnoea	10	1.8	0	2.9	0	0
Gastrointestinal disorders						
Stomatitis [c]	42	3.3	0	8	0	0
Diarrhoea	21	1.5	0	3.6	0	0
Nausea	18	<1	0	8	0	0
Vomiting	15	<1	0	3.6	0	0
Dry mouth	6.2	0	0	4.4	0	0
Skin and subcutaneous tissue disorders						
Rash	28	1.1	0	5.1	0	0
Dry skin	12	<1	0	4.4	0	0
Pruritus	12	<1	0	2.9	0	0
General disorders and administration site conditions						
Fatigue	23	3.3	0	17	<1	0
Asthenia	22	1.8	0	9.5	<1	0
Mucosal inflammation	17	1.1	0	1.5	0	0
Oedema peripheral	13	<1	0	3.6	0	0
Pyrexia	5.5	0	0	2.2	0	0
Investigations						
Weight decreased	5.5	0	0	<1	0	0
Median Duration of Treatment		**141**			**60**	

CTCAE Version 3.0

[a] All infections reported including pneumonia, aspergillosis, candidiasis and sepsis

[b] Includes alveolitis, interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar haemorrhage, and pulmonary toxicity

[c] Stomatitis (including aphthous stomatitis) and mouth and tongue ulceration

Other notable adverse reactions occurring in at least one phase III trial more frequently with Afinitor than with placebo, but with an incidence of <5% are listed below. All terms included are based on the highest percentage reported in a phase III trial.

Blood and lymphatic system disorders
Uncommon: Pure red cell aplasia (<1%)

Metabolism and nutrition disorders
Common: dehydration (2.5%), exacerbation of pre-existing diabetes mellitus (1.1%)
Uncommon: new onset of diabetes mellitus (<1%)

Psychiatric disorders
Common: insomnia (3.3%)

Nervous system disorders
Uncommon: ageusia (<1%)

Vascular disorders
Common: haemorrhage (4.7%, at various locations)
Uncommon: deep vein thrombosis (<1%)

Cardiac disorders
Uncommon: congestive cardiac failure (<1%)

Respiratory, thoracic and mediastinal disorders
Common: pulmonary embolism (1.5%), haemoptysis (1.1%)
Uncommon: acute respiratory distress syndrome (<1%)

Gastrointestinal disorders
Common: oral pain (3.7%), abdominal pain (3.6%), dyspepsia (2.9%),dysphagia (2.6%)

Eye disorders
Common: eyelid oedema (3.3%), conjunctivitis (1.5%)

Skin and subcutaneous tissue disorders
Common: hand and foot syndrome (4.7%), erythema (3.6%), acneiform dermatitis (3.3%), onychoclasis (2.9%), skin exfoliation (1.8%)

Musculoskeletal and connective tissue disorders
Common: arthralgia (2.8%)

Renal and urinary disorders
Common: proteinuria (2.5%), renal failure (2.3%, including acute renal failure), increased daytime urination (1.8%)

General disorders and administration site conditions
Common: chest pain (1.1%).
Uncommon: impaired wound healing (<1%)

Key observed laboratory abnormalities were reported in at least one phase III trial at a higher rate in the Afinitor arm than in the placebo arm.

In the phase III trials, the majority of observed key laboratory abnormalities were reported with an incidence of ≥10% (listed in decreasing frequency):

Decreased hematology parameters include hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia). Increased clinical chemistry parameters include cholesterol, triglycerides, glucose, aspartate transaminases, creatinine, alanine transaminases, and bilirubin. Decreased clinical chemistry parameters include phosphate and potassium.

Most of observed abnormalities were mild (grade 1) or moderate (grade 2). Grade 4 abnormalities include reductions in lymphocytes (2.2%), hemoglobin (2%), and potassium (2%), neutrophils, platelets, and phosphate (each <1%) and increases in creatinine (1%), cholesterol, AST, ALT, bilirubin, and glucose (each <1%).

Table 9 Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced HR+ BC

Laboratory parameter	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[b]						
Hemoglobin decreased	68	6	0.6	40	0.8	0.4
WBC decreased	58	1	0	28	5	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
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] Exemestane (25 mg/day)
[b] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.

Table 10 Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced pNET

Laboratory parameter	AFINITOR 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

Table 11 Key laboratory abnormalities reported at a higher rate in the Afinitor arm than in the placebo arm in patients with RCC

Laboratory parameter	Afinitor 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematology[a)]						
Haemoglobin decreased	92	12	1.1	79	5.1	<1
Lymphocytes decreased	51	16	2.2	28	5.1	0

Laboratory parameter	Afinitor 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Platelets decreased	23	1.1	0	2.2	0	<1
Neutrophils decreased	14	0	<1	3.6	0	0
Clinical chemistry						
Cholesterol increased	77	4.4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1.5	0
Creatinine increased	50	1.5	0	34	0	0
Phosphate decreased	37	6.2	0	8.0	0	0
Aspartate transaminase (AST) increased	25	<1	<1	6.6	0	0
Alanine transaminase (ALT) increased	21	1.1	0	3.6	0	0
Bilirubin increased	2.9	<1	<1	2.2	0	0

CTCAE Version 3.0

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

SEGA

The data described below reflect exposure to Afinitor (n=28) in a phase II study for the treatment of SEGA. In total, 17 of the 28 patients were exposed to Afinitor for ≥21 months. Total exposure was 55.2 patient-years. The median age of patients was 11 years (range 3 to 34).

The most common adverse reactions (incidence ≥ 10% and suspected to be related to treatment by the investigator) were infections, stomatitis, pyrexia, acneiform dermatitis, diarrhoea, acne, cough, hypertriglyceridaemia, and decreased white blood cell count. The only grade 3 adverse reactions were infections (single cases of sinusitis, pneumonia, tooth infection, and viral bronchitis), and single cases of stomatitis and decreased white blood cell count. No grade 4 adverse reactions were reported.

Table 12 summarises the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 5%. Adverse reactions 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.

Table 12 Adverse reactions reported in at least 5% of patients

	Frequency	Afinitor N=28		
		All grades %	Grade 3 %	Grade 4 %
Any adverse reaction		**100**	**18**	**0**
Infections and infestations				
Upper respiratory tract infection	Very common	82	0	0
Sinusitis	Very common	39	4	0
Otitis media	Very common	36	0	0
Cellulitis	Very common	21	0	0
Body tinea	Very common	14	0	0
Gastroenteritis	Very common	18	0	0
Skin infection	Very common	14	0	0
Gastric infection	Very common	14	0	0
Otitis externa	Very common	14	0	0
Pharyngitis	Very common	11	0	0
Pneumonia	Common	7	0	0
Urinary tract infection	Common	7	0	0
Infection	Common	7	0	0
Furuncle	Common	7	0	0
Metabolism and nutrition disorders				
Hypertriglyceridaemia[a]	Very common	11	0	0
Respiratory, thoracic and mediastinal disorders				
Cough	Very common	11	0	0
Pharyngeal inflammation	Common	7	0	0
Gastrointestinal disorders				
Stomatitis	Very common	86	4	0
Diarrhoea	Very common	21	0	0
Gastritis	Common	7	0	0
Vomiting	Common	7	0	0
Skin and subcutaneous tissue disorders				
Dermatitis acneiform	Very common	25	0	0
Acne	Very common	11	0	0
General disorders and administration site conditions				
Pyrexia	Very common	25	0	0
Investigations				
White blood cell count decreased[b]	Very common	11	4	0
Blood immunoglobulin G decreased	Common	7	0	0
Blood triglycerides increased[a]	Common	7	0	0
Renal and urinary disorders				
Proteinuria	Common	7	0	0

CTCAE Version 3.0

[a] Reported as a laboratory abnormality in 43% of patients

[b] Reported as a laboratory abnormality in 54% of patients

Other notable adverse reactions (with an incidence of < 5%) include:

Psychiatric disorders
Common: anxiety (3.6%)

Nervous system disorders
Common: somnolence (3.6%)

Vascular disorders
Common: hypertension (3.6%)

Respiratory, thoracic and mediastinal disorders
Common: Pharyngeal inflammation, increased upper airway secretion, Oropharyngeal or rhinorrhea pain (3.6%)

Skin and subcutaneous tissue disorders
Common: dry skin (3.6%), pityriasis rosea (3.6%)

General disorders and administration site conditions
Common: fatigue (3.6%), peripheral oedema (3.6%)

Eye disorders
Common: ocular hyperaemia (3.6%)

Investigations
Single grade 1 reactions are not included.

General

Key laboratory abnormalities not reported as adverse drug reactions

Single cases of grade 3 elevated aspartate transaminase (AST) concentrations and low absolute neutrophil count (ANC) were reported. No grade 4 laboratory abnormalities were noted. Laboratory abnormalities observed in > 1 patient (and listed in decreasing order of frequency) included elevations in AST concentrations (89%), total cholesterol (64%), alanine transaminase (ALT) (43%), glucose (25%), and creatinine (11%), and reductions haemoglobin (39%), glucose (29%), and platelet counts (21%). Most of these laboratory abnormalities were mild (grade 1).

Adverse Reactions of special interest

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 ones) and proteinuria. Monitoring of renal function is recommended (see PRECAUTIONS section).

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

DOSAGE AND ADMINISTRATION

Afinitor should be administered orally once daily at the same time every day (preferably in the morning), either consistently in a fasting state or consistently after no more than a light fat-free meal (see Pharmacokinetics).

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 tablets should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

If a dose is missed, the patient should take the next dose at the next scheduled time. Patients should not take two doses to make up for the one that they missed.

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

Adults

Dosing in hormone receptor-positive advanced breast cancer, 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 reactions may require temporary dose reduction and/or interruption of Afinitor therapy. If dose reduction is required, the suggested dose is 5 mg daily (see Precautions).

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 dose to 5 mg daily. Further dose reduction to 5 mg every other day or 2.5 mg daily may be required to manage adverse reactions (see Precautions).

Strong CYP3A4 or PgP 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 Precautions).

Dosing in SEGA associated with TS

Treatment with Afinitor should be initiated by a physician experienced in the treatment of patients with TS and with access to everolimus therapeutic drug monitoring services. Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for 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 Interactions with Other Medicines).

The recommended starting dose of Afinitor for treatment of patients with SEGA is according to Table 13:

Table 13 Recommended starting dose of Afinitor for treatment of patients with SEGA

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

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

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL. If concentrations are below 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability (see Pharmacokinetics).

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 Pharmacokinetics).

Responses have been observed at trough concentrations as low as 2 ng/mL; as such, once acceptable efficacy has been achieved, additional dose increase may not be necessary. Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of therapy (see Precautions). If dose reduction is required for patients receiving 2.5 mg daily, alternate day dosing should be considered.

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 daily dose by approximately 50%. Further dose reduction may be required to manage adverse reactions (see Precautions). Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued the 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 Precautions).

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 5 to 10 ng/mL. If

concentrations are below 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, checking the trough level and assessing tolerability before increasing the dose. If the strong inducer is discontinued the 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 Precautions).

Therapeutic drug monitoring for patients treated for SEGA

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for SEGA using a validated bioanalytical LC/MS method. 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 inducers or inhibitors (see Precautions). Dosing should be titrated with the objective of attaining everolimus trough concentrations of 5 to 10 ng/mL, subject to tolerability (see Pharmacokinetics).

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

Paediatric population

- Hormone receptor-positive advanced breast cancer, 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 SEGA are consistent with those for the adult SEGA population. Afinitor has not been studied in paediatric SEGA patients < 3 years of age and is currently not recommended for use in this age group.

Elderly patients (≥ 65 years)

No dosage adjustment is required (see Pharmacokinetics).

Patients with renal impairment

No dosage adjustment is required (see Pharmacokinetics).

Patients with hepatic impairment

Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin and renal cell carcinoma:

- the dose should be reduced to 5 mg daily in patients with moderate hepatic impairment (Child-Pugh class B).
- For patients with severe hepatic impairment (Child-Pugh class C): Everolimus has not been evaluated in patients with severe hepatic impairment and is not recommended for use in this patient population (see Precautions and Pharmacokinetics).

SEGA:

- the dose should be reduced by approximately 50% and titrate to trough concentrations of 5 to 15 ng/mL
- For patients with severe hepatic impairment (Child-Pugh class C): Everolimus has not been evaluated in patients with severe hepatic impairment and is not recommended for use in this patient population (see Precautions and Pharmacokinetics).

OVERDOSAGE

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 2000 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

2.5 mg tablet: White to slightly yellowish, elongated tablet with a bevelled edge and no score engraved with “LCL” on one side and “NVR” on the other. Packs of 30, 50, 60 and 100, 120 tablets.

5 mg tablet: White to slightly yellowish, elongated tablet with a bevelled edge and no score engraved with “5” on one side and “NVR” on the other. Packs of 30, 50, 60 and 100, 120 tablets.

10 mg tablet: White to slightly yellowish, elongated tablet with a bevelled edge and no score engraved with “UHE” on one side and “NVR” on the other. Packs of 30, 50, 60, 100 and 120 tablets.

Not all pack sizes may be marketed.
Store below 30°C in the original packaging. Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
(ABN No: 18 004 244 160)
54 Waterloo Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

6 August 2009

DATE OF MOST RECENT AMENDMENT

22 May 2013

® = Registered Trademark