

## PRODUCT MONOGRAPH

Pr **AFINITOR**<sup>®</sup>  
(everolimus tablets)  
2.5 mg, 5 mg, 7.5 mg and 10 mg

Pr **AFINITOR**<sup>®</sup> **DISPERZ**<sup>™</sup>  
(everolimus tablets for oral suspension)  
2 mg, 3 mg and 5 mg

Antineoplastic Agent  
(mTOR kinase inhibitor)

Novartis Pharmaceuticals Canada Inc.  
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AFINITOR is a registered trademark.

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Pr **AFINITOR**<sup>®</sup>  
(everolimus tablets)

Pr **AFINITOR**<sup>®</sup> **DISPERZ**<sup>™</sup>  
(everolimus tablets for oral suspension)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
<b>AFINITOR</b> <sup>®</sup>		
Oral	Tablet 2.5 mg, 5 mg, 7.5 mg and 10 mg	Butylated hydroxytoluene (E321), crospovidone, hypromellose, lactose anhydrous, lactose monohydrate, magnesium stearate.  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>
<b>AFINITOR</b> <sup>®</sup> <b>DISPERZ</b> <sup>™</sup>		
Oral	Tablet for oral suspension 2 mg, 3 mg and 5 mg	Butylated hydroxytoluene (E321), cellulose microcrystalline, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol, silica colloidal anhydrous.  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

AFINITOR<sup>®</sup> (everolimus) is indicated for the treatment of postmenopausal women with hormone receptor-positive, HER2- negative advanced breast cancer in combination with exemestane after recurrence or progression following treatment with letrozole or anastrozole.

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

AFINITOR is indicated for the treatment of well- or moderately differentiated neuroendocrine

tumours of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease that has progressed within the last 12 months.

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

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

The effectiveness of AFINITOR in gastrointestinal or lung NET is based on demonstrated progression-free survival (PFS) benefit in a phase III placebo-controlled study in patients whose disease had progressed within 6 months of randomization. An overall survival (OS) benefit or improvement in quality of life (QOL) has not been demonstrated. Subgroup analyses suggested that patients with better prognosis benefited less from AFINITOR treatment (see **CLINICAL TRIALS**).

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

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

AFINITOR is indicated for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell morphology, after failure of initial treatment with either of the VEGF-receptor TKIs<sup>1</sup> sunitinib or sorafenib.

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

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

The effectiveness of AFINITOR is based on an analysis of change in SEGA volume.

Prescribers should take into consideration that surgical resection can be curative, while treatment with AFINITOR has been shown only to reduce the SEGA volume.

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<sup>1</sup> VEGF receptor TKIs = vascular endothelial growth factor receptor tyrosine kinase inhibitors

The pharmacokinetic properties of AFINITOR and AFINITOR DISPERZ have been evaluated in clinical comparative bioavailability trials (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). AFINITOR DISPERZ has **not** been studied in clinical safety and efficacy trials.

AFINITOR is indicated for the treatment of adult patients ( $\geq 18$  years of age) with renal angiomyolipoma associated with tuberous sclerosis complex (TSC), who do not require immediate surgery.

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

AFINITOR DISPERZ is indicated as adjunctive treatment of seizures associated with Tuberous Sclerosis Complex (TSC) in patients 2 years and older, with a definite diagnosis of TSC, who are not satisfactorily controlled with current therapies.

Only patients with a definite diagnosis of TSC participated in the seizures related clinical trial. Therefore, AFINITOR DISPERZ should not be used for the treatment of any type of seizure in any other patient population (see **CONTRAINDICATIONS** and **CLINICAL TRIALS**).

AFINITOR DISPERZ is the only formulation that should be used for the treatment of patients with seizures associated with TSC.

**Geriatrics ( $\geq 65$  years of age):**

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

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

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

decreased appetite.

**Paediatrics (< 18 years of age):**

AFINITOR is not recommended for use in paediatric cancer patients.

AFINITOR and AFINITOR DISPERZ have not been studied in paediatric patients with SEGA < 1 year of age and are not recommended for use in this age group. There are limited efficacy and safety data in patients 1 to 3 years of age with AFINITOR in patients with SEGA (see **WARNINGS AND PRECAUTIONS, Special Populations**).

AFINITOR DISPERZ has not been studied in paediatric patients <2 years of age with seizures associated with TSC and is not recommended for use in this age group.

AFINITOR and AFINITOR DISPERZ are not recommended for use in paediatric patients with renal angiomyolipoma.

**CONTRAINDICATIONS**

- AFINITOR (everolimus) and AFINITOR DISPERZ are contraindicated in patients who are hypersensitive to the drug, to other rapamycin derivatives or to any of the excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** (see also **WARNINGS AND PRECAUTIONS**).
- AFINITOR (everolimus) and AFINITOR DISPERZ are contraindicated for the treatment of seizures (of any type) in populations other than those with a definite diagnosis of TSC (see **CLINICAL TRIALS**).

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

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

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

**SEGA associated with TSC:**

- Treatment with AFINITOR or AFINITOR DISPERZ should be initiated by a qualified healthcare professional experienced in the treatment of patients with TSC and with access to everolimus therapeutic drug monitoring services.
- Therapeutic drug monitoring of everolimus blood concentrations is **required** for patients treated for SEGA (see **DOSAGE AND ADMINISTRATION, Therapeutic drug monitoring for patients treated for SEGA**).
- The optimal duration of AFINITOR therapy for patients with SEGA is not known; however, SEGA re-growth has been reported to occur once therapy is discontinued (see

**DOSAGE AND ADMINISTRATION, SEGA volume monitoring for patients treated with AFINITOR and CLINICAL TRIALS, SEGA associated with Tuberous Sclerosis Complex).**

- Non-clinical data suggests that there is a risk of delayed developmental landmarks and delayed reproductive development in patients taking everolimus (see **Special Populations, Paediatrics** below and **TOXICOLOGY**).
- Dosage forms (AFINITOR and AFINITOR DISPERZ™) are **not** interchangeable (see **DOSAGE AND ADMINISTRATION, Dosing Considerations, Switching dosage forms**)

**Renal Angiomyolipoma associated with TSC:**

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

The following are clinically significant adverse events:

- Non-infectious pneumonitis, including fatalities (see “**Respiratory**” section below)
- Infections, including fatalities (see “**Immune**” section below)
- Renal failure, including fatalities (see “**Renal**” section below)

## **General**

### **Drug-Drug Interactions**

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

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

Co-administration with strong inducers of CYP3A4 and/or PgP should be avoided due to the risk of reduced effectiveness of the drug. If AFINITOR or AFINITOR DISPERZ must be co-administered with a strong inducer of CYP3A4 and/or PgP, the patient should be carefully monitored for clinical response. Consider a dose increase of AFINITOR or AFINITOR DISPERZ when co-administered with anticonvulsants that are strong inducers of CYP3A4 if alternative treatment is not possible. However, there are limited clinical data with this dose adjustment in patients with renal angiomyolipoma receiving an anticonvulsant that is a strong inducer of CYP3A4 (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

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

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

### **Carcinogenesis and Mutagenesis**

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

### **Functional carcinoid tumour**

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

### **Endocrine and Metabolism**

**Hyperlipidaemia:** Hypercholesterolaemia and hypertriglyceridaemia have been reported in patients taking AFINITOR (see **ADVERSE REACTIONS**). Monitoring of fasting lipid profile is recommended prior to the start of AFINITOR or AFINITOR DISPERZ therapy and periodically thereafter. Consider dose reduction, dose interruption or discontinuation, as well as management with appropriate medical therapy (see **DOSAGE AND ADMINISTRATION, Dosing Considerations, Table 15**).

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



type 2 diabetes has occurred with AFINITOR treatment (see **ADVERSE REACTIONS**).

### **Gastrointestinal**

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

For mouth ulcers and stomatitis, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine- or thyme-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless oral fungal infection has been diagnosed (see **DOSAGE AND ADMINISTRATION, Table 15** and **DRUG INTERACTIONS**).

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

### **Haematologic**

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

### **Haemorrhage**

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

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

### **Immune**

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

**Infections:** Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see **ADVERSE REACTIONS**). Localised and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jirovecii pneumonia (PJP) and viral infections including reactivation of hepatitis B virus have been described in patients taking 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 **WARNINGS AND PRECAUTIONS, Special Populations, Paediatrics**).

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

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

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

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

### **Musculoskeletal and Connective Tissue Disorders**

**Rhabdomyolysis:** There have been unconfirmed reports of rhabdomyolysis presenting as myalgia, muscle pain and weakness with significantly elevated creatine kinase in patients treated with AFINITOR. During AFINITOR or AFINITOR DISPERZ therapy, patients should be monitored for the possible development of rhabdomyolysis especially if they are prescribed a

concomitant statin. Patients on treatment with AFINITOR or AFINITOR DISPERZ should be advised to report promptly symptoms including muscle pain, weakness, or dark urine. If rhabdomyolysis is diagnosed, institute treatment promptly and consider interruption or discontinuation of AFINITOR or AFINITOR DISPERZ (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

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

### **Peri-operative Considerations**

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

### **Renal**

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

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

### **Respiratory**

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

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

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR or AFINITOR DISPERZ 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 or AFINITOR DISPERZ may be reintroduced at a daily dose approximately 50% lower than the dose previously administered (see **DOSAGE AND ADMINISTRATION, Table 15**).

For cases of Grade 3 non-infectious pneumonitis, interrupt AFINITOR or AFINITOR DISPERZ until, resolution to less than or equal to Grade 1. AFINITOR or AFINITOR DISPERZ may be reintroduced at a daily dose approximately 50% lower than the dose previously administered, depending on the individual clinical circumstances. If toxicity recurs at Grade 3, consider discontinuation of AFINITOR or AFINITOR DISPERZ. For cases of Grade 4 non-infectious pneumonitis, AFINITOR or AFINITOR DISPERZ therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) should be considered. The development of pneumonitis has also been reported at a reduced dose (see **DOSAGE AND ADMINISTRATION, Table 15**).

### **Sporadic lymphangiomyomatosis (LAM)**

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

### **Vascular**

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

### **Special Populations**

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

**Nursing women:** It is not known whether everolimus is excreted in breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking AFINITOR or AFINITOR DISPERZ should therefore not breastfeed during treatment and for 2 weeks after the last dose.

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

If amenorrhoea develops in a woman of childbearing potential who is receiving AFINITOR or AFINITOR DISPERZ, use of a highly effective method of contraception should continue.

In the renal angiomyolipoma associated with TSC clinical trial, secondary amenorrhoea has been reported in 15% of females receiving everolimus and in 4% of females receiving placebo. In the SEGA associated with TSC trial, amenorrhea occurred in 17% of females receiving everolimus and in none of the females receiving placebo. The mechanism is unknown. Early referral of patients with menstrual irregularities to endocrine specialists is recommended (see **ADVERSE REACTIONS**).

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

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

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

**Paediatrics ( $< 18$  years of age):** AFINITOR and AFINITOR DISPERZ is not recommended for use in paediatric cancer patients.

AFINITOR and AFINITOR DISPERZ have not been studied in paediatric patients with SEGA  $< 1$  year of age and are not recommended for use in this age group. There are limited efficacy and safety data in patients 1 to 3 years of age with AFINITOR in patients with SEGA.

AFINITOR DISPERZ has not been studied in paediatric patients  $< 2$  years of age with seizures associated with TSC and is not recommended for use in this age group.

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

Non-clinical data suggest that there is a risk of delayed developmental landmarks and delayed reproductive development in patients taking everolimus. In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females, and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day (see **TOXICOLOGY**).

Although a conclusive determination cannot be made due to the lack of a comparator arm in the open label follow-up periods of two phase III studies and a phase II study, AFINITOR did not appear to adversely impact growth and pubertal development in the 409 paediatric patients treated with AFINITOR in clinical trials with an estimated exposure of 944.20 patient treatment years (PTY).

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

AFINITOR and AFINITOR DISPERZ are not recommended for use in paediatric patients with renal angiomyolipoma associated with TSC in the absence of AFINITOR or AFINITOR DISPERZ treatment for SEGA.

The overall type, frequency and severity of adverse events across the age groups were similar, with the exception of infections, which occurred at a higher frequency and severity in patients <6 years of age. A total of 46 out of 137 patients (34%) <6 years had Grade 3/4 infections, compared to 49 out of 272 patients (18%) 6 to <18 years and 24 out of 203 patients (12%) ≥18 years. In the clinical trial conducted in patients with seizures associated with TSC, two fatal cases due to infection were reported in 409 patients <18 years receiving everolimus.

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

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

recommended for use in patients  $\geq 18$  years of age with seizures associated with TSC who have severe hepatic impairment (Child-Pugh C). The AFINITOR DISPERZ dose should be reduced in patients  $\geq 18$  years of age with seizures associated with TSC who have mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Impairment**).

### **Monitoring and Laboratory Tests**

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

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

## **ADVERSE REACTIONS**

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

#### **Adverse Reaction Overview**

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

The most common treatment-emergent adverse events irrespective of causality (incidence  $\geq 30\%$ ) were stomatitis, infections, rash, fatigue, diarrhoea and decreased appetite. Grade 3-4 events were observed more frequently among patients receiving AFINITOR plus exemestane than patients receiving placebo plus exemestane [grade 3 (40.9% vs. 22.3%, respectively) and grade 4 (8.7% vs. 5.0%, respectively)]. The most common grade 3-4 adverse events (incidence  $\geq 3\%$ ) were stomatitis, infections, fatigue, dyspnoea and pneumonitis. Specific grade 3 or grade 4 infections were: pneumonia (1.2%), sepsis (0.3%), gastroenteritis (0.6%), and primary atypical pneumonia (0.4%). The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were hypercholesterolaemia, hyperglycaemia, increased AST, anaemia, leukopenia,

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<sup>2</sup> N=2 patients (0.4%) in the AFINITOR plus exemestane arm only

thrombocytopenia, lymphopenia, increased ALT and hypertriglyceridaemia. The most common grade 3-4 laboratory abnormalities (incidence  $\geq$  3%) were lymphopenia, anaemia, hyperglycaemia, increased gamma-glutamyltransferase, decreased potassium, increased AST, increased ALT and thrombocytopenia. Fatal adverse reactions occurred in 7/482 (1.5%) of patients who received AFINITOR plus exemestane, with one death each due to pneumonia, sepsis, staphylococcal sepsis, tumour haemorrhage, ischemic stroke, completed suicide and renal failure. One death (0.4%) due to pneumonia occurred among 238 patients on the placebo plus exemestane arm.

The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the AFINITOR plus exemestane and placebo plus exemestane treatment groups, respectively. The most commonly reported AEs leading to discontinuation in the AFINITOR plus exemestane arm were: pneumonitis (4.4% of patients), stomatitis (2.5%), dyspnoea (1.9%), fatigue (1.9%), decreased appetite (1.7%), anaemia (1.7%) and rash (1.5%). The incidence of dose adjustments was 64% among patients receiving AFINITOR in the AFINITOR plus exemestane arm and 21% among patients receiving placebo in the placebo plus exemestane arm. Adverse events necessitating dose adjustments (interruptions or reductions) were more frequent among patients in the AFINITOR plus exemestane arm than in the placebo plus exemestane arm (60% versus 12%, respectively). The most commonly reported AEs that necessitated dose interruption or reduction for the AFINITOR plus exemestane arm were stomatitis (23.7% of patients), pneumonitis (7.3%) and thrombocytopenia (5.2%).

### **Clinical Trial Adverse Reactions**

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

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

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

	AFINITOR + exemestane N=482			Placebo + exemestane N=238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Any Adverse Event</b>	<b>100</b>	<b>41</b>	<b>9</b>	<b>90</b>	<b>22</b>	<b>5</b>
<b>Gastrointestinal Disorders</b>						
Stomatitis <sup>a</sup>	67	8	0	11	0.8	0
Diarrhoea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0



	AFINITOR + exemestane N=482			Placebo + exemestane N=238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Constipation	14	0.4	0	13	0.4	0
Dry mouth	11	0	0	7	0	0
<b>General Disorders and Administration Site Conditions</b>						
Fatigue	36	4	0.4	27	1	0
Oedema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
<b>Infections and Infestations</b>						
Infections <sup>b</sup>	50	4	1	25	2	0
<b>Investigations</b>						
Weight decreased	25	1	0	6	0	0
<b>Metabolism and Nutrition Disorders</b>						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycaemia	14	5	0.4	2	0.4	0
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0
Pain in extremity	9	0.4	0	11	2	0
<b>Nervous System Disorders</b>						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
<b>Psychiatric disorders</b>						
Insomnia	13	0.2	0	8	0	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	24	0.6	0	12	0	0
Dyspnoea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis <sup>c</sup>	19	4	0.2	0.4	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>						
Rash	39	1	0	6	0	0
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
<b>Vascular Disorders</b>						
Hot flush	6	0	0	14	0	0

CTCAE Version 3.0

<sup>a</sup> Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

	AFINITOR + exemestane N=482			Placebo + exemestane N=238		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%

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

<sup>c</sup> Includes pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis

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

Cardiac disorders: Tachycardia (3%)

Ear and labyrinth disorders: Deafness (0.8%)

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

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

Nervous system disorders: Ageusia (1%)

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

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

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

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

### **Abnormal Haematologic and Clinical Chemistry Findings**

Clinically relevant laboratory abnormalities are presented in Table 2.

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

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

CTCAE Version 3.0

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

## Adverse Events in Advanced Pancreatic Neuroendocrine Tumours

### Adverse Reaction Overview

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

The most common adverse reactions (incidence  $\geq 30\%$ ) were stomatitis, rash, diarrhoea, fatigue, oedema, abdominal pain, nausea, fever and headache. The most common grade 3/4 adverse reactions (incidence  $\geq 5\%$ ) were stomatitis and diarrhoea. The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were decreased haemoglobin, hyperglycaemia, alkaline

phosphatase increased, hypercholesterolaemia, bicarbonate decreased and increased aspartate transaminase (AST). The most common grade 3/4 laboratory abnormalities (incidence  $\geq 3\%$ ) were hyperglycaemia, lymphopenia, decreased haemoglobin, hypophosphataemia, increased alkaline phosphatase, neutropenia, increased aspartate transaminase (AST), potassium decreased and thrombocytopenia.

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

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

### **Clinical Trial Adverse Reactions**

Table 3 compares the incidence of treatment-emergent adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

**Table 3 Adverse reactions reported in at least 10% of patients and at a higher rate in the AFINITOR arm than in the placebo arm (PNET)**

	AFINITOR N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Any adverse reaction</b>	<b>100</b>	<b>49</b>	<b>13</b>	<b>98</b>	<b>32</b>	<b>8</b>
<b>Gastrointestinal disorders</b>						
Stomatitis <sup>a</sup>	70	7	0	20	0	0
Diarrhoea <sup>b</sup>	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
<b>General disorders and administration site conditions</b>						
Fatigue/malaise	45	3	0.5	27	2	0.5

	AFINITOR N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
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
<b>Infections and infestations</b>						
Nasopharyngitis/rhinitis/URI	25	0	0	13	0	0
Urinary tract infection	16	0	0	6	0.5	0
<b>Investigations</b>						
Weight decreased	28	0.5	0	11	0	0
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	30	1	0	18	1	0
Diabetes mellitus	10	2	0	0.5	0	0
<b>Musculoskeletal and connective tissue disorders</b>						
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
<b>Nervous system disorders</b>						
Headache/migraine	30	0.5	0	15	1	0
Dysgeusia	19	0	0	5	0	0
Dizziness	12	0.5	0	7	0	0
<b>Psychiatric disorders</b>						
Insomnia	14	0	0	8	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough/productive cough	25	0.5	0	13	0	0
Epistaxis	22	0	0	1	0	0
Dyspnoea/dyspnoea exertional	20	2	0.5	7	0.5	0
Pneumonitis <sup>c</sup>	17	3	0.5	0	0	0
Oropharyngeal pain	11	0	0	6	0	0
<b>Skin and subcutaneous disorders</b>						
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
<b>Vascular disorders</b>						
Hypertension	13	1	0	6	1	0

	AFINITOR N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Median duration of treatment (wks)</b>	<b>37</b>			<b>16</b>		

CTCAE Version 3.0

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

<sup>b</sup> Includes diarrhoea, enteritis, enterocolitis, colitis, defecation urgency and steatorrhoea.

<sup>c</sup> Includes pneumonitis, interstitial lung disease, pulmonary fibrosis and restrictive pulmonary disease.

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

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

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

Psychiatric disorders: Depression (6%)

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

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

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

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

Haematologic disorders: Pure red cell aplasia (0.5%)

Metabolism and nutrition disorders: Dehydration (6%)

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

### **Abnormal Haematological and Clinical Chemistry Findings**

Clinically relevant laboratory abnormalities are presented in Table 4.

**Table 4 Clinically relevant laboratory abnormalities reported in  $\geq 10\%$  of patients and at a higher rate in the AFINITOR arm than in the placebo arm (PNET)**

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

CTCAE Version 3.0

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

### Adverse Reaction Overview

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

Serious adverse events (SAEs) were reported more frequently in AFINITOR-treated group (42.1%) than in the placebo group (19.4%). While the incidence of specific individual SAEs was low for both treatment groups, the most commonly reported SAEs in AFINITOR group,

irrespective of causal relationship to the study drug, were abdominal pain (5.4%), pyrexia (4.5%), diarrhea (4.0%), anemia (3.0%), pneumonia (3.0%), small intestinal obstruction (3.0%), asthenia (2.5%), fatigue (2.5%), vomiting (2.5%), and pneumonitis (2.0%).

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

The most frequent adverse events (AEs) ( $\geq 5\%$ ), irrespective of causality, requiring dose adjustment or interruption were anaemia, stomatitis, diarrhea, fatigue, oedema peripheral, pyrexia, pneumonitis. The most frequent AEs (irrespective of causality) leading to treatment discontinuation were stomatitis (3.0%), GGT increased (1.5%) and diarrhea (1.5%). Other AEs occurred in  $\leq 1\%$  of patients each.

The most common ( $\geq 10\%$ ) adverse events (irrespective of causality) requiring medical intervention during AFINITOR treatment were anemia, stomatitis, diarrhea, abdominal pain, nausea, pyrexia, oedema peripheral, urinary tract infection, pneumonitis, cough, rash and hypertension.

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

### Clinical Trial Adverse Reactions

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

	AFINITOR N=202			Placebo N=98		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Any adverse reaction</b>	<b>99</b>	<b>57</b>	<b>12</b>	<b>89</b>	<b>21</b>	<b>7</b>
<b>Blood and lymphatic system disorders</b>						
Anemia	22	5	1	12	3	0
<b>Gastrointestinal disorders</b>						
Stomatitis <sup>a</sup>	63	9	0	22	0	0



Diarrhea	41	8	1	31	2	0
Nausea	26	3	1	17	1	0
Vomiting	15	4	0	12	2	0
<b>General disorders and administration site conditions</b>						
Edema peripheral	39	3	0	6	1	0
Fatigue	37	4	1	36	1	0
Asthenia	23	2	1	8	0	0
Pyrexia	23	1	1	8	0	0
<b>Infections and infestations</b>						
Infections <sup>b</sup>	58	8	3	29	1	1
<b>Investigations</b>						
Weight decreased	22	2	0	11	1	0
<b>Metabolism and nutrition disorders</b>						
Decreased appetite	22	1	0	17	1	0
Hyperglycemia	12	5	0	3	0	0
<b>Musculoskeletal and connective tissue disorders</b>						
Arthralgia	12	1	0	8	0	0
<b>Nervous system disorders</b>						
Dysgeusia	18	1	0	4	0	0
<b>Psychiatric disorders</b>						
Insomnia	10	0	0	7	1	0
<b>Respiratory, thoracic and mediastinal disorders</b>						
Cough	27	0	0	20	0	0
Dyspnea	20	3	0	11	1	1
Pneumonitis <sup>c</sup>	16	2	0	2	0	0
Epistaxis	13	1	0	3	0	0
<b>Skin and subcutaneous disorders</b>						
Rash	30	1	0	9	0	0
Pruritus	17	1	0	9	0	0
<b>Vascular disorders</b>						
Hypertension	12	4	0	8	3	0
Grading according to CTCAE Version 4.03						
<sup>a</sup> Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration and mucosal inflammation.						
<sup>b</sup> Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock and viral myocarditis.						
<sup>c</sup> Includes pneumonitis and interstitial lung disease.						

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

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

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

Eye disorders: Eyelid oedema (4%)

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

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

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

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

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

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

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

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

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

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

### **Abnormal Haematological and Clinical Chemistry Findings**

Clinically relevant laboratory abnormalities are presented in Table 6.

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

	AFINITOR N=202			Placebo N=98		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
<b>Hematology</b>						
Hemoglobin decreased	81	5	0	41	2	0
Lymphocytes decreased	66	15	2	32	2	0
White blood cell count decreased	49	2	0	17	0	0
Platelets decreased	33	2	1	11	0	0
Neutrophils decreased	32	2	0	15	3	0
<b>Clinical chemistry</b>						
Creatinine increased	82	2	1	82	1	1
Cholesterol increased	71	0	0	37	0	0
Aspartate transaminase (AST) increased	57	1	1	34	2	0
Glucose (fasting) increased	55	6	0	36	1	0
Alanine transaminase (ALT) increased	46	5	1	39	1	0
Phosphate decreased	43	4	0	15	2	0
Triglycerides increased	30	3	1	8	1	0
Potassium decreased	27	4	2	12	3	0
Albumin decreased	18	0	0	8	0	0

Grading according to CTCAE Version 4.03

## Adverse Events in Metastatic RCC

### Adverse Reaction Overview

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

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

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

## Clinical Trial Adverse Reactions

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

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

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

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Any Adverse Event</b>	<b>97</b>	<b>52</b>	<b>13</b>	<b>93</b>	<b>23</b>	<b>5</b>
<b>Gastrointestinal Disorders</b>						
Stomatitis <sup>a</sup>	44	4	<1	8	0	0
Diarrhoea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
<b>Blood and Lymphatic System Disorders</b>						
Anaemia	38	9	<1	15	4	<1
<b>Infections and Infestations<sup>b</sup></b>	<b>37</b>	<b>7</b>	<b>3</b>	<b>18</b>	<b>1</b>	<b>0</b>
<b>General Disorders and Administration Site Conditions</b>						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Oedema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	30	<1	0	16	0	0
Dyspnoea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis <sup>c</sup>	14	4	0	0	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Metabolism and Nutrition Disorders</b>						
Anorexia	25	1	0	14	<1	0
Hypercholesterolaemia	20	3	0	2	0	0
Hypertriglyceridaemia	15	1	0	2	0	0
Hyperglycaemia	12	6	0	2	1	0
<b>Nervous System Disorders</b>						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Pain in extremity	10	1	0	7	0	0
<b>Median Duration of Treatment (d)</b>	<b>141</b>			<b>60</b>		

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<sup>a</sup> Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

<sup>b</sup> Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%) and sepsis (<1%).

<sup>c</sup> Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity and alveolitis.

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

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

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

Investigations: Blood creatinine increased (9%)

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

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

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasia (4%), skin

lesion (4%), acneiform dermatitis (3%), acne (<1%), angioedema (0.7%)

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

Psychiatric disorders: Insomnia (9%)

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

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

Vascular disorders: Hypertension (4%), haemorrhage (3%)<sup>§</sup>, deep vein thrombosis (<1%)

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

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

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

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

<sup>§</sup>Excluding epistaxis

### **Abnormal Haematological and Clinical Chemistry Findings**

Clinically relevant laboratory abnormalities are presented in Table 8.

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

Laboratory parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Haematology<sup>a</sup></b>						
Haemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
<b>Clinical chemistry</b>						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

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<sup>a</sup> Includes reports of anaemia, leucopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia

## Adverse Events in Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

### Adverse Reaction Overview

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

The most common treatment-emergent adverse reaction irrespective of causality (incidence  $\geq 30\%$ ) was stomatitis. The most common grade 3-4 adverse events (incidence  $\geq 2\%$ ) were stomatitis, amenorrhoea and convulsion. The most common clinically relevant laboratory abnormalities (incidence  $\geq 50\%$ ) were increased cholesterol and triglycerides and decreased haemoglobin. The most common clinically relevant grade 3/4 laboratory abnormality (incidence  $\geq 2\%$ ) was decreased phosphate. A single death was reported in the AFINITOR arm as a result of

status epilepticus in a patient with a prior history of intractable seizures.

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

### **Clinical Trial Adverse Reactions**

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

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

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

	AFINITOR 10 mg/day N=79			Placebo N=39		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Any Adverse Event</b>	<b>100</b>	<b>25</b>	<b>5</b>	<b>97</b>	<b>8</b>	<b>5</b>
<b>Blood and Lymphatic System Disorders</b>						
Anaemia	11	0	0	3	0	0
Leukopenia	10	0	0	8	0	0
<b>Gastrointestinal Disorders</b>						
Stomatitis <sup>a</sup>	78	6	0	23	0	0
Nausea	16	0	0	13	0	0
Vomiting	15	0	0	5	0	0
Diarrhoea	14	0	0	5	0	0
Abdominal pain	11	0	0	8	3	0
<b>General Disorders and Administration Site Conditions</b>						
Oedema peripheral	13	1	0	8	0	0
<b>Infections and Infestations</b>						
Upper respiratory tract	11	0	0	5	0	0



	AFINITOR 10 mg/day N=79			Placebo N=39		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
infection						
<b>Investigations</b>						
Blood lactate dehydrogenase increased	11	0	0	3	0	0
<b>Metabolism and Nutrition Disorders</b>						
Hypercholesterolaemia	23	1	0	3	0	0
Hypophosphataemia	11	0	0	3	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Arthralgia	13	0	0	5	0	0
<b>Nervous System Disorders</b>						
Headache	22	0	0	21	3	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	20	0	0	13	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>						
Acne	22	0	0	5	0	0
Rash <sup>b</sup>	11	0	0	0	0	0
Eczema	10	0	0	8	0	0

Grading according to CTCAE Version 3.0

<sup>a</sup> Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis and glossodynia.

<sup>b</sup> Includes rash, erythema, rash erythematous, palmar erythema, rash macular

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

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

Blood and lymphatic system disorders: Thrombocytopenia (8%)

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

Immune system disorders: Hypersensitivity (3%)

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

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

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

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

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

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

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

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

Vascular disorders: Hypertensive crisis (1%)

### **Abnormal Haematological and Clinical Chemistry Findings**

Clinically relevant laboratory abnormalities are presented in Table 10 below.

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

Laboratory parameter	AFINITOR 10 mg/day N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
<b>Haematology</b>						
Haemoglobin decreased	61	0	0	49	0	0
White blood cells (WBC) decreased	37	0	0	21	0	0
Lymphocytes decreased	20	1	0	8	0	0
Platelets decreased	19	0	0	3	0	0
<b>Clinical chemistry</b>						
Cholesterol increased	85	1	0	46	0	0
Triglycerides increased	52	0	0	10	0	0
Phosphate decreased	49	5	0	15	0	0
Alkaline phosphatase increased	32	1	0	10	0	0

Laboratory parameter	AFINITOR 10 mg/day N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Aspartate transaminase (AST) increased	23	1	0	8	0	0
Alanine transaminase (ALT) increased	20	1	0	15	0	0
Glucose (fasting) increased	14	0	0	8	0	0

Grading according to CTCAE Version 3.0

Further long term follow-up with a median duration of exposure of 47 months resulted in the following additional key laboratory abnormalities: partial thromboplastin time increased (63%), prothrombin time increased (40%), fibrinogen decreased (38%); and notable adverse events: nasopharyngitis (44.6%), urinary tract infection (31%), proteinuria (18%), bronchitis (14.3%), pyrexia (13%), oropharyngeal pain (13%), pruritus (12%), gastroenteritis (12%), blood lactate dehydrogenase increased (11%), dizziness (11%) and myalgia (11%), dental conditions (tooth abscess [7.1%], tooth infection [6.3%], and periodontitis [5.4%]), and metrorrhagia (5.4%). Blood follicle stimulating hormone (FSH) increased and blood luteinizing hormone (LH) increased was reported in 2 male patients (5.1%; 2/39 male patients). One of these 2 patients also reported blood testosterone decreased (2.6%; 1/39 male patients).

### **Adverse Events in SEGA associated with Tuberous Sclerosis Complex**

#### **Adverse Reaction Overview**

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

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

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

## **Clinical Trial Adverse Reactions**

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

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

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

	AFINITOR N=78			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
<b>Any adverse reaction</b>	<b>97</b>	<b>36</b>	<b>3</b>	<b>92</b>	<b>23</b>	<b>3</b>
<b>Gastrointestinal disorders</b>						
Stomatitis <sup>a</sup>	62	9	0	26	3	0
Vomiting	22	1	0	13	0	0
Diarrhoea	17	0	0	5	0	0
Constipation	10	0	0	3	0	0
<b>Infections and infestations</b>						
Respiratory tract infection <sup>b</sup>	31	1	1	23	0	0
Gastroenteritis <sup>c</sup>	10	4	1	3	0	0
Pharyngitis streptococcal	10	0	0	3	0	0
Ear infection <sup>f</sup>	18	3	0	15	3	0
<b>General disorders and administration site conditions</b>						
Pyrexia	23	6	0	18	3	0
Fatigue	14	0	0	3	0	0
<b>Psychiatric and behavioural disorder</b>						
Anxiety, aggression or other behavioural disturbance <sup>d</sup>	21	5	0	3	0	0
<b>Skin and subcutaneous tissue disorders</b>						
Rash <sup>e</sup>	21	0	0	8	0	0
Acne	10	0	0	5	0	0
Grading according to CTCAE Version 3.0						

- <sup>a</sup> Includes mouth ulceration, stomatitis and lip ulceration
- <sup>b</sup> Includes respiratory tract infection, upper respiratory tract infection and respiratory tract infection viral
- <sup>c</sup> Includes gastroenteritis, gastroenteritis viral and gastrointestinal infection
- <sup>d</sup> Includes agitation, anxiety, panic attack, aggression, abnormal behaviour and obsessive compulsive disorder
- <sup>e</sup> Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic and urticaria
- <sup>f</sup> Includes otitis media, ear infection, ear infection bacterial, otitis media acute

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

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

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

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

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

Immune system disorders: Hypersensitivity (3%)

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

Investigations: Blood luteinising hormone increased (1%)

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

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

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

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

### **Abnormal Haematological and Clinical Chemistry Findings**

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

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

	AFINITOR N=78	Placebo N=39

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

Grading according to CTCAE Version 3.0

Further long-term follow-up with a medium duration of exposure of 47 months resulted in the following additional notable adverse events and key laboratory abnormalities: nasopharyngitis (35%), cough (26%), pneumonia (25%), sinusitis (20%), bronchitis (18%), otitis media (18%), headache (15%), decreased appetite (14%), hyperglycemia (13%), hypertension (11%), urinary tract infection (9%), decreased fibrinogen (8%), oropharyngeal pain (6%), cellulitis (6%), abdominal pain (5%), weight decrease (5%), irritability (5%) and elevated creatinine (5%) and azoospermia (1%).

## Clinical Trial Adverse Events in Patients with Seizures Associated with TSC

### Adverse Reaction Overview

The data described below are based on a randomized, double-blind, multicenter, three-arm, parallel-group, phase-III study of AFINITOR DISPERZ versus placebo as adjunctive therapy conducted in patients with seizures associated with TSC. A total of 247 patients received AFINITOR DISPERZ (Low dose/low trough [LT] range: 3 to 7 ng/mL, n=117; High dose/high trough [HT] range: 9 to 15 ng/mL, n = 130) or placebo (n=119), added to each patient's concomitant AED therapy.

The most common adverse reactions reported for AFINITOR DISPERZ with an incidence  $\geq$  20% (in either the LT or HT arms) were stomatitis (55% AFINITOR DISPERZ LT, 64% AFINITOR DISPERZ HT) and diarrhea (17%, 22%). The most common Grade 3-4 adverse reactions (incidence  $\geq$  2%) were stomatitis (3%, 4%), neutropenia (2%, 2%), pneumonia (1%, 2%), and irregular menstruation (0%, 2%)(see Table 13). The most common clinically relevant laboratory abnormalities (incidence  $\geq$  30%) were hypercholesterolemia (85%, 85%), hypertriglyceridemia (43%, 38%), neutropenia (25%, 37%), and anemia (26%, 30%). The most common clinically relevant Grade 3-4 laboratory abnormality (incidence  $\geq$  2%) was neutropenia (4%, 6%) (see Table 14). The most common serious adverse events (incidence  $\geq$  1%) were pneumonia (0.9%,

3%), status epilepticus (2%, 2%), headache (0%, 2%), seizure (2%, 0.8%), mouth ulceration (2%, 0%), pharyngitis (2%, 0%), and urinary tract infection (2%, 0%).

Adverse reactions leading to study drug discontinuation occurred in 5% and 3% of patients in the AFINITOR DISPERZ LT and HT arms, respectively, and in 2% of patients in the placebo arm. The most common adverse reaction (incidence  $\geq$  1%) leading to AFINITOR DISPERZ discontinuation was stomatitis (2% AFINITOR DISPERZ LT, 2% AFINITOR DISPERZ HT, 0% placebo). Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 24% and 35% of patients in the AFINITOR DISPERZ LT and HT arms, respectively (Placebo: 8%). The most common adverse reactions (incidence  $\geq$  3%) leading to dose adjustments in the AFINITOR DISPERZ LT or HT arms were stomatitis (11%, 16%) including mouth ulceration (7%, 4%), pneumonia (0.9%, 4%), and pyrexia (3%, 2%).

**Table 13 Adverse events, irrespective of causality, by MedDRA Preferred Term reported in at least 10% of patients and at a higher rate in the AFINITOR DISPERZ arm than in the placebo arm during the Core treatment phase (Seizures associated with TSC)**

	AFINITOR DISPERZ						Placebo		
	LT target of 3-7 ng/mL			HT target of 9-15 ng/mL					
	N=117			N=130			N=119		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%	%	%	%
<b>Any adverse reactions</b>									
<b>Gastrointestinal disorders</b>									
Stomatitis <sup>a</sup>	55	3	0	64	4	0	9	0	0
Diarrhoea	17	0	0	22	0	0	5	0	0
Vomiting	12	0	0	10	2	0	9	0	0
<b>Infections and infestations</b>									
Nasopharyngitis	14	0	0	16	0	0	16	0	0
Upper respiratory tract infection	13	0	0	15	0	0	13	1	0
<b>General disorders and administration site conditions</b>									
Pyrexia	20	0	0	14	1	0	5	0	0
<b>Respiratory, thoracic and mediastinal disorders</b>									
Cough	11	0	0	10	0	0	3	0	0
<b>Skin and subcutaneous tissue disorders</b>									
Rash <sup>b</sup>	6	0	0	10	0	0	3	0	0

<sup>a</sup>Includes reports of stomatitis, mouth ulceration, aphthous ulcer, lip ulceration, tongue ulceration, mucosal inflammation, gingival pain  
<sup>b</sup>Includes reports of rash, rash erythematous, rash generalized, erythema, rash maculo-papular, rash macular

Other adverse events occurring with AFINITOR DISPERZ treated patients with an incidence of < 10% and considered clinically relevant include (%AFINITOR DISPERZ LT, % AFINITOR DISPERZ HT):

Gastrointestinal disorders: constipation (0%, 4%), nausea (1%, 3%), flatulence (0%, 2%), gastritis (1%, 1%), abdominal pain (3%, 0%), abdominal pain upper (2%, 5%)

General disorders and administration site conditions: fatigue (3%, 5%)

Infections and infestations: pharyngitis (5%, 6%), pneumonia (2%, 4%), sinusitis (0.9%, 4%), urinary tract infection (3%, 2%), pharyngitis streptococcal (0%, 2%), gastroenteritis viral (0%, 1%), gingivitis (3%, 1%), otitis media (2%, 1%), cellulitis (1%, 1%)

Investigations: blood lactate dehydrogenase increased (0%, 1%), blood luteinizing hormone increased (1%, 0%)

Metabolism and nutritious disorders: decreased appetite (9%, 7%)

Nervous system disorders: headache (3%, 9%)

Psychiatric disorders: irritability (2%, 2%), aggression (2%, 1%), insomnia (3%, 1%)

Renal and urinary disorders: proteinuria (0%, 2%)

Reproductive and breast disorders: amenorrhea (7%, 3%; in female patients aged 10 to 55 years), irregular menstruation (7%, 9%; in female patients aged 10 to 55 years), menorrhagia (3%, 3%; in female patients aged 10 to 55 years)

Respiratory, thoracic and mediastinal disorders: epistaxis (3%, 5%), pneumonitis (0%, 1%)

Skin and subcutaneous tissue disorders: acne (3%, 6%), dry skin (3%, 2%)

Vascular disorders: hypertension (2%, 2%)

**Abnormal Haematological and Clinical Chemistry Findings**

Clinically relevant laboratory abnormalities reported more frequently with AFINITOR DISPERZ than placebo are presented in Table 14.

**Table 14 Clinically relevant laboratory abnormalities reported in at a higher rate in the AFINITOR DISPERZ arm than in the placebo arm during the Core treatment phase (Seizures associated with TSC)**

	AFINITOR DISPERZ						Placebo		
	LT target of 3-7 ng/mL			HT target of 9-15 ng/mL					
	N=117			N=130			N=119		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4



	%	%	%	%	%	%	%	%	%
<b>Hematology</b>									
Neutropenia	25	4	0	37	5	0.8	23	7	0
Anemia	27	1	0	30	0	0	21	1	0
Leukopenia	14	0	0	25	0	0	18	0	0
Thrombocytopenia	12	0	0	15	0	0	6	0	0
<b>Clinical Chemistry</b>									
Hypercholesterolemia	85	0	0	85	0.8	0	58	0	0
Hypertriglyceridemia	43	2	0	38	0.8	0.8	22	0	0
Elevated alanine transaminase (ALT)	17	0	0	22	0	0	6	0	0
Elevated aspartate transaminase (AST)	13	0	0	18	0	0	4	0	0
Hyperglycemia	19	0	0	18	0	0	17	0	0
Elevated alkaline phosphatase	24	0	0	16	0	0	29	0	0
Hypophosphatemia	9	1	0	16	0.8	0.8	3	0	0
Grading according to CTCAE version 4.03									

Updated safety information from 361 patients treated with AFINITOR DISPERZ in the Core and/or Extension treatment phases for a median duration of 20.8 (0.5 to 37.9) months identified the following additional notable adverse reactions: angioedema (0.3%) and sepsis (0.8%).

### **Post-Market Adverse Reactions**

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

Blood and lymphatic system disorders: febrile neutropenia

Immune system disorders: hepatitis B reactivation, including fatal outcome (reactivation of infections is an expected event during periods of immunosuppression), angioedema with and without concomitant use of ACE inhibitors

Infections and infestations: pneumocystis jirovecii pneumonia (PJP)

Musculoskeletal and connective tissue disorders: rhabdomyolysis

Renal and urinary disorders: renal failure events, including fatal outcome (monitoring of renal function is recommended), proteinuria

Reproductive system and breast disorders: secondary amenorrhoea

Respiratory, thoracic and mediastinal disorders: pulmonary embolism

## DRUG INTERACTIONS

### Overview

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

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

### Drug-Drug Interactions

#### **Agents that may increase everolimus blood concentrations:**

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

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

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

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

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

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

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

#### **Agents that may decrease everolimus blood concentrations:**

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

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

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

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

**Agents whose plasma concentrations may be altered by everolimus:**

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between 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 everolimus. However, these studies were carried out with a 2 mg oral dose of everolimus. The effects of a 10 mg dose have not been studied and therefore pharmacological interactions cannot be ruled out in this setting.

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

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

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

Everolimus increased pre-dose concentrations of the antiepileptic drugs (AEDs) carbamazepine, clobazam, and the clobazam metabolite N-desmethyloclobazam by about 10%. The increase in the

pre-dose concentrations of these AEDs may not be clinically significant but dose adjustments for AEDs with a narrow therapeutic index e.g. carbamazepine may be considered.

#### CYP3A4 Substrates (AEDs)

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

#### Other Anti-Epileptic Drugs (AEDs)

Everolimus had no impact on the pre-dose concentration of other AEDs, including valproic acid, topiramate, oxcarbazepine, phenobarbital, phenytoin and primidone

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

Co-administration of AFINITOR and exemestane (a drug which is metabolized in part by CYP3A4) increased exemestane  $C_{min}$  and  $C_{2h}$  by 45% and 71%, respectively. However, the corresponding oestradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

#### **Pharmacodynamic drug interactions:**

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

#### **Vaccinations:**

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

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

#### **Drug-Food Interactions**

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

#### **Drug-Herb Interactions**

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

### **Drug-Laboratory Test Interactions**

Interactions between AFINITOR or AFINITOR DISPERZ and laboratory tests have not been studied.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

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

AFINITOR (everolimus) is available in two dosage forms, tablets (AFINITOR) and tablets for oral suspension (AFINITOR DISPERZ). AFINITOR and AFINITOR DISPERZ are **not** interchangeable and should **not** be combined to achieve the desired dose (see **Switching dosage forms** below).

#### **AFINITOR Tablets**

AFINITOR (tablets) may be used in all approved oncology indications and for the renal angiomyolipoma associated with tuberous sclerosis complex (TSC) and subependymal giant cell astrocytoma (SEGA) associated with TSC indications. For patients with SEGA associated with TSC, AFINITOR must be used in conjunction with therapeutic drug monitoring (see **Therapeutic drug monitoring for patients treated for SEGA and/or seizures associated with TSC** below).

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

#### **AFINITOR DISPERZ (Tablets for Oral Suspension)**

AFINITOR DISPERZ (tablets for oral suspension) should only be used for the treatment of patients with SEGA and/or seizures associated with TSC. For patients with SEGA and/or seizures associated with TSC, AFINITOR DISPERZ must be used in conjunction with therapeutic drug monitoring (see **Therapeutic drug monitoring for patients treated for SEGA and/or seizures associated with TSC** below).

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

**Management of Adverse Reactions:**

Management of severe or intolerable suspected adverse drug reactions may require temporary dose interruption (with or without dose reduction) or discontinuation of AFINITOR or AFINITOR DISPERZ therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered (see **Table 15** and **WARNINGS AND PRECAUTIONS**). For dose reductions below the lowest available tablet strength, alternate day dosing should be considered.

Table 15 summarizes recommendations for dose interruption, reduction, or discontinuation of AFINITOR or AFINITOR DISPERZ in the management of adverse reactions. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**Table 15 AFINITOR or AFINITOR DISPERZ dose adjustment and management recommendations for adverse drug reactions**

<b>Adverse Drug Reaction</b>	<b>Severity<sup>a</sup></b>	<b>AFINITOR or AFINITOR DISPERZ Dose Adjustment<sup>b</sup> and Management Recommendations</b>
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 <sup>c</sup>	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 <sup>c</sup> ; O <sub>2</sub> indicated	Interrupt treatment until symptoms resolve to ≤ grade 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.

<b>Adverse Drug Reaction</b>	<b>Severity<sup>a</sup></b>	<b>AFINITOR or AFINITOR DISPERZ Dose Adjustment<sup>b</sup> and Management Recommendations</b>
Stomatitis	Grade 1 Asymptomatic or mild symptoms, intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2  Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to grade $\leq 1$ . Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade $\leq 1$ . 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). <sup>d</sup>
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade $\leq 1$ . Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste). <sup>d</sup>
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy.
Other non-haematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade $\leq 1$ . Re-initiate treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade $\leq 1$ . Re-initiate treatment at a lower dose.
	Grade 3	Temporary dose interruption until recovery to grade $\leq 1$ . Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at a lower dose.

<b>Adverse Drug Reaction</b>	<b>Severity<sup>a</sup></b>	<b>AFINITOR or AFINITOR DISPERZ Dose Adjustment<sup>b</sup> and Management Recommendations</b>
		If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 (<LLN <sup>e</sup> - 75.0 x 10 <sup>9</sup> /L)	No dose adjustment required.
	Grade 2 (<75.0 - 50.0 x 10 <sup>9</sup> /L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose.
	Grade 3 (<50.0 - 25.0 x 10 <sup>9</sup> /L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose.
	Grade 4 (<25.0 x 10 <sup>9</sup> /L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose.
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN <sup>e</sup> - 1.5 x 10 <sup>9</sup> /L)	No dose adjustment required.
	Grade 2 (<1.5 - 1.0 x 10 <sup>9</sup> /L)	No dose adjustment required.
	Grade 3 (<1.0 - 0.5 x 10 <sup>9</sup> /L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at the same dose.
	Grade 4 (<0.5 x 10 <sup>9</sup> /L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at a lower dose.
Febrile neutropenia	Grade 3 ANC <sup>f</sup> <1.0 x 10 <sup>9</sup> /L with a single temperature of >38.3°C (101°F) or a	Temporary dose interruption until recovery of ANC to ≥ 1.25 x 10 <sup>9</sup> /L and no fever.  Re-initiate treatment at a lower dose.



Adverse Drug Reaction	Severity <sup>a</sup>	AFINITOR or AFINITOR DISPERZ Dose Adjustment <sup>b</sup> and Management Recommendations
	sustained temperature of $\geq 38^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ ) for more than one hour.	
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

<sup>a</sup> 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.

<sup>b</sup> If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

<sup>c</sup> Activities of daily living (ADL)

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

<sup>e</sup> Lower limit of normal (LLN)

<sup>f</sup> Absolute Neutrophil Count (ANC)

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

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

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

**Strong inhibitors of CYP3A4/PgP:** Avoid the use of concomitant strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or PgP, due to the risk of reduced

effectiveness of the drug (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

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

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

Renal angiomyolipoma associated with TSC:

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

SEGA associated with TSC:

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

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

Seizures associated with TSC:

For patients with seizures associated with TSC receiving concomitant strong CYP3A4 inducers (e.g., enzyme inducing antiepileptic drugs carbamazepine, phenobarbital, and phenytoin) at the start of treatment with everolimus, increase the starting dose of AFINITOR DISPERZ to attain trough concentrations of 5 to 15 ng/mL (see recommendations outlined in Table 16). Further

adjust the dose by increments of 1 to 4 mg as necessary to maintain the target trough concentration (see **Therapeutic drug monitoring for patients treated for SEGA and/or seizures associated with TSC** below, **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

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

#### **SEGA and/or seizures associated with TSC:**

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

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

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

#### **Recommended Dose and Dosage Adjustment**

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

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

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

**Renal Angiomyolipoma associated with Tuberous Sclerosis Complex:** Optimal duration of

treatment with AFINITOR is not known.

### **Special Populations and Conditions**

#### **Geriatrics (≥ 65 years):**

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

#### **Paediatrics (< 18 years):**

AFINITOR or AFINITOR DISPERZ is not recommended for use in paediatric patients with renal angiomyolipoma associated with TSC.

#### **Renal impairment:**

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

#### **Hepatic impairment:**

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

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

### **Missed Dose**

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

### **Administration**

#### **AFINITOR**

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

#### **SEGA and/or seizures associated with Tuberous Sclerosis Complex**

## **Recommended Dose and Dosage Adjustment**

Individualise dosing based on body surface area (BSA, in m<sup>2</sup>), calculated using the Dubois formula<sup>3</sup>.

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

### *Starting dose and target trough concentrations in SEGA associated with TSC*

The recommended starting daily dose for AFINITOR or AFINITOR DISPERZ for the treatment of patients with SEGA associated with TSC is 4.5 mg/m<sup>2</sup>, rounded to the nearest strength of AFINITOR or AFINITOR DISPERZ. Different strengths of AFINITOR can be combined to attain the desired dose. Likewise, different strengths of AFINITOR DISPERZ can be combined to attain the desired dose. The two dosage forms should **not** be combined to achieve the desired dose.

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

### *Starting dose and target trough concentrations in seizures associated with TSC*

The recommended starting daily dose for AFINITOR DISPERZ for the treatment of seizures associated with TSC is shown in Table 16. The starting dose should be rounded to the nearest available strength of AFINITOR DISPERZ. Different strengths of AFINITOR DISPERZ can be combined to attain the desired dose. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/mL.

**Table 16**                      **AFINITOR DISPERZ starting dose in TSC with refractory seizures**

<b>Age</b>	<b>Starting dose without co-administration of CYP3A4/PgP inducer</b>	<b>Starting dose with co-administration of CYP3A4/PgP inducer</b>
<6 years	6 mg/m <sup>2</sup>	9 mg/m <sup>2</sup>
≥6 years	5 mg/m <sup>2</sup>	8 mg/m <sup>2</sup>

AFINITOR DISPERZ is the only formulation that should be used for the treatment of patients with seizures associated with TSC.

<sup>3</sup> BSA = (W<sup>0.425</sup> x H<sup>0.725</sup>) x 0.007184 (weight (W) is in kilograms and height (H) is in centimetres)

*Dose titration for SEGA (AFINITOR and AFINITOR DISPERZ) and/or seizures (AFINITOR DISPERZ) associated with TSC.*

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

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

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

### **Therapeutic drug monitoring for SEGA and/or seizures associated with TSC**

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

Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after the initial dose, after any change in dose or dosage form (between AFINITOR and AFINITOR DISPERZ), after an initiation or change in co-administration of inducers or inhibitors of CYP3A4 /PgP (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**) or after any change in hepatic (Child-Pugh) status (see **Recommended Dose and Dosage Adjustment**, **Patients with hepatic impairment** below and **ACTION AND CLINICAL PHARMACOLOGY**).

#### *Long-term dose monitoring*

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

### **Switching dosage forms**

The two dosage forms (AFINITOR and AFINITOR DISPERZ) are **not** interchangeable. Do not combine the two dosage forms to achieve the desired dose. Consistently use the same dosage form, as appropriate for the indication being treated (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations**).

### **SEGA volume monitoring for patients treated with AFINITOR or AFINITOR DISPERZ**

SEGA volume should be evaluated approximately 3 months after commencing AFINITOR or AFINITOR DISPERZ therapy and periodically thereafter. In the phase II and phase III clinical studies, SEGA volume monitoring was performed at baseline, Month 3, Month 6 and every 6

months thereafter. The optimal schedule of monitoring and the optimal duration of AFINITOR therapy are unknown, but SEGA progressions were reported in 13 of the 111 patients approximately 8 to 56 months after initiation of AFINITOR therapy by independent central review in the phase III study. Six patients progressed while on AFINITOR remained on treatment as they were considered to be experiencing clinical benefit. No patient required surgical intervention for SEGA during the course of the study. Subsequent dose adjustments should take into consideration changes in SEGA volume, corresponding trough concentration and tolerability. Responses have been observed at trough concentrations as low as 2 ng/mL; as such, once acceptable efficacy has been achieved, additional dose increase is not necessary.

### **Special Populations and Conditions**

#### **Hepatic impairment:**

##### Patients with SEGA associated with TSC, $\geq 18$ years of age

- Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B) – 50% of the dose calculated based on BSA (rounded to the nearest strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended

##### Patients with seizures associated with TSC, $\geq 18$ 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

##### Patients $< 18$ years of age

AFINITOR and AFINITOR DISPERZ are not recommended for patients  $< 18$  years of age with SEGA or seizures associated with TSC and concomitant hepatic impairment.

#### **Paediatrics ( $< 18$ years):**

Dosing recommendation for paediatric patients with SEGA are consistent with those for the corresponding adult population.

Dosing recommendations for paediatric patients  $\geq 6$  years of age with seizures associated with TSC are consistent with those for the corresponding adult population. The recommended AFINITOR DISPERZ starting dose for patients  $< 6$  year of age and patients  $\geq 6$  years of age is provided in Table 16.

AFINITOR and AFINITOR DISPERZ are not recommended for patients  $< 18$  years of age with SEGA who have any degree of hepatic impairment. AFINITOR DISPERZ is not recommended for patients  $< 18$  years of age with seizures associated with TSC who have any degree of hepatic impairment (see **Hepatic impairment** above).

### **Missed Dose**

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

### **Administration**

*SEGA associated with TSC*

### **AFINITOR**

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

*SEGA and/or seizures associated with TSC*

### **AFINITOR DISPERZ**

AFINITOR DISPERZ tablets for oral suspension should be administered as a suspension only and should not be swallowed whole, chewed, or crushed. The suspension can be prepared in an oral syringe or in a small drinking glass. Care should be taken to ensure the entire dose is administered.

Administer the suspension immediately after preparation. Discard the suspension if not administered within 60 minutes of preparation. Prepare the suspension in water only.

A complete and illustrated set of instructions for the tablet for oral suspension is provided in **Part III: CONSUMER INFORMATION**.

#### **Using an oral syringe:**

- Place the prescribed dose of AFINITOR DISPERZ into a 10 mL syringe. Do not exceed a total of 10 mg per syringe. If higher doses are required, prepare an additional syringe. Do not break or crush tablets.
- Draw approximately 5 mL of water and 4 mL of air into the syringe.
- Place the filled syringe into a container (tip up) for 3 minutes, until the AFINITOR DISPERZ tablets are in suspension.
- Gently invert the syringe 5 times immediately prior to administration.
- After administration of the prepared suspension, draw approximately 5 mL of water and 4 mL of air into the same syringe, and swirl the contents to suspend remaining particles. Administer the entire contents of the syringe.



### **Using a small drinking glass:**

- Place the prescribed dose of AFINITOR DISPERZ into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg of AFINITOR DISPERZ per glass. If higher doses are required, prepare an additional glass. Do not break or crush tablets.
- Allow 3 minutes for suspension to occur.
- Stir the contents gently with a spoon, immediately prior to drinking.
- After administration of the prepared suspension, add 25 mL of water and stir with the same spoon to re-suspend remaining particles. Administer the entire contents of the glass.

### **Switching dosage forms**

The two dosage forms (AFINITOR and AFINITOR DISPERZ) are **not** interchangeable. Do not combine the two dosage forms to achieve the desired dose. Use one dosage form or the other.

When switching dosage forms, the dose should be adjusted to the closest milligram strength of the new dosage form and the everolimus trough concentration should be assessed approximately 2 weeks later (see **Therapeutic drug monitoring for patients treated for SEGA and/or seizures associated with TSC** above).

## **OVERDOSAGE**

For management of suspected drug overdose, contact your regional poison control centre.
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In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2,000 mg/kg (limit test).

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

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

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Everolimus is an inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signalling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream of the PI3K/AKT pathway, which is dysregulated in the majority of human cancers. Consistent with the central regulatory role of mTORC1, its inhibition by everolimus has been shown to reduce cell proliferation, glycolysis and angiogenesis in solid tumours *in vivo*, both through direct anti-tumour cell activity and inhibition of the tumour stromal compartment.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the PI3K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (AI)-resistant and long-term oestrogen-deprived breast cancer cells. In *in vitro* models of breast cancer cells, resistance to AIs due to Akt activation can be reversed by co-administration with everolimus.

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

### **Pharmacodynamics/Exposure response relationships**

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

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

### **Pharmacokinetics**

**Absorption:** After administration of AFINITOR to patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack.  $C_{max}$  is dose-proportional with daily dosing between 5 and 10 mg. With single doses of 20 mg and higher, the increase in  $C_{max}$  is less than dose-proportional; however, AUC shows dose-proportionality over the 5 to 70 mg dose range. Steady-state was achieved within 2 weeks with the daily dosing regimen. There

was a significant correlation between  $AUC_{0-\tau}$  and pre-dose trough concentration at steady-state on the daily regimen.

**Table 17 Summary Statistics of Main Pharmacokinetic Parameters of Everolimus in the Pivotal Phase III Trial**

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

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

**Relative bioavailability of tablets for oral suspension:** In comparative bioavailability studies, the  $C_{max}$  of everolimus associated with the tablet for oral suspension when administered as a suspension in water was lower than that of the intact everolimus tablets ( $C_{max}$  of the tablets for oral suspension was 64% to 80% of the intact everolimus tablets). In addition, the  $AUC_{0-\infty}$  of the everolimus tablets for oral suspension was 86% to 91% that of intact everolimus tablets. Similarly,  $AUC_{0-72h}$  was 86 to 90 % that of the intact everolimus tablets. However, the predicted trough ( $C_{min}$ ) concentrations of everolimus at steady-state after daily administration were similar for both formulations (see **Table 31 and Table 32, CLINICAL TRIALS, Comparative Bioavailability Studies**).

**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 elimination studies have been undertaken in cancer patients; however, data are available from the transplantation setting. Following the administration of a single dose of radio-labelled everolimus in conjunction with cyclosporine, 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine over 10 days. The parent substance was not detected in urine or faeces.

### **Special Populations and Conditions**

#### **Paediatrics:**

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

In patients with seizures associated with TSC receiving AFINITOR DISPERZ, a trend was observed toward lower  $C_{min}$  normalized to dose (as  $mg/m^2$ ) in younger patients. Median  $C_{min}$  normalized to  $mg/m^2$  dose was lower for the younger age groups (<6 years), indicating that everolimus clearance (normalized to body surface area) was higher in younger patients (see **DOSAGE AND ADMINISTRATION**, Table 16).

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

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

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

**Hepatic Impairment:** The influence of hepatic impairment on the pharmacokinetics of AFINITOR was assessed in two independent single oral dose studies in adult volunteers. One study evaluated the pharmacokinetics of everolimus in 8 volunteers with moderate hepatic impairment (Child-Pugh B) and 8 volunteers with normal hepatic function. Compared to normal volunteers, there was a 2.2-fold increase in exposure ( $AUC_{0-inf}$ ) for subjects with moderate hepatic impairment. A second study evaluated the pharmacokinetics of AFINITOR in 7 volunteers with mild hepatic impairment (Child-Pugh A), 8 volunteers with moderate hepatic impairment (Child-Pugh B), 6 volunteers with severe hepatic impairment (Child-Pugh C) and 13 volunteers with normal hepatic function. Compared to normal volunteers, there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure ( $AUC_{0-inf}$ ) for volunteers with mild, moderate and severe hepatic impairment, respectively. Simulations of multiple dose pharmacokinetics support

the dosing recommendations in hepatic impaired patients based on their Child-Pugh status. Dose adjustment is recommended for patients with hepatic impairment. Dosing recommendations are based on the combined results of the two studies (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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

## **STORAGE AND STABILITY**

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

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

## **SPECIAL HANDLING INSTRUCTIONS**

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

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Tablets**

AFINITOR (everolimus) tablets are elongated, white to slightly yellow in colour with a bevelled edge and no score. AFINITOR tablets are available in four strengths: 2.5 mg, 5 mg, 7.5 mg and 10 mg.

#### 2.5 mg:

The tablets are engraved with “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.

#### 7.5 mg:

The tablets are engraved with “7P5” on one side and “NVR” on the other.

#### 10 mg:

The tablets are engraved with “UHE” on one side and “NVR” on the other.

### *Non-medicinal Ingredients*

Butylated hydroxytoluene, crospovidone, hypromellose, lactose anhydrous, lactose monohydrate, magnesium stearate.

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

AFINITOR 7.5 mg are supplied in blister packs (7 blisters/card, 4 cards/carton).

### **Tablets for oral suspension**

AFINITOR DISPERZ tablets for oral suspension are round, flat, white to slightly yellowish in colour with a bevelled edge and no score. AFINITOR DISPERZ tablets for oral suspension are available in three strengths: 2 mg, 3 mg and 5 mg.

#### 2 mg:

The tablets are engraved with “D2” on one side and “NVR” on the other.

#### 3 mg:

The tablets are engraved with “D3” on one side and “NVR” on the other.

#### 5 mg:

The tablets are engraved with “D5” on one side and “NVR” on the other.

### *Non-medicinal Ingredients*

Butylated hydroxytoluene, cellulose microcrystalline, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol and silica colloidal anhydrous.

AFINITOR DISPERZ 2 mg, 3 mg and 5 mg tablets for oral suspension are supplied in blister packs (10 blisters/card, 3 cards/carton).

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

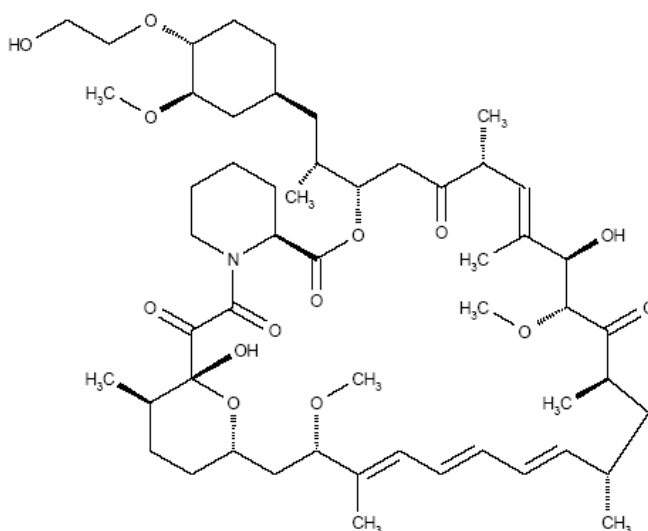
Common name: Everolimus

Chemical name: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-Dihydroxy-12-[(1R)-2-[(1S, 3R, 4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo [30.3.1.0<sup>4,9</sup>]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

Molecular formula: C<sub>53</sub>H<sub>83</sub>NO<sub>14</sub>

Molecular mass: 958.2

Structural formula:



#### Physicochemical properties

Physical description: White to faintly white powder

Solubility: The drug substance is practically insoluble in water, but it is soluble in organic solvents.

pH: Because the solubility in water is very low (<0.01 %) the pH of an aqueous solution was not determined. The pH value of 0.1 %

suspension of several batches in 1 % aqueous solution of KNO<sub>3</sub> were measured and the values lie in the range 4-6.

pKa:	No pKa value can be determined (neutral compound).
Partition Coefficient:	Because of the low solubility of everolimus stabilized with BHT in water and in aqueous buffers, the partition coefficient could not be determined.
Melting Point:	Not applicable since the drug substance is amorphous.

## CLINICAL TRIALS

### Safety and Efficacy Studies

#### **Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer**

##### **Study Y2301 (BOLERO-2)**

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

Refractory disease to NSAIs was defined as:

- Recurrence while on or within 12 months of the end of adjuvant treatment with letrozole or anastrozole
- or
- Progression while on or within 1 month of the end of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer

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

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



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

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

A total of 724 patients were randomized to the combination AFINITOR plus exemestane (n = 485) or placebo plus exemestane (n = 239). The two treatment groups were generally balanced with respect to baseline demographics, tumour burden, disease characteristics and history of prior anti-neoplastic therapies (see Table 18). Overall, 84% of patients were considered to be sensitive to prior endocrine therapy. The median age of patients was 61 years (range 28 to 93 years). Patients in the placebo plus exemestane arm did not cross-over to AFINITOR at the time of progression.

**Table 18 Demographic and Disease Characteristics (Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer)**

<b>Demographic or disease characteristic</b>	<b>AFINITOR plus exemestane N=485 n (%)</b>	<b>Placebo plus exemestane N=239 n (%)</b>	<b>All patients N=724 n (%)</b>
<b>Age category (years) (n [%])</b>			
< 65 years	290 (59.8)	159 (66.5)	449 (62.0)
≥ 65 years to <75 years	123 (25.4)	58 (24.3)	181 (25.0)
≥ 75 years	72 (14.8)	22 (9.2)	94 (13.0)
<b>Race</b>			
Caucasian	361 (74.4)	186 (77.8)	547 (75.6)
Asian	98 (20.2)	45 (18.8)	143 (19.8)
Black	13 (2.7)	3 (1.3)	16 (2.2)
Other	13 (2.7)	5 (2.1)	18 (2.5)
<b>Current disease status</b>			
Metastatic	483 (99.6)	239 (100.0)	722 (99.7)
Locally advanced	2 (0.4)	0	2 (0.3)
<b>Metastatic site of cancer</b>			
Bone	370 (76.3)	184 (77.0)	554 (76.5)
Visceral (excluding CNS)	283 (58.4)	143 (59.8)	426 (58.8)
CNS	6 (1.2)	0	6 (0.8)
Other	245 (50.5)	137 (57.3)	382 (52.8)
<b>ECOG performance status</b>			
0	293 (60.4)	142 (59.4)	435 (60.1)
1	174 (35.9)	84 (35.1)	258 (35.6)
2	9 (1.9)	7 (2.9)	16 (2.2)
Missing	9 (1.9)	6 (2.5)	15 (2.1)
<b>Prior anti-neoplastic therapy</b>			

<b>Demographic or disease characteristic</b>	<b>AFINITOR plus exemestane N=485 n (%)</b>	<b>Placebo plus exemestane N=239 n (%)</b>	<b>All patients N=724 n (%)</b>
Any non-steroidal aromatase inhibitor (NSAI)	485 (100)	239 (100)	724 (100)
Prior hormonal therapy other than NSAI	281 (57.9)	146 (61.1)	427 (59.0)
<b>Chemotherapy</b>	337 (69.5)	156 (65.3)	493 (68.1)
Neoadjuvant /adjuvant setting	211 (43.5)	95 (39.7)	306 (42.3)
Advanced setting (one line)	125 (25.8)	58 (24.3)	183 (25.3)
Other therapy	38 (7.8)	13 (5.4)	51 (7.0)

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

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

Subsequently, the trial remained blinded to investigators and patients to permit OS data to mature. Updated efficacy results (excluding OS) with an additional 5 months of follow-up (overall median follow-up of 12.5 months and documentation of 87% of targeted PFS events) demonstrated a significant clinical benefit of AFINITOR plus exemestane over placebo plus exemestane by a 2.3-fold prolongation in median PFS (median: 7.36 months versus 3.19 months), resulting in a 56 % risk reduction of progression or death (PFS HR 0.44; 95% CI: 0.36, 0.53); one-sided log-rank test p-value <0.0001 per local investigator assessment (see Table 19 and Figure 1).

The analysis of PFS based on independent central radiological assessment was supportive (see Table 19).

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

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

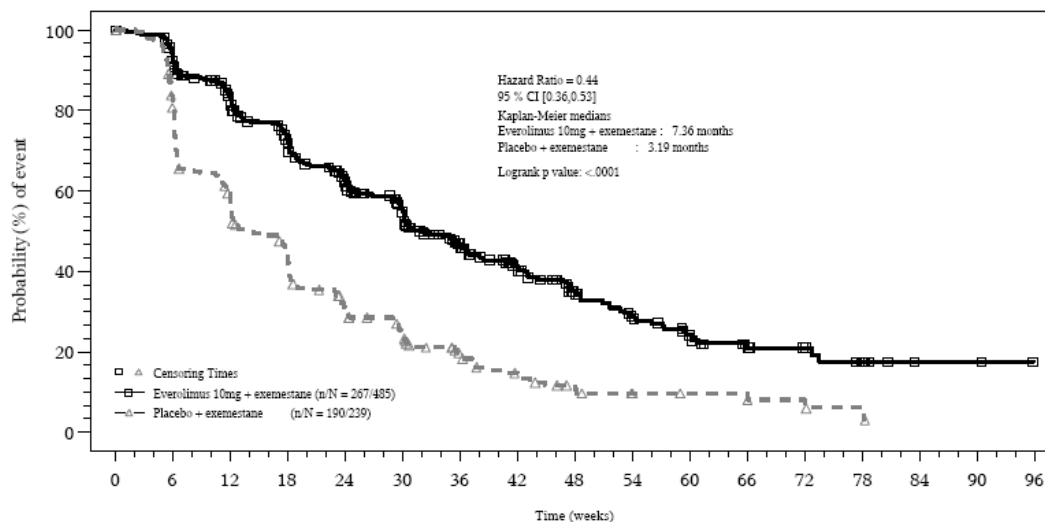
1.04)]. The final OS analysis is planned at 398 deaths.

**Table 19 Efficacy Results at a Median Follow-up of 12.5 Months (Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer)**

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

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

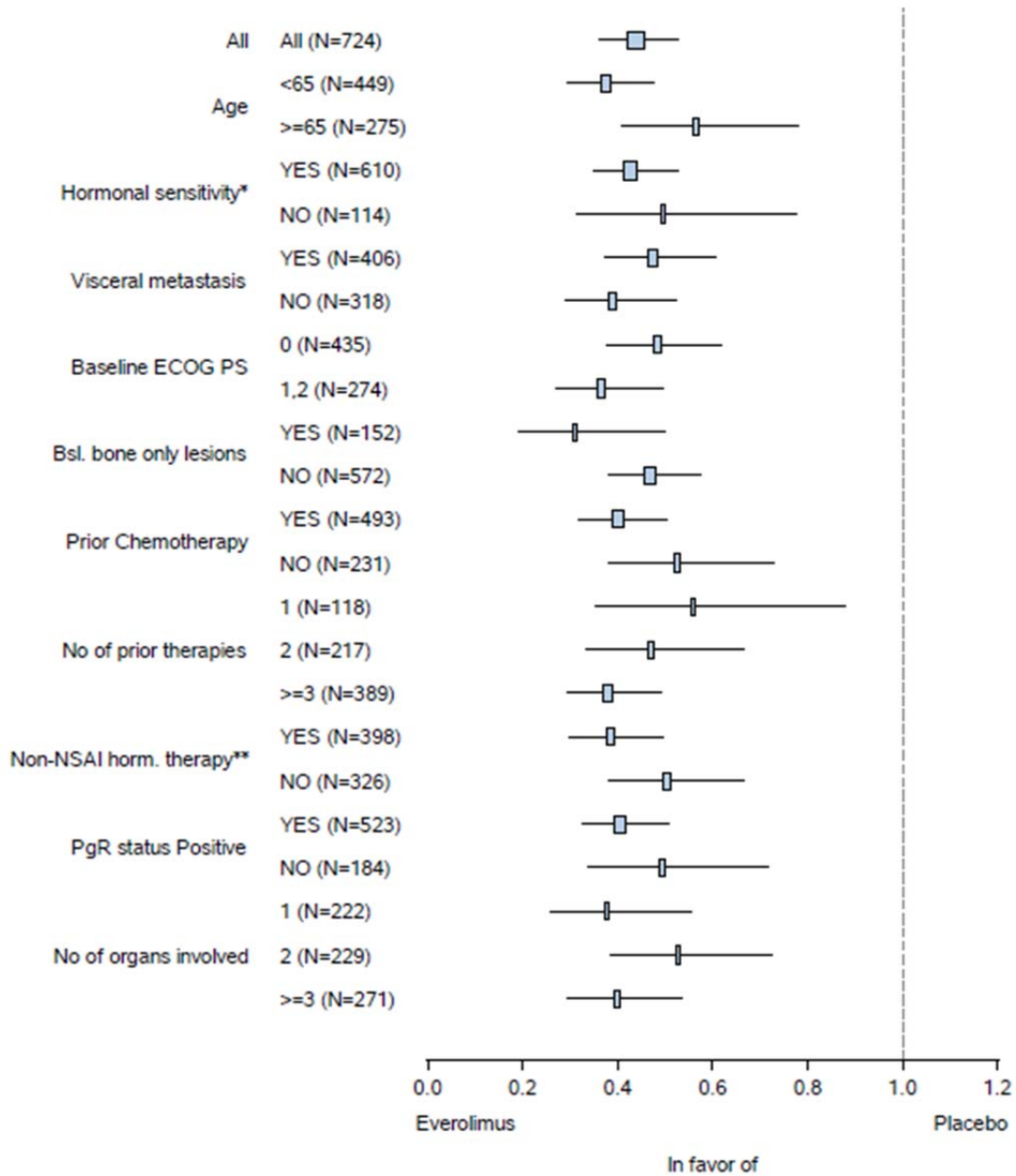
**Figure 1 Kaplan-Meier Progression-free Survival Curves at a Median Follow-up of 12.5 Months**



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

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

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



Hazard ratio was obtained using unstratified Cox proportional hazard model.

\* sensitivity to prior hormonal therapy

\*\* anti-estrogens, LHRH analogs and progestins

## Pancreatic Neuroendocrine Tumours (PNET)

### Study C2324 (RADIANT-3)

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

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

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

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

**Table 20 Demographic and Disease Characteristics (PNET)**

<b>Demographic or disease characteristic</b>	<b>AFINITOR N=207 n (%)</b>	<b>Placebo N=203 n (%)</b>	<b>Total N=410 N (%)</b>
<b>Age (years)</b>			
Mean (standard deviation)	57.1 (12.2)	56.2 (11.4)	56.5 (11.8)
Median	58.0	57.0	58.0
Range	23 - 87	20 - 82	20 - 87
<b>Age group (years) (n [%])</b>			
< 65 years	146 (70.5)	153 (75.4)	299 (72.9)
≥ 65 years	61 (29.5)	50 (24.6)	111 (27.1)
<b>Gender</b>			
Male	110 (53.1)	117 (57.6)	227 (55.4)
Female	97 (46.9)	86 (42.4)	183 (44.6)
<b>Race</b>			
Caucasian	146 (75.4)	166 (81.8)	322 (78.5)
Asian	40 (19.3)	34 (16.7)	74 (18.0)
Black	9 (4.3)	2 (1.0)	11 (2.7)
Other	2 (1.0)	1 (0.5)	3 (0.7)
<b>Histologic grade</b>			
Well differentiated	170 (82.1)	171 (84.2)	341 (83.2)
Moderately differentiated	35 (16.9)	30 (14.8)	65 (15.9)
Unknown	2 (1.0)	2 (1.0)	4 (1.0)

<b>Demographic or disease characteristic</b>	<b>AFINITOR N=207 n (%)</b>	<b>Placebo N=203 n (%)</b>	<b>Total N=410 N (%)</b>
<b>WHO performance status</b>			
0	139 (67.1)	133 (65.5)	272 (66.3)
1	62 (30.0)	64 (31.5)	126 (30.7)
2	6 (2.9)	6 (2.9)	12 (2.9)
<b>Prior long-acting somatostatin analogue therapy</b>	101 (48.8)	102 (50.2)	203 (49.5)

The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001) (see Table 21 and Figure 3). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analogue use. The PFS results by investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 21.

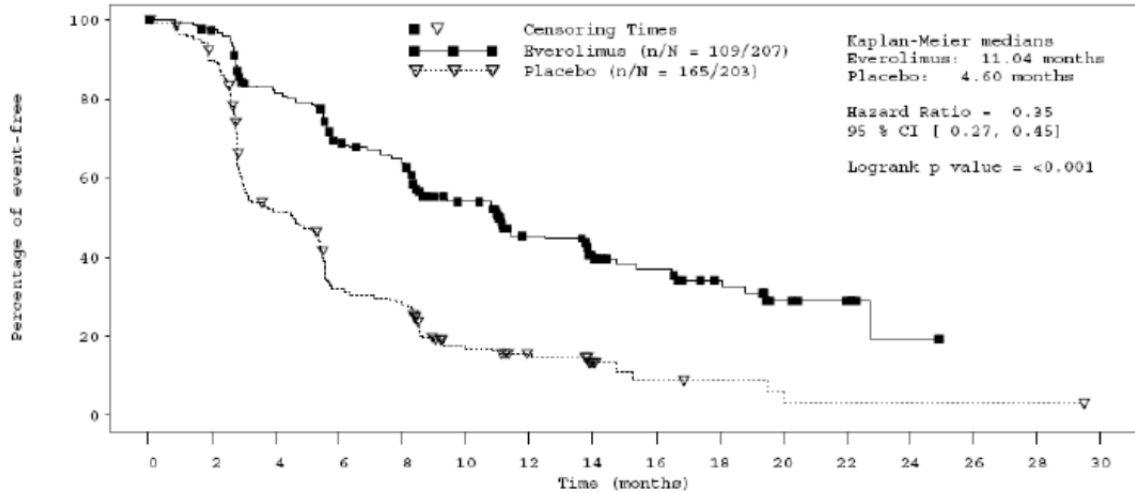
**Table 21 Progression Free Survival Results (PNET)**

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

<sup>a</sup> Includes adjudication for discrepant assessments between investigator radiological review and central radiological review

<sup>b</sup> one-sided p-value from a stratified log-rank test

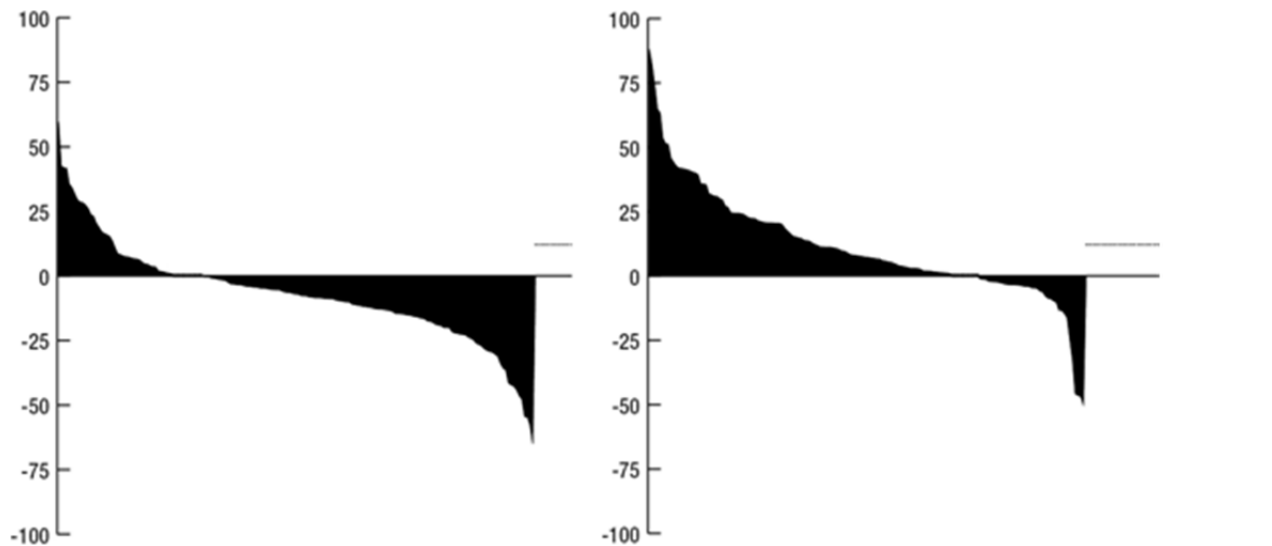
**Figure 3 Kaplan-Meier Investigator-Determined Progression-free Survival Curves**



No. of patients still at risk																
Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Everolimus	207	189	152	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

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

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



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

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

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

## Advanced, Non-Functional Neuroendocrine Tumours of Gastrointestinal or Lung Origin

### Study T2302 (RADIANT-4)

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

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

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

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

**Table 22 Demographic and Disease Characteristics (GI or lung NET)**

Demographic variable	AFINITOR N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
Age (years)			
Median (min-max)	65 (22 – 86)	60 (24 – 83)	63 (22 – 86)
Age category (years) – n (%)			
<65	100 (48.8)	59 (60.8)	159 (52.6)
≥ 65	105 (51.2)	38 (39.2)	143 (47.4)
Gender – n (%)			
Male	89 (43.4)	53 (54.6)	142 (47.0)
Female	116 (56.6)	44 (45.4)	160 (53.0)



Demographic variable	AFINITOR N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
WHO performance status – n (%)			
0	149 (72.7)	73 (75.3)	222 (73.5)
1	55 (26.8)	24 (24.7)	79 (26.2)
2	1 (0.5)	0	1 (0.3)
Primary tumour site			
Lung	63 (30.7)	27 (27.8)	90 (29.8)
Ileum	47 (22.9)	24 (24.7)	71 (23.5)
Rectum	25 (12.2)	15 (15.5)	40 (13.2)
CUP	23 (11.2)	13 (13.4)	36 (11.9)
Jejunum	16 (7.8)	6 (6.2)	22 (7.3)
Stomach	7 (3.4)	4 (4.1)	11 (3.6)
Duodenum	8 (3.9)	2 (2.1)	10 (3.3)
Colon	5 (2.4)	3 (3.1)	8 (2.6)
Other	6 (2.9)	2 (2.1)	8 (2.6)
Caecum	4 (2.0)	1 (1.0)	5 (1.7)
Appendix	1 (0.5)	0	1 (0.3)
Tumour Grade			
Grade 1	129 (62.9)	65 (67.0)	194 (64.2)
Grade 2	75 (36.6)	32 (33.0)	107 (35.4)
Time from initial diagnosis to randomization			
≤6 months	26 (12.7)	12 (12.4)	38 (12.6)
>6 months - ≤12 months	37 (18.0)	13 (13.4)	50 (16.6)
>12 months - ≤18 months	14 (6.8)	12 (12.4)	26 (8.6)
>18 months - ≤24 months	12 (5.9)	9 (9.3)	21 (7.0)
>24 months - ≤36 months	29 (14.1)	13 (13.4)	42 (13.9)
>36 months	87 (42.4)	38 (39.2)	125 (41.4)
Previous treatments			
Any prior antineoplastic therapy <sup>1</sup>	159 (77.6)	82 (84.5)	241 (79.8)
Any prior radiotherapy	44 (21.5)	19 (19.6)	63 (20.9)
Any prior surgery	121 (59.0)	70 (72.2)	191 (63.2)
Any loco-regional therapy	23 (11.2)	10 (10.3)	33 (10.9)
Any prior medications	63 (30.7)	29 (29.9)	92 (30.5)
Any prior chemotherapy	54 (26.3)	23 (23.7)	77 (25.5)
Any prior hormonal therapy	1 (0.5)	1 (1.0)	2 (0.7)
Any prior immunotherapy	7 (3.4)	5 (5.2)	12 (4.0)
Any prior targeted therapy	2 (1.0)	0	2 (0.7)
Any prior other therapy	2 (1.0)	4 (4.1)	6 (2.0)
Prior SSA treatment			
Yes	109 (53.2)	54 (55.7)	163 (54.0)
Disease stage			
I	0	1 (1.0)	1 (0.3)
II	2 (1.0)	3 (3.1)	5 (1.7)
III	7 (3.4)	3 (3.1)	10 (3.3)
IV	196 (95.6)	90 (92.8)	286 (94.7)
Disease sites			
Liver	163 (79.5)	76 (78.4)	239 (79.1)
Lymph node/Lymphatic system	85 (41.5)	45 (46.4)	130 (43.0)
Lung	45 (22.0)	20 (20.6)	65 (21.5)
Bone	42 (20.5)	15 (15.5)	57 (18.9)
Peritoneum	25 (12.2)	8 (8.2)	33 (10.9)
Liver tumour burden			
0%	34 (16.6)	14 (14.4)	48 (15.9)

Demographic variable	AFINITOR N=205 n (%)	Placebo N=97 n (%)	Total N=302 n (%)
>0-10%	119 (58.0)	61 (62.9)	180 (59.6)
>10-25%	29 (14.1)	8 (8.2)	37 (12.3)
>25-50%	9 (4.4)	4 (4.1)	13 (4.3)
>50%	12 (5.9)	10 (10.3)	22 (7.3)
Unknown	2 (1.0)	0	2 (0.7)

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

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

The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 52% risk reduction of progression or death (HR 0.48; 95% CI: 0.35, 0.67; one-sided stratified log-rank test p-value <0.001) per independent assessment (see Table 23 and Figure 5). The analysis of PFS based on local investigator assessment was supportive.

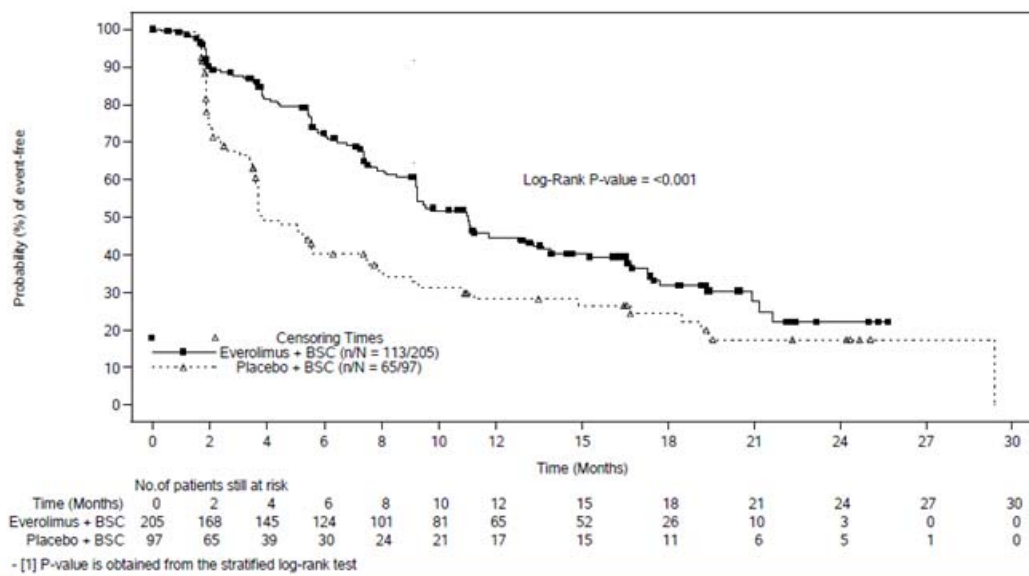
**Table 23 RADIANT-4 – Progression Free Survival results**

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

<sup>a</sup>Hazard ratio from a stratified Cox model

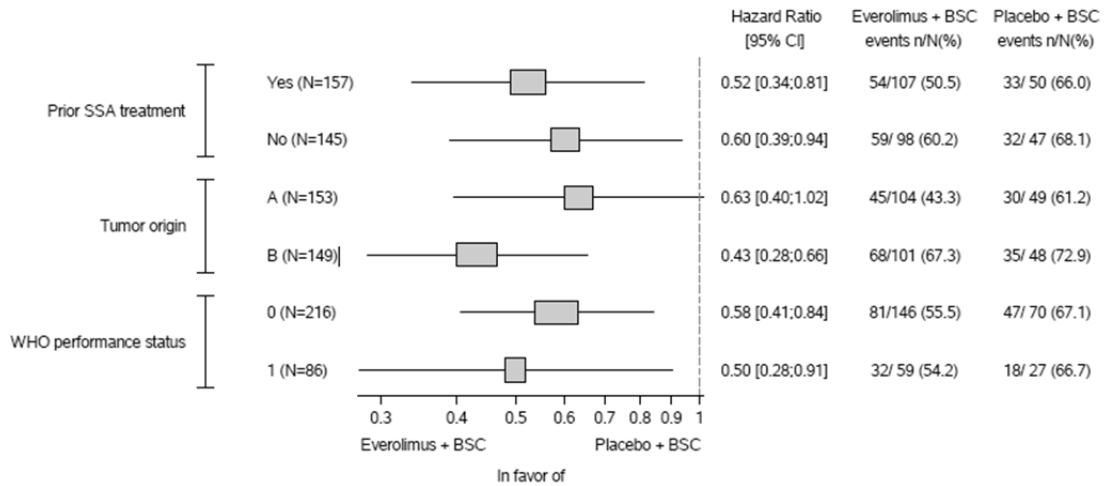
<sup>b</sup>One-sided p-value from a stratified log-rank test

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



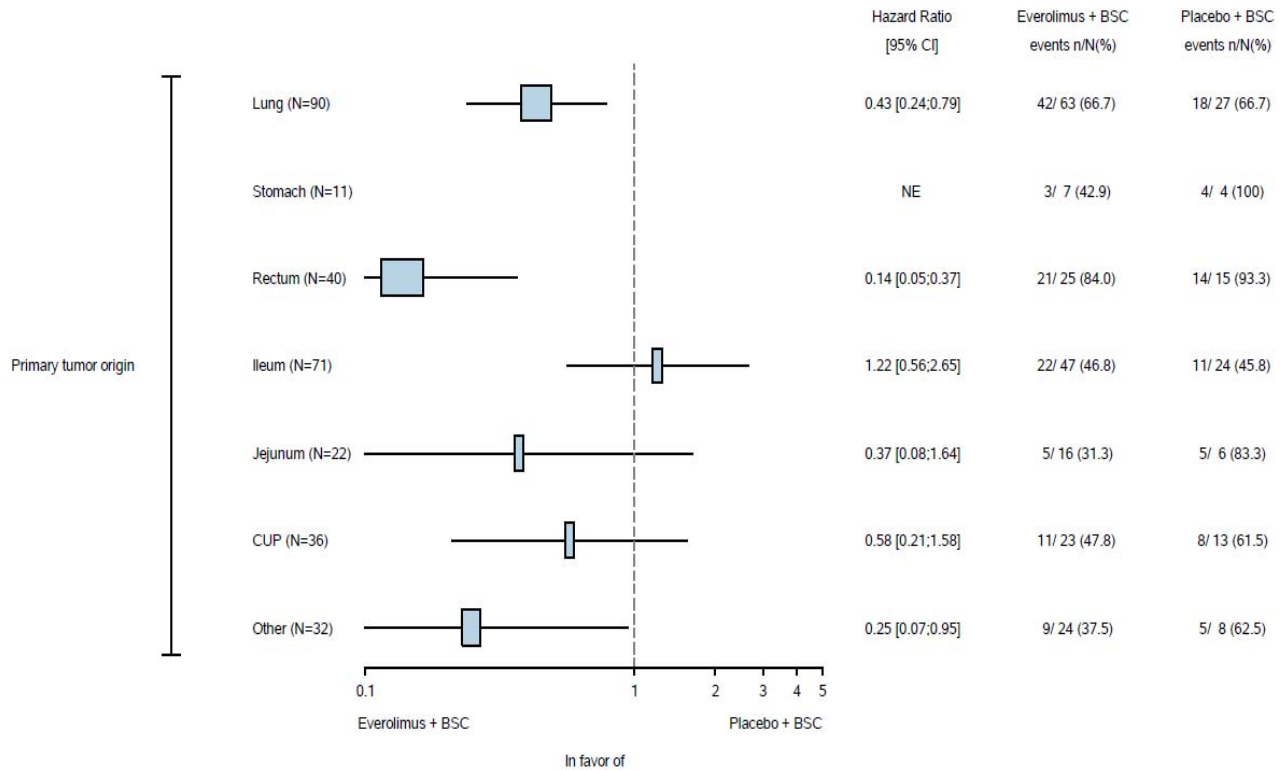
The overall PFS benefit favored AFINITOR across demographic and prognostic stratification subgroups (See Figure 6). Stratum A (appendix, cecum, jejunum, ileum, duodenum, and carcinoma of unknown primary (CUP)) corresponds to better prognosis and that stratum B (lung, stomach, rectum, and colon (with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

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



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

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



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

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

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

### **Lack of Efficacy in Locally Advanced or Metastatic Functional Carcinoid Tumours**

#### **Study C2325 (RADIANT-2)**

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

#### **Metastatic RCC**

The safety and efficacy of AFINITOR in the treatment of metastatic renal cell carcinoma (mRCC) were studied in a single randomised phase III trial.

#### **Study C2240 (RECORD-1)**

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

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms and quality of life. After documented radiological progression, patients could be unblinded by the investigator: those 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 (see Table 24).

**Table 24 Demographic and Disease Characteristics (mRCC)**

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

Results from a planned interim analysis showed that AFINITOR was superior to placebo for the primary endpoint of progression-free survival (PFS), with a statistically significant 67% reduction in the risk of progression or death. At 6 months, PFS rates were 36% for AFINITOR therapy compared with 9% for placebo (see Table 25 and Figure 8).

**Table 25 Progression Free Survival results (mRCC)**

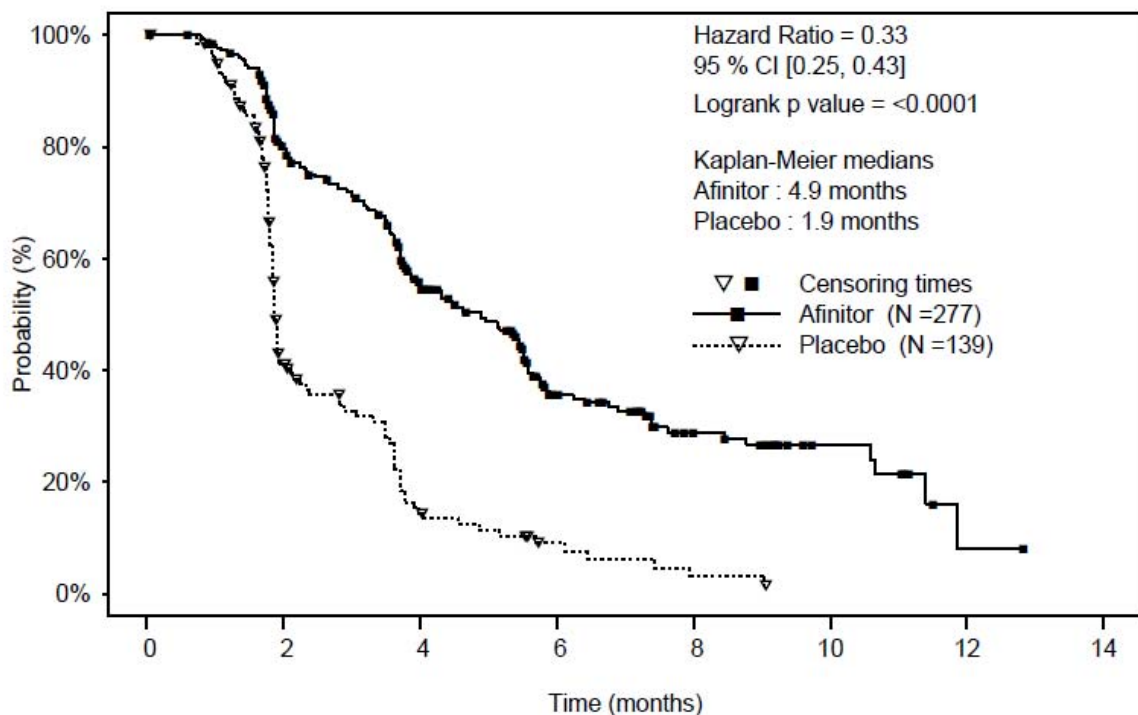
Population	N	AFINITOR N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value <sup>a</sup>
		<b>Median progression-free survival (months) (95% CI)</b>			
<b>Primary analysis</b>					
All (blinded independent central review)	416	4.9 (4.0 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 <sup>a</sup>
<b>Supportive/sensitivity analyses</b>					

Population	N	AFINITOR N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value <sup>a</sup>
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 <sup>a</sup>
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 <sup>b</sup>
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 <sup>b</sup>
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.013 <sup>b</sup>

<sup>a</sup> Log-rank test stratified by prognostic score

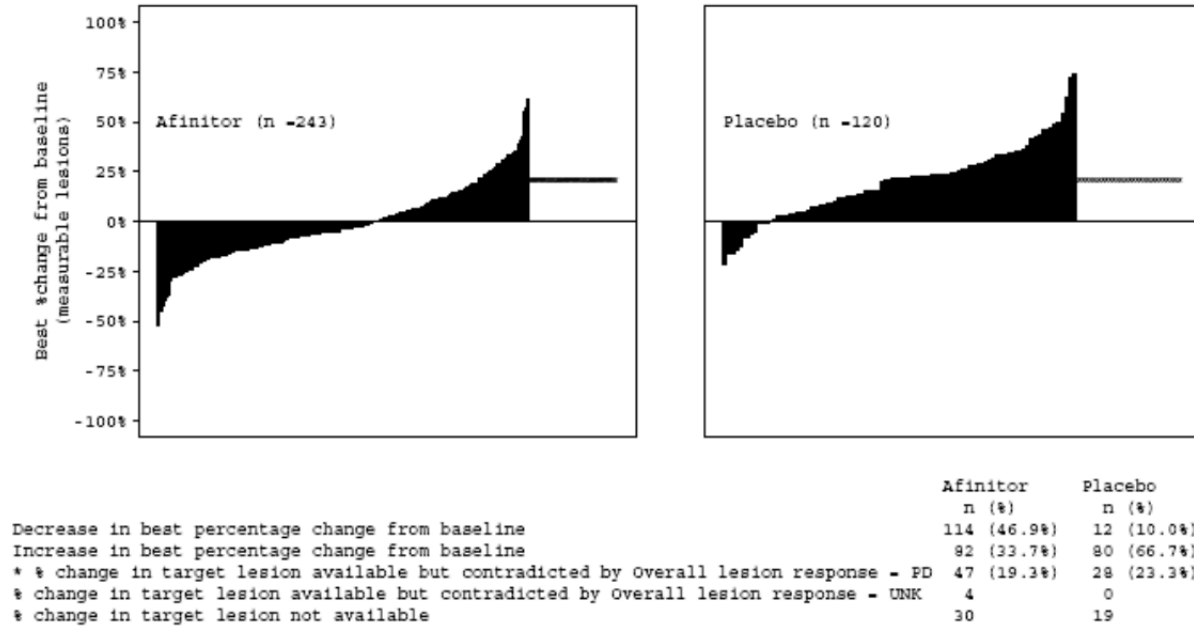
<sup>b</sup> Unstratified, two-sided log-rank test

**Figure 8 Kaplan-Meier progression-free survival curves**



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

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



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 may have confounded the detection of any treatment-related difference in overall survival.

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

### Renal Angiomyolipoma associated with Tuberous Sclerosis Complex

The safety and efficacy of AFINITOR in the treatment of renal angiomyolipoma associated with tuberous sclerosis complex (TSC) were studied in a phase III trial.

#### M2302 (EXIST-2)

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

The primary efficacy endpoint for the trial was angiomyolipoma response rate based on independent central radiology review. Response was defined as:  $\geq 50\%$  reduction in the sum of angiomyolipoma volume relative to baseline, plus absence of new angiomyolipoma  $\geq 1.0$  cm in longest diameter, plus no increases in renal volume  $> 20\%$  from nadir, plus absence of grade  $\geq 2$



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

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

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

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

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

**Table 26 Demographic and Disease Characteristics (Full Analysis Set) (Renal Angiomyolipoma associated with TSC)**

<b>Demographic or disease characteristic</b>	<b>AFINITOR N=79</b>	<b>Placebo N=39</b>
<b>Age (years)</b>		
N	79	39
Mean (SD)	32.5 (10.4)	31.0 (9.6)
Median	32.0	29.0
Range	18 – 61	18 - 58
<b>Age (years), n (%)</b>		
18 to < 30	35 (44.3)	20 (51.3)
≥ 30	44 (55.7)	19 (48.7)
<b>Gender, n (%)</b>		
Female	52 (65.8)	26 (66.7)
Male	27 (34.2)	13 (33.3)
<b>Race, n (%)</b>		
Caucasian	71 (89.9)	34 (87.2)
Asian	7 (8.9)	4 (10.3)
Other <sup>1</sup>	1 (1.3)	1 (2.6)
<b>Diagnosis of TSC<sup>2</sup></b>		
n (%)		
At least two major features	77 (97.5)	36 (92.3)
Only one major feature and at least two	0	0

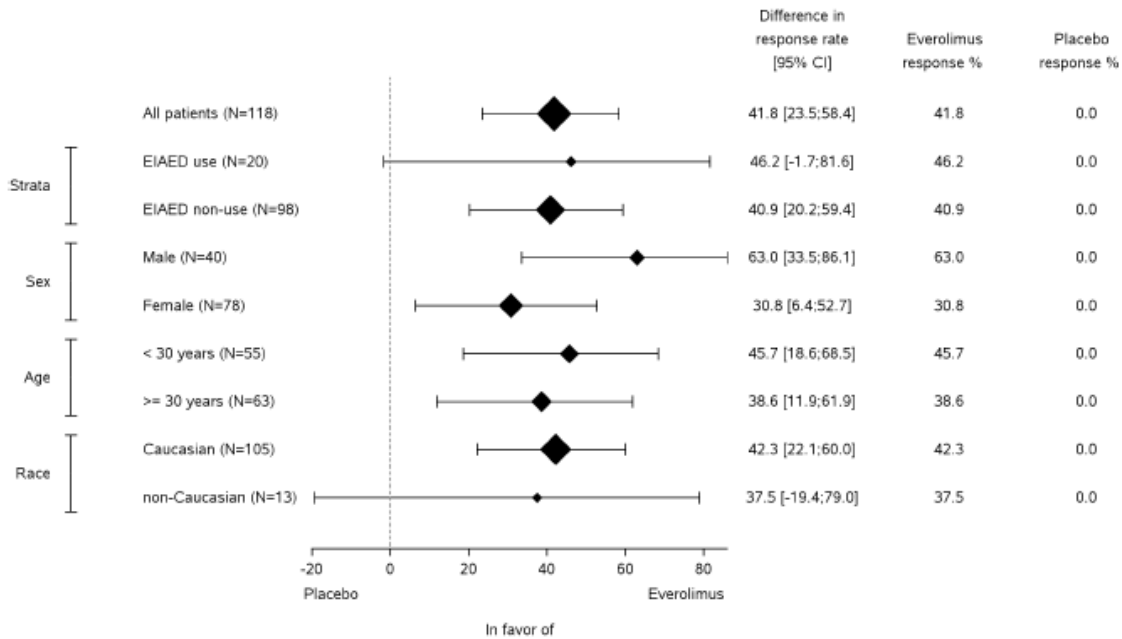
<b>Demographic or disease characteristic</b>	<b>AFINITOR N=79</b>	<b>Placebo N=39</b>
minor features		
<b>EIAED use/EIAED non-use (n, %)</b>		
EIAED use	13 (16.5)	7 (17.9)
EIAED non-use	66 (83.5)	32 (82.1)
<b>Longest diameter of largest angiomyolipoma<sup>2</sup></b>		
≥ 8cm	22 (27.8)	12 (30.8)
≥ 4cm and <8cm	45 (57.0)	19 (48.7)
≥ 3cm and <4cm	6 (7.6)	4 (10.3)
< 3cm	5 (6.3)	2 (5.1)
<b>Number of target angiomyolipoma lesions ≥ 1cm in longest diameter (n, %)</b>		
1-5	32 (40.5)	15 (38.5)
6-10	46 (58.2)	23 (59.0)
<b>Number of patients with angiomyolipoma lesions present in (n, %)</b>		
One kidney only	13 (16.7)	11 (28.9)
Both kidneys	65 (83.3)	27 (71.1)
<b>Sum of volumes of target angiomyolipoma lesions (cm<sup>3</sup>)<sup>2</sup></b>		
Median	85.4	119.8
Range	8.6 – 1611.5	3.0 – 4520.0
<b>Prior anti-angiomyolipoma therapy (surgery/invasive procedure)</b>		
Renal embolization	19 (24.1)	9 (23.1)
Nephrectomy	14 (17.7)	8 (20.5)
<b>Number of patients with ≥ 1 skin lesion at baseline</b>	77 (97.5)	37 (94.9)

<sup>1</sup> Other was applied to patients of mixed race

<sup>2</sup> Baseline kidney CT/MRI assessments were per central radiology review

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

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

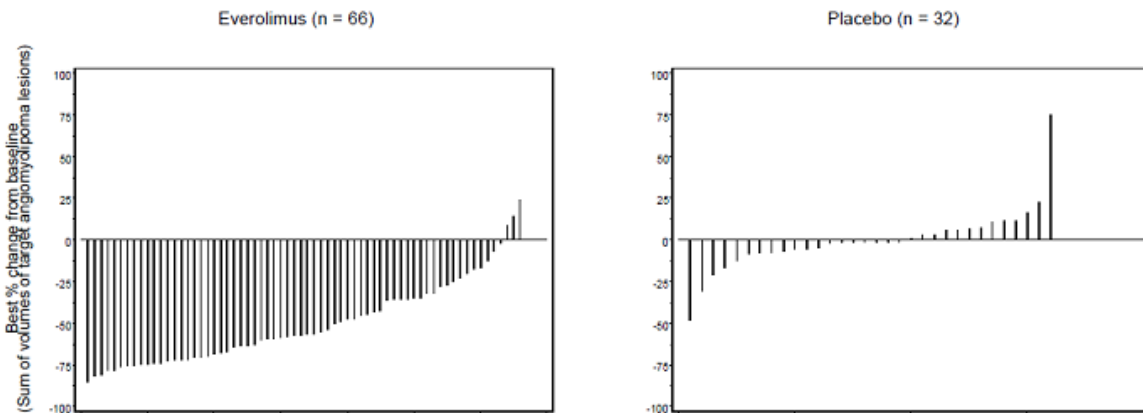


**Table 27 Angiomyolipoma Response**

	Primary Analysis			Final analysis
	AFINITOR N=79	Placebo N=39	p-value	AFINITOR N=112
Angiomyolipoma response rate <sup>a</sup> - %	41.8	0	<0.0001	58.0
95% CI	(30.8, 53.4)	(0.0, 9.0)		(48.3, 67.3)

<sup>a</sup> Per independent central radiology review

**Figure 11 Waterfall plot: Angiomyolipoma shrinkage: best percentage change from baseline (Full Analysis Set)<sup>1,2</sup> at primary analysis**



<sup>1</sup> Per independent central radiology review

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

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

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

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

### **SEGA associated with Tuberous Sclerosis Complex**

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

#### **Study M2301 (EXIST-1)**

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

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

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

Of the 117 patients enrolled, 78 were randomised to AFINITOR and 39 were randomised to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies. The median duration of blinded study treatment was 52.2 weeks (range 24 to 89 weeks) for patients receiving AFINITOR and 46.6 weeks (range 14 to 88 weeks) for those receiving placebo.

**Table 28 Demographic and Disease Characteristics**

<b>Demographic or disease characteristic</b>	<b>AFINITOR N=78 n (%)</b>	<b>Placebo N=39 n (%)</b>	<b>Total N=117 n (%)</b>
<b>Age (years)</b>			
Mean (standard deviation)	10.1 (5.9)	10.3 (7.3)	10.2 (6.4)
Median	9.5	7.1	9.5
Range	1.0 to 23.9	0.8 to 26.6	0.8 to 26.6
<b>Age group (years) (n [%])</b>			
< 3	13 (16.7)	7 (17.9)	20 (17.1)
3 to < 18	55 (70.5)	26 (66.7)	81 (69.2)
≥ 18	10 (12.8)	6 (15.4)	16 (13.7)
<b>Gender</b>			
Male	49 (62.8)	18 (46.2)	67 (57.3)
Female	29 (37.2)	21 (53.8)	50 (42.7)
<b>Race</b>			
Caucasian	73 (93.6)	36 (92.6)	109 (93.2)
Black	3 (3.8)	1 (2.6)	4 (3.4)
Other <sup>a</sup>	1 (1.3)	2 (5.1)	3 (2.6)
<b>Number of target SEGA lesions</b>			
Bilateral SEGA	63 (80.8)	30 (76.9)	93 (79.5)
≥ 2	36 (46.2)	14 (35.9)	50 (42.7)
<b>Brain MRI assessment</b>			
Inferior growth	19 (24.4)	11 (28.2)	30 (25.6)
Evidence of deep parenchymal invasion	8 (10.3)	3 (7.7)	11 (9.4)

<b>Demographic or disease characteristic</b>	<b>AFINITOR N=78 n (%)</b>	<b>Placebo N=39 n (%)</b>	<b>Total N=117 n (%)</b>
Radiographic evidence of hydrocephalus	8 (10.3)	0 (0.0)	8 (6.8)
<b>Skin and subcutaneous tissue disorders</b>			
At least one skin lesion	72 (92.3)	38 (97.4)	110 (94.0)
<b>Prior SEGA-related surgery</b>	6 (7.7)	2 (5.1)	8 (6.8)

<sup>a</sup> 'Other' was applied to patients who were of mixed race

Results showed that AFINITOR was superior to placebo for the primary endpoint of best overall SEGA response ( $p < 0.0001$ ) (Table 29). At the time of primary analysis, all SEGA responses were on-going and the median duration of response was 5.3 months (range 2.1 to 8.4 months).

Patients initially treated with placebo were allowed to cross over to AFINITOR at the time of SEGA progression and upon recognition that treatment with AFINITOR was superior to treatment with placebo. All patients receiving at least one dose of AFINITOR were followed until drug discontinuation or study completion. At the time of final analysis, the median duration of exposure to AFINITOR among all such patients was 204.9 weeks (range 8.1 to 253.7). The best overall SEGA response rate had increased to 57.7% (95% CI: 47.9, 67.0) at the final analysis (Table 29).

**Table 29 SEGA response (Study EXIST-1)**

<b>Primary analysis<sup>3</sup></b>				<b>Final analysis<sup>4</sup></b>
	<b>AFINITOR N=78</b>	<b>Placebo N=39</b>	<b>p-value</b>	<b>AFINITOR</b>
SEGA response rate <sup>1,2</sup> (%)	34.6	0	<0.0001	57.7
95% CI	24.2, 46.2	0.0, 9.0		47.9, 67.0

<sup>1</sup> Per independent central radiology review

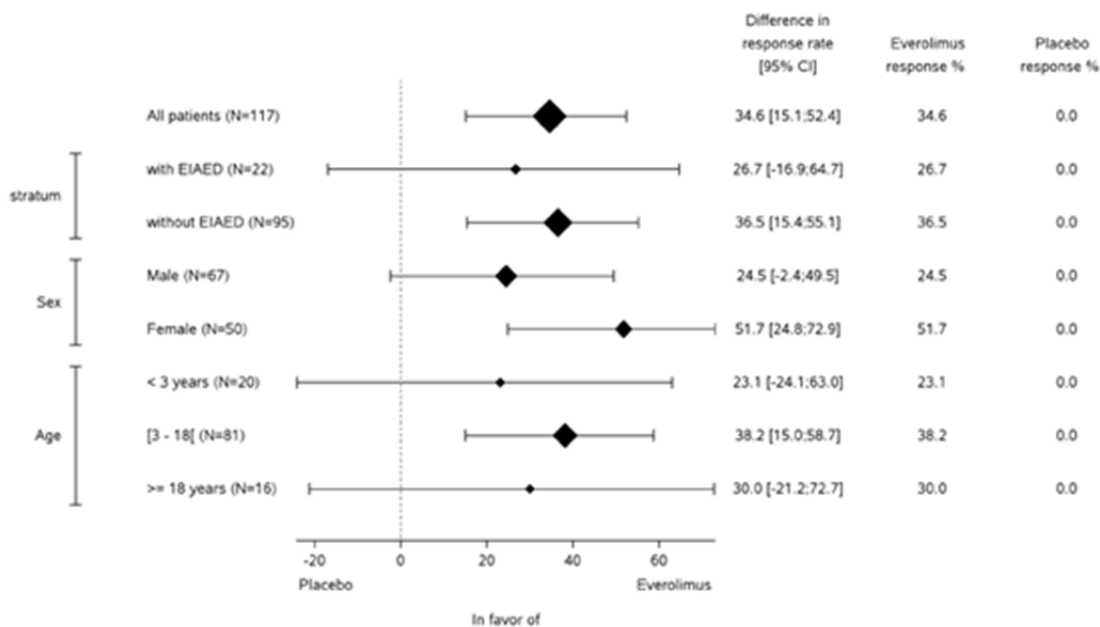
<sup>2</sup> SEGA responses were confirmed with a repeat scan. Response was defined as:  $\geq 50\%$  reduction in the sum of SEGA volume relative to baseline, plus no unequivocal worsening of non-target SEGA lesions, plus absence of new SEGA  $\geq 1$  cm in longest diameter, plus no new or worsening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

<sup>3</sup> Primary analysis for double blind period

<sup>4</sup> Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.9 weeks

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

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



During the double blind period, reduction of SEGA volume was evident within the initial 12 weeks of treatment with AFINITOR: 29.7% (22/74) of patients had  $\geq 50\%$  reductions in volume and 73.0% (54/74) of patients had  $\geq 30\%$  reductions in volume. At Week 24, 41.9% (31/74) of patients had  $\geq 50\%$  reductions and 78.4% (58/74) of patients had  $\geq 30\%$  reductions in SEGA volume.

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

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

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

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

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

### Seizures associated with Tuberous Sclerosis Complex

#### Study M2304 (EXIST-3)

The safety and efficacy of AFINITOR DISPERZ as adjunctive therapy in the treatment of seizures associated with tuberous sclerosis complex (TSC) were studied in a randomized, double-blind, placebo-controlled, multicenter, phase III trial. This study included 366 patients (247 patients were exposed to everolimus and 119 received placebo). The patients' mean age was approximately 13 years (Median: 10 years; Range: 2 to 56 years). All patients had a definite diagnosis of TSC. Approximately half the patients were male.

Patients had partial-onset seizures with or without secondary generalization and were not satisfactorily controlled with combinations of anti-epileptic drugs (AEDs). During the 8-week Baseline phase, patients were required to have  $\geq 16$  seizures per 28 days. The Core treatment phase of the study was 18 weeks in duration (including a 6 week Titration period and a 12 week Maintenance period). The study consisted of three arms and compared two doses of everolimus (low trough [LT]: 3-7 ng/mL and high trough [HT]: 9-15 ng/mL) with placebo. Across all arms, approximately 95% of the patients completed the Core treatment phase of the study.

#### Study Results

A statistically significant treatment effect was observed for both doses of AFINITOR DISPERZ relative to placebo ( $p=0.003$  [LT] and  $p<0.001$  [HT]) for the median percent reduction from Baseline in seizure frequency during the Maintenance period of the Core Treatment Phase. This was supported by the analysis of responder rate during the Maintenance period of the Core treatment phase (Table 30). Efficacy results from the entire Core Treatment Phase (Titration + Maintenance periods) support the results from the Maintenance period of the Core Treatment Phase.

**Table 30 Median Percent Reduction in Seizure Frequency and Proportion of Patients with at least a 50% Reduction in Seizure Frequency from Baseline (Full Analysis Set)**

Efficacy Results <sup>a</sup>	AEDs + Placebo  N=119	AEDs + AFINITOR DISPERZ	
		LT Target 3-7 ng/mL N=117	HT Target 9-15 ng/mL N=130
Median percent reduction from Baseline during the Maintenance period of the Core treatment phase	14.9	29.3	39.6
p-value versus placebo		0.003	<0.001
Responder Rate from Baseline during the Maintenance period of the Core treatment phase	15.1	28.2	40.0



p-value versus placebo <sup>c</sup>		0.008	<0.001
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<sup>a</sup> The primary efficacy endpoint was the median percent reduction from Baseline during the Maintenance period of the Core treatment phase. Responder rate was defined as percentage of patients who achieved at least a 50% reduction from Baseline in seizure frequency during the Maintenance period of the Core treatment phase.

At the end of the Core treatment phase, roughly 4% of the patients in AFINITOR DISPERZ arms became seizure-free vs about 1% in placebo.

There were no significant differences in seizure control as a function of gender. Data on race were limited (approximately 35% of the patients were non-Caucasian).

### **Comparative Bioavailability Studies**

Table 31 presents the results of a randomized, open label, cross-over study in 53 healthy volunteers comparing the bioavailability of the AFINITOR DISPERZ 5 mg tablet for oral suspension to the AFINITOR 5 mg tablet.

**Table 31 Single dose bioavailability study 1**

<b>Everolimus</b> <b>(1 x 5 mg AFINITOR tablet and 1 x 5 mg AFINITOR DISPERZ tablet for oral suspension)</b> <b>From measured data</b>  <b>Geometric Mean</b> <b>Arithmetic Mean (CV %)</b>				
<b>Parameter</b>	<b>AFINITOR DISPERZ 5 mg Tablet for oral suspension (Test)</b>	<b>AFINITOR 5 mg Tablet (Reference)</b>	<b>Ratio of Geometric Means</b>	<b>90% Confidence Interval</b>
AUC <sub>0-72h</sub> (ng.h/mL)	190.11 196.62 (26.00)	211.56 220.44 (32.29)	0.90	0.85, 0.95
AUC <sub>0-∞</sub> (ng.h/mL)	230.95 238.17 (24.90)	252.47 262.63 (31.38) <sup>1</sup>	0.91	0.86, 0.96
C <sub>MAX</sub> (ng/mL)	25.73 26.59 (25.55)	31.98 33.09 (29.22)	0.80	0.75, 0.86
T <sub>MAX</sub> <sup>§</sup> (h)	1.5 (0.5, 4.0)	1.00 (0.5, 3.0)		
T <sub>1/2</sub> <sup>‡</sup> (h)	34.92 (19.23) <sup>2</sup>	33.30 (15.14)		

<sup>1</sup> N=52 for AUC<sub>0-∞</sub> for the 5 mg tablet

<sup>2</sup> N=52 for T<sub>1/2</sub> for the 5 mg tablet for oral suspension

<sup>§</sup> Expressed as median (range)

<sup>‡</sup> Expressed as the arithmetic mean (CV%)

Table 32 presents the results of a randomized, open label, cross-over study in 51 healthy

volunteers comparing the bioavailability of the AFINITOR DISPERZ 5 mg tablet for oral suspension to the 5 x 1 mg everolimus tablets.

**Table 32 Single dose bioavailability study 2**

<b>Everolimus</b> <b>(5 x 1 mg everolimus tablets and 1 x 5 mg AFINITOR DISPERZ tablet for oral suspension)</b> <b>From measured data</b>  <b>Geometric Mean</b> <b>Arithmetic Mean (CV %)</b>				
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Parameter	AFINITOR DISPERZ 5 mg Tablet for oral suspension (Test)	5 x 1 mg everolimus tablets (Reference)	Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-72h</sub> (ng.h/mL)	186.49 194.78 (31.28)	214.11 224.32 (32.72)	0.86	0.80, 0.93
AUC <sub>0-∞</sub> (ng.h/mL)	219.69 230.62 (33.55)	254.62 266.76 (32.79)	0.86	0.80, 0.93
C <sub>MAX</sub> (ng/mL)	25.45 26.68 (30.62)	39.68 41.10 (27.95)	0.64	0.60, 0.68
T <sub>MAX</sub> <sup>§</sup> (h)	1.50 (0.5, 4.0)	0.50 (0.5, 2.0)		
T <sub>1/2</sub> <sup>‡</sup> (h)	32.81 (20.08)	34.03 (31.60)		

<sup>§</sup> Expressed as median (range).

<sup>‡</sup> Expressed as the arithmetic mean (CV%).

## DETAILED PHARMACOLOGY

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

### Nonclinical Pharmacology

#### ***In vitro* pharmacology**

Everolimus binds with high affinity to the intracellular immunophilin, FKBP-12 resulting in inhibition of the mTORC1 complex and consequently, suppression of downstream events such as S6K and 4EBP activity and cell-cycle arrest from G1 to S phase. No activity was found against the following kinases: HER-1, HER-2, KDR, IGF1-R, FGFR-1, c-met, c-src, c-kit, and CDK1. Everolimus shows a very broad inhibition of tumour cell lines (i.e. inhibits tumour proliferation) of different histotypes *in vitro* with high sensitivity to anti-proliferative effects in some cells (as determined by measuring the number of cells) (IC<sub>50</sub> <1 nM) and insensitivity in others (IC<sub>50</sub> >1 µM), although the majority of cell lines tested (80%) had IC<sub>50</sub> values <100 nM. Specifically, in

renal cancer models, everolimus showed significant activity: a panel of 16 human RCC cell lines were tested *in vitro* for anti-proliferative activity of everolimus; 14 were sensitive to everolimus treatment with IC<sub>50</sub>s in the low/sub nM range, while two renal cell lines were insensitive (IC<sub>50</sub> >2500 nM). The sensitivity of RCC cell lines was similar to that described for other histotypes *in vitro*. VHL genetic status did not affect the anti-proliferative response to everolimus in the renal cell panel *in vitro*: three out of the four VHL wild-type lines were very sensitive to everolimus treatment with similar IC<sub>50</sub>s (in the low/sub nM range) as observed in the VHL negative lines. Moreover, exogenous expression of VHL in a VHL negative background had little effect and the two lines defined as insensitive to everolimus treatment were VHL wild type (Caki-1) and VHL negative (Caki-2).

### ***In vivo* pharmacology**

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

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

### **Safety Pharmacology**

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

In stably transfected HEK293 cells, everolimus inhibited hERG currents by 18% at 10 µM (concentration experimentally verified). Higher concentrations could not be tested because of solubility limitations. In sheep isolated Purkinje fibres, everolimus prolonged the action potential duration at 90% repolarization (APD90) by 5.0% at 1.04 µM and 4.7% at 10.0 µM (nominal concentrations). In male pigs (N=4) anaesthetized with ketamine and sodium pentobarbital, everolimus at escalating intravenous doses of 0, 0.01, 0.1, 1, and 10 mg/kg was not observed to affect the mean arterial blood pressure, systolic blood pressure, diastolic blood

pressure, heart rate, or ECG parameters over 30 minute post-dose observation periods. The study lacked a time-matched vehicle control arm.

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

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

### **Nonclinical Pharmacokinetics**

See also **ACTION AND CLINICAL PHARMACOLOGY**.

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

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

**Metabolism:** Everolimus is mainly eliminated by metabolism in the mouse, rat, monkey and human. Everolimus was the main circulating drug-related component in blood of all species. In all species everolimus formed a large number of metabolites. The metabolite patterns in the blood were comparable in all species including man. Everolimus is essentially metabolized

through oxidation by CYP3A4 in the liver and to some extent in the gut wall. Therefore, co-mediations that are strong inducers of CYP3A4 have the potential to reduce everolimus metabolism *in vivo*. Conversely, everolimus inhibited competitively the metabolism of the CYP3A4 substrate cyclosporine ( $K_i = 2.3 \mu\text{mol/L}$ ) and was also a mixed inhibitor of the metabolism of the CYP2D6 substrate dextromethorphan ( $K_i = 1.7 \mu\text{mol/L}$ ) *in vitro*. Apart from parent drug, essentially five main metabolite peaks P36, P40, P42, P50 and P57, containing six metabolites were observed. The main metabolites P40, P36, P42, P50 and P57 were approximately two orders of magnitudes less active than everolimus in a mixed lymphocyte reaction (MLR) assay. Essentially the same metabolites of everolimus in humans were formed by at least one of the animal species *in vivo* and/or *in vitro*.

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

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

## **Human Pharmacology**

### **Absorption and Distribution**

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

### **Metabolism and Elimination**

The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man is CYP3A4. Everolimus is a moderate inhibitor of P-gP-like mediated efflux systems. After an oral  $^{14}\text{C}$ -labelled dose of everolimus, 85% of the radioactivity was recovered within 10 days in faeces (80%) and urine (5%). Unchanged everolimus accounted for about 40% of the AUC of total radioactivity in blood but was not detected in faeces or urine. Japanese and Caucasian cancer patients with similar liver functions have similar CL/F values. Age and weight (both over the

adult ranges) and gender do not have significant effects on pharmacokinetics of everolimus in cancer and transplant patients. Pharmacokinetics in healthy subjects are not altered by Japanese or Asian ethnicity. Black renal transplant patients have a 20% higher apparent clearance compared with non-blacks. As expected from the low renal excretion of parent compound, post-transplant renal impairment does not affect the pharmacokinetics of everolimus. Mean exposure ( $AUC_{0-\infty}$ ) to everolimus is increased in patients with hepatic impairment. In one study, compared to normal subjects, there was a 2.2-fold increase in exposure for subjects with moderate hepatic impairment (Child-Pugh B, score 7 to 9). In a second study there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure for subjects with mild (Child-Pugh A, score 5 to 6), moderate (Child-Pugh B, score 7 to 9) and severe (Child-Pugh C, score 10 to 15) hepatic impairment respectively, compared to normal subjects. The strong inhibitor of CYP3A4 and PgP, ketoconazole, increases everolimus  $AUC_{0-\infty}$  15.0-fold. The moderate inhibitors of CYP3A4 and PgP, erythromycin and verapamil, increase everolimus  $AUC_{0-\infty}$  4.4-fold and 3.5-fold, respectively. The CYP3A4 substrate and inhibitor of PgP, cyclosporine (NEORAL<sup>®</sup>) increases everolimus  $AUC_{0-\infty}$  2.7-fold. The CYP3A4 substrate atorvastatin did not influence the pharmacokinetics of everolimus. The CYP3A4 and PgP substrate paclitaxel did not influence the pharmacokinetics of everolimus. The everolimus doses used in these drug interaction studies ranged from 1 to 4 mg. Drug interaction studies at the 10 mg dose have not been conducted. The strong inducer rifampin decreases everolimus  $AUC_{0-\infty}$  to 0.4-times the pre-treatment value. Pravastatin and gemcitabine are not substrates of CYP3A4 and do not have effects on the pharmacokinetics of everolimus. Co-administration of everolimus and SANDOSTATIN LAR did not have clinically significant effects on the pre-dose trough concentrations of everolimus and octreotide.

## TOXICOLOGY

### Single Dose Toxicity Studies

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

### Repeated Dose Toxicity Studies

Repeated dose toxicity studies were performed in mice over 13 weeks, in rats up to 26 weeks, in minipigs up to 4 weeks and in monkeys up to 52 weeks. The study design and major findings of the repeated dose toxicity studies are shown in Table 33. The monkey was selected as a non-rodent species because gastrointestinal intolerance of everolimus was seen in the oral rising-dose study in the dog, precluding this species from treatment for longer periods. Similar findings have been reported with rapamycin in this species.

#### **Table 33      Repeated dose toxicity studies**

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
Mouse	13 weeks	Oral, gavage	10m, 10f	0, 0.15, 0.5, 1.5, 5, 15	<ul style="list-style-type: none"> <li>• <math>\geq 0.15</math> mg/kg: higher incidence of swollen spleen</li> <li>• <math>\geq 0.5</math> mg/kg: reduced testes and epididymides weight, depletion of germ cells and vacuolation of the germinal epithelium of testis, reduced sperm content and germ cells in tubular lumina of epididymides (m), skin lesions (f), increased microvesiculation of zona glomerulosa and/or zona fasciculate of the adrenals (m), thymic atrophy</li> <li>• <math>\geq 1.5</math> mg/kg: higher liver weight (m), slightly higher cholesterol (m), skin lesions (+m), foamy alveolar macrophages (f), reduced ovarian follicular development and atrophy of uterus (f)</li> <li>• <math>\geq 5</math> mg/kg: lower body weight gain (m), higher incidence of skin abrasions (m), higher cholesterol (+f), reduced uterus weight (f), renal tubular degeneration with karyomegaly and interstitial inflammation (m), foamy alveolar macrophages (+m)</li> <li>• 15 mg/kg: high incidence of skin abrasions (+f), higher creatinine concentrations (m), lower albumin and A/G ratio (m), reduced thymus weight and higher spleen weight (m), higher liver weight (+f), renal tubular degeneration with karyomegaly and interstitial inflammation (+f)</li> <li>• NTEL=0.15 (m), and 0.5 (f)</li> </ul>
Rat	2 weeks	Oral, gavage	4m, 4f	0, 2.5, 10, 40 (everolimus), 40 (rapamycin)	<ul style="list-style-type: none"> <li>• <math>\geq 2.5</math> mg/kg: reduced body weight gain, food intake (m); decrease in lymphocytes, platelets and albumin; thymic atrophy; lymphoid depletion of spleen and lymph nodes; atrophy/decreased secretion of prostate and seminal vesicles; increased focal myocardial degeneration; decreased extramedullary splenic haemopoiesis; increase in alveolar</li> </ul>

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					<p>macrophages in lungs</p> <ul style="list-style-type: none"> <li>• <math>\geq 10</math> mg/kg: reduced body weight gain, food intake (+f); increased cholesterol (m); skin lesions; bone marrow depletion (m)</li> <li>• 40 mg/kg: increased WBC/neutrophils; degenerative changes in testes; increased incidence of dioestrus stage. No major differences in toxicity profile compared with rapamycin</li> <li>• NTEL &lt; 2.5 mg/kg</li> </ul>
Rat	2 weeks	Oral, gavage	10m, 10f	0, 1.5, 15 (in microemulsion), 0, 1.5, 15 (in solid dispersion)	<ul style="list-style-type: none"> <li>• No relevant differences in toxicity profile and exposure between microemulsion and solid dispersion</li> </ul>
Rat	4 weeks (with 2 week recovery)	Oral, gavage	10m, 10f, additional 6m, 6f in recovery	0, 0.5, 1.5, 5, 15, Recovery: 0, 15	<ul style="list-style-type: none"> <li>• <math>\geq 0.5</math> mg/kg: reduced body weight gain, food intake (m); haemo-concentration; low platelets; increased cholesterol (m); chronic myocarditis (m)</li> <li>• <math>\geq 1.5</math> mg/kg: reduced body weight gain, food intake (+f); increased triglycerides (f); chronic myocarditis (+f); medullary atrophy of thymus; foamy alveolar macrophages; loss of germ cells in testes; atrophy/reduced secretion of seminal vesicles; interstitial cell hypertrophy of ovaries; depletion of secretory granules in salivary glands</li> <li>• <math>\geq 5</math> mg/kg: Increased neutrophils; increased cholesterol (+f); low albumin; anterior suture line opacities in lens; swelling/disruption of anterior cortical lens fibres; atrophy/reduced secretion of prostate; uterus atrophy; thinning of cortical bone</li> <li>• 15 mg/kg: Reduced sperm counts in testes; reduced contents in epididymides. Recovery of changes except for lungs, heart, eyes and testes</li> <li>• NTEL approx. 0.5 mg/kg</li> </ul>
Rat	4 weeks (with 2 week recovery)	Oral, gavage	10m, 10f, additional	0, 0.1, 0.25, 0.5, 1.5,	<ul style="list-style-type: none"> <li>• <math>\geq 0.5</math> mg/kg: Medullary atrophy of</li> </ul>



Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
	week recovery)		6m, 6f in recovery	Recovery: 0, 15	<p>thymus</p> <ul style="list-style-type: none"> <li>• 1.5 mg/kg: Reduced body weight gain, food intake; anterior suture line opacities in lens; haemo-concentration; decreased platelets; increased cholesterol (m); chronic myocarditis; increased alveolar macrophages; interstitial cell hyperplasia of ovaries; uterus atrophy; depletion of secretory granules in salivary glands. Recovery of changes except for heart</li> <li>• EM: Alveolar macrophages in lungs with vacuoles and multi-lamellar bodies</li> <li>• NTEL = 0.5 mg/kg</li> </ul>
Rat	26 weeks (with 4 weeks recovery)	Oral, gavage	20m, 20f, additional 5m, 5f in recovery	0, 0.05, 0.1, 0.15, 0.5, 1.5, Recovery: 0, 1.5	<ul style="list-style-type: none"> <li>• <math>\geq 0.15</math> mg/kg: reduced body weight gain (f); medullary atrophy of thymus (f)</li> <li>• <math>\geq 0.5</math> mg/kg: haemo-concentration (m); low platelets (m); increased amylase (m); medullary atrophy of thymus (+m); lymphoid atrophy of LN; pigment (lipofuscin) in renal tubular epithelial cells; increased hydronephrosis (m); increased alveolar macrophages and perivascular lymph. infiltration; mucus cell hypertrophy/plasia of stomach; follicular cell hypertrophy/vacuolation of thyroids (m)</li> <li>• 1.5 mg/kg: reduced body weight gain (+m), food intake; hemo-concentration (+f); low platelets (+f); increased neutrophils; increased cholesterol (m) and amylase (+f), decreased albumin (m) and iron; interstitial pneumonitis (m); splenic haemosiderosis; depletion of germ cells, tubular vacuolation and spermatid giant cells in testes. Recovery of changes except for lungs or testes</li> <li>• Special investigations on the liver drug metabolizing enzyme levels and on the overall metabolism: Minor increase in total metabolite</li> </ul>

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					<p>formation and reduction of P450 2B1/2</p> <ul style="list-style-type: none"> <li>• NTEL = 0.15 mg/kg</li> </ul>
Monkey	24 days	Oral, gavage	1m, 1f	1 (4d), 2 (3d), 4 (4d), 10 (3d), 20 (4d), 40 (3d) 60 (3d) 5-7 d washout after each dose of 10 and above	<ul style="list-style-type: none"> <li>• <math>\geq 2</math> mg/kg: quietness (f)</li> <li>• <math>\geq 20</math> mg/kg: increased WBC</li> <li>• <math>\geq 40</math> mg/kg: quietness (m), piloerection and huddled posture (f)</li> <li>• 60 mg/kg: piloerection and huddled posture (+m); reduced lymphoid activity in thymus, spleen, LN</li> </ul>
Monkey	2 weeks	Oral, gavage	1m, 1f	0, 5, 15, 45	<ul style="list-style-type: none"> <li>• <math>\geq 5</math> mg/kg: piloerection, rash on chest; increased fibrinogen (m), activated partial thromboplastin time; decreased lymphoid activity in thymus, spleen and LN; sub-endocardial/interstitial haemorrhage in heart; reduced cellularity of bone marrow (f)</li> <li>• <math>\geq 15</math> mg/kg: quietness; increased fibrinogen (+f); subendocard./interstitial haemorrhage in heart (m)</li> <li>• 45 mg/kg: rough coat, huddled posture (f); body weight loss and reduced food intake; increased glucose and cholesterol (m); decreased phosphorus (m); increased globulins; sub-endocardial/interstitial haemorrhage in heart (f); reduced cellularity of bone marrow (f)</li> <li>• NTEL &lt; 5 mg/kg</li> </ul>
Monkey	4 weeks (with 2 week recovery)	Oral, gavage	3m, 3f additional 2m, 2f in recovery	0, 1.5, 5, 15 Recovery: 0, 15	<ul style="list-style-type: none"> <li>• <math>\geq 1.5</math> mg/kg: reduced food intake (f); increased fibrinogen; decreased phosphorus; splenic lymphoid atrophy</li> <li>• <math>\geq 5</math> mg/kg: increase in skin lesions; reduced food intake (+m); reduced RBC parameters; increased <math>\alpha 2/\beta</math> globulins, decreased albumin and Alb/Glob ratio (m); thymic medullary atrophy; increased histiocytosis in small intestine (f)</li> <li>• 15 mg/kg: pilo-erection, reddening of abdomen (m); increased WBC, neutrophils, monocytes; increased alanine and aspartate</li> </ul>

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					<p>aminotransferases; increased <math>\alpha 2/\beta</math> globulins and decreased albumin and Alb/Glob ratio (+f); reduced urine sodium; increased histiocytosis in small intestine (+m)</p> <ul style="list-style-type: none"> <li>• NTEL = 1.5 mg/kg</li> </ul>
Monkey	26 weeks	Oral, gavage	4m, 4f additional 4m, 4f in control and 2m, 2f at high-dose	0, 0.1, 0.5, 1.5, 5	<ul style="list-style-type: none"> <li>• <math>\geq 0.5</math> mg/kg: increased skin lesions (m); reduced body weight gain; splenic lymphoid atrophy; lymphoid depletion in LN; macrophage aggregation in small intestine</li> <li>• <math>\geq 1.5</math> mg/kg: early sacrifice (2m) in weeks 14/25 due to poor health condit.; increased skin lesions (+f); reduced food intake; reduced RBC parameters; increased neutrophils/monocytes, fibrinogen; decreased phosphorus; increased cholesterol; thymic cortical and medullary atrophy; myocardial degeneration/necrosis (1m); degranulation of pancreat. exocrine cells (m); reduced follicular development and atresia of ovaries</li> <li>• 5 mg/kg: early termination in weeks 9/10 due to skin lesions, poor health, body weight loss; in-creased <math>\alpha 2/\beta</math> globulins and decreased albumin and Alb/Glob ratio; increased triglycerides, increased mucosal inflammation of large intestine; myocardial degeneration/necrosis (m); degranulation of pancreatic exocrine cells and increased islet cell degeneration; vacuolation of adrenals</li> <li>• Virology: coxsackievirus in plasma (including pretest) and heart tissue</li> <li>• NTEL = 0.5 mg/kg</li> </ul>
Monkey	39/52 weeks	Oral, gavage	4m, 4f	0, 0.1, 0.3, 0.9	<ul style="list-style-type: none"> <li>• <math>\geq 0.3</math> mg/kg: diarrhoea/soft faeces (m); reduced body weight/food intake (2m); increased neutrophils (f); inflammatory changes in GI tract; atrophy of testes</li> <li>• 0.9 mg/kg: termination after 39 weeks; 1m and 2f sacrificed early due to poor health condition</li> </ul>

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					<p>consequent to diarrhoea/soft faeces and inflammation/ ulceration of large intestine; body weight loss and reduced food intake; increased fibrinogen (f)</p> <ul style="list-style-type: none"> <li>• NOAEL = 0.1 mg/kg</li> </ul>
Minipig	2 weeks	Oral, gavage	1m, 1f	0, 0.5, 1.5, 5	<ul style="list-style-type: none"> <li>• <math>\geq 0.5</math> mg/kg: decreased platelets and lymphocytes; increased creatinine (f); increased seminiferous tubular atrophy in testes; thymic cortical lymphocytolysis; decreased germinal centre activity in LN</li> <li>• <math>\geq 1.5</math> mg/kg: decreased albumin, <math>\gamma</math>-globulins and Alb/Glob ratio; increase in <math>\beta 1</math> globulins</li> <li>• 5 mg/kg: early sacrifice (f) due to pneumonitis; increased creatinine (m)</li> </ul>
Minipig	4 weeks (with 4 week recovery)	Oral, gavage	3m, 3f additional 2m, 2f in recovery	0, 1.5, 5, 15 Recovery: 15	<ul style="list-style-type: none"> <li>• <math>\geq 1.5</math> mg/kg: diarrhoea related to increased coccidial infestation of intestine (m); reduced body weight gain and food intake (m); increased fibrinogen and neutrophils (m); decreased albumin and alb/glob ratio (m); decreased phosphorus, alkaline phosphatase and <math>\gamma</math>-globulins; increased <math>\alpha 2</math> and <math>\beta 1</math> globulins; increased percent. of <math>\beta</math>-lipoproteins and decreased percent. of chylomicrons (m); thymic atrophy; atrophy/decreased lymphoid activity in LN; myelitis and focal encephalitis (m); increased dermatitis; increased testicular tubular atrophy and oligospermia in epididymides</li> <li>• <math>\geq 5</math> mg/kg: lymphoid depletion of spleen (1f); necrotic follicles in uterus; microvacuolation of adrenals</li> <li>• 15 mg/kg: diarrhoea with one death (m)/early sacrifices (3m/1f) due to intestinal erosion with coccidial infestation; reduced body weight gain and food intake; decreased platelets (m); increased urea and creatinine (2f); decreased cholinesterase; increased LDL (LDL-3 to LDL-6) and decreased</li> </ul>

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					HDL-2a; lymphoid depletion of spleen (m); vacuolation of exocrine pancreatic cells with necrosis (m); atrophy of vagina and uterus. Recovery of all changes except for the testes. <ul style="list-style-type: none"> <li>• NTEL &lt; 1.5 mg/kg</li> </ul>

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

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

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

### **Genotoxicity and Carcinogenicity Studies**

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

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

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

rats were limited to slightly affected body weight and survival in the F1-generation at  $\geq 0.1$  mg/kg, and did not indicate a specific toxic potential.

### **Study in Juvenile Animals**

In a rat oral juvenile development study, the administration of everolimus at 0.15, 0.5 and 1.5 mg/kg on post partum days 7 to 70 with 13- and 26-week recovery periods resulted in systemic toxicity at all doses, including decreased absolute body weight gain, food consumption, delayed attainment of some developmental landmarks, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding (where young animals appeared to be more susceptible), it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse effects of everolimus as compared to adult animals.

In juvenile monkeys (approximately 1 year old), the oral treatment with everolimus at dosages up to 0.5 mg/kg for 4 weeks did not cause relevant toxicity.

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## PART III: CONSUMER INFORMATION

**PrAFINITOR®**  
(everolimus tablets)  
**and**  
**PrAFINITOR® DISPERZ™**  
(everolimus tablets for oral suspension)

**This leaflet is part III of a three-part “Product Monograph” published when AFINITOR® and AFINITOR® DISPERZ™ were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AFINITOR or AFINITOR DISPERZ. Contact your doctor or pharmacist if you have any questions about the drug.**

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

### ABOUT THIS MEDICATION

#### What the medication is used for:

AFINITOR is used in the treatment of:

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

AFINITOR DISPERZ is used in the treatment of:

- seizures associated with TSC in children and adults whose seizures are not controlled well by antiepileptic medicines. AFINITOR DISPERZ is the only formulation that should be used for the treatment of patients with seizures associated with TSC.

AFINITOR and AFINITOR DISPERZ are used in the treatment of:

- patients with subependymal giant cell astrocytoma (SEGA), a brain tumour seen with a genetic condition

called tuberous sclerosis complex (TSC), who are not suitable for surgery.

#### What it does:

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

#### When it should not be used:

If you are allergic (hypersensitive) to everolimus, or sirolimus (RAPAMUNE®), temsirolimus (TORISEL®), or any of the other ingredients in AFINITOR or AFINITOR DISPERZ listed below in the *What the nonmedicinal ingredients are* section.

#### What the medicinal ingredient is:

Everolimus

#### What the nonmedicinal ingredients are:

**AFINITOR:** Butylated hydroxytoluene (E321), crospovidone, hypromellose, lactose anhydrous, lactose monohydrate and magnesium stearate.

**AFINITOR DISPERZ:** Butylated hydroxytoluene (E321), cellulose microcrystalline, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol and silica colloidal anhydrous.

#### What dosage forms it comes in:

##### **AFINITOR**

AFINITOR tablets are supplied as 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets that are white to slightly yellowish, elongated, with a bevelled edge and no score.

Each 2.5 mg tablet contains 2.5 mg everolimus and is engraved with “LCL” on one side and “NVR” on the other.

Each 5 mg tablet contains 5 mg everolimus and is engraved with “5” on one side and “NVR” on the other.

Each 7.5 mg tablet contains 7.5 mg everolimus and is engraved with “7P5” on one side and “NVR” on the other.

Each 10 mg tablet contains 10 mg everolimus and is engraved with “UHE” on one side and “NVR” on the other.

For 2.5 mg, 5 mg and 10 mg, each blister pack contains 10 tablets and there are 3 blister packs in a carton.

For 7.5 mg, each blister pack contains 7 tablets and there are 4

blister packs in a carton.

**AFINITOR DISPERZ (for treatment of SEGA and/or seizures associated with TSC)**

AFINITOR DISPERZ tablets for oral suspension are supplied as 2 mg, 3 mg and 5 mg tablets for oral suspension that are white to slightly yellowish, round, flat tablets with a bevelled edge and no score.

Each 2 mg tablet for oral suspension contains 2 mg everolimus and is engraved with “D2” on one side and “NVR” on the other.

Each 3 mg tablet for oral suspension contains 3 mg everolimus and is engraved with “D3” on one side and “NVR” on the other.

Each 5 mg tablet for oral suspension contains 5 mg everolimus and is engraved with “D5” on one side and “NVR” on the other.

Each blister pack contains 10 tablets for oral suspension and there are 3 blister packs in each carton.

**BEFORE you use AFINITOR or AFINITOR DISPERZ talk to your doctor or pharmacist if you:**

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

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

**Angiomyolipoma of the kidney associated with TSC:** AFINITOR and AFINITOR DISPERZ are not to be used in children or adolescents under 18 years of age with angiomyolipoma of the kidney associated with TSC.

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

**Seizures associated with TSC:** AFINITOR DISPERZ can be used in patients two years of age and older who have normal liver function.

**What you should know during AFINITOR or AFINITOR DISPERZ treatment**

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

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

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

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

**SEGA associated with TSC:** AFINITOR and AFINITOR DISPERZ should be prescribed and managed only by a doctor experienced in treating patients with tuberous sclerosis complex.

The best possible duration of treatment with AFINITOR or AFINITOR DISPERZ for patients with SEGA is not known; however, SEGA re-growth has been seen once therapy is stopped.

AFINITOR or AFINITOR DISPERZ are not to be used in children and adolescents (below 18 years of age) who have liver problems.

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

AFINITOR and AFINITOR DISPERZ are **not** interchangeable. See **PROPER USE OF THIS MEDICATION**.

Serious side effects which have been reported with the use of AFINITOR include:

- Non-infectious pneumonitis (including interstitial lung disease)
- Infections
- Kidney failure

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

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

#### **Monitoring during your treatment with AFINITOR or AFINITOR DISPERZ:**

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

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

If you receive AFINITOR DISPERZ for the treatment of seizures associated with TSC, regular blood tests are necessary to measure how much everolimus is in your blood. This will help your doctor decide how much AFINITOR DISPERZ you need to take.

### **INTERACTIONS WITH THIS MEDICATION**

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

- drugs to treat infections (antifungals like ketoconazole, itraconazole; voriconazole or fluconazole; antibiotics like clarithromycin, telithromycin or erythromycin)
- drugs to treat tuberculosis, such as rifampicin or rifabutin
- St. John's wort (also known as *Hypericum perforatum*)
- drugs to stop seizures or fits (anticonvulsants like phenytoin, carbamazepine, oxcarbazepine or phenobarbital)
- drugs to treat AIDS/HIV like ritonavir, amprenavir, fosamprenavir, efavirenz, or nevirapine
- drugs to treat heart conditions or high blood pressure (such as verapamil or diltiazem)
- angiotensin-converting enzyme (ACE) inhibitors, medicines used to treat high blood pressure or other cardiovascular problems

- a class of medications called “statins” (like atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin) to treat high levels of lipids or cholesterol in the blood
- cyclosporine, a medicine to stop the body from rejecting organ transplants
- aprepitant, a medicine to prevent nausea and vomiting
- midazolam, a medicine used to treat acute seizures, or used as a sedative before or during surgery or a medical procedure
- drugs containing pimozone, quinidine or ergotamine, as the concentration of these drugs in your blood may be affected if these drugs are taken together with AFINITOR or AFINITOR DISPERZ

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

For patients with seizures associated with TSC who are taking anti-seizure medications, a change in anti-seizure medication dose (up or down) may require a change in AFINITOR DISPERZ dose.

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

### **PROPER USE OF THIS MEDICATION**

**AFINITOR and AFINITOR DISPERZ are not interchangeable. Make sure you are using the correct tablets prescribed for you and check with the pharmacist. Do not mix use of the two formulations. Do not switch use of the products without direction by your doctor.**

Your doctor will tell you exactly how many tablets of AFINITOR or AFINITOR DISPERZ to take. Follow your doctor's instructions carefully.

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

#### **AFINITOR**

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

#### **AFINITOR DISPERZ (for treatment of SEGA or seizures associated with TSC)**

Do not chew, crush, or swallow the AFINITOR DISPERZ tablets for oral suspension. Mix AFINITOR DISPERZ in tap water or non-sparkling water only, to prepare the suspension. Do not use juice or any other liquids (see **Preparation of suspension**). Take AFINITOR DISPERZ tablets as a suspension only. You can prepare the suspension in an oral syringe or in a small drinking glass. The suspension must be taken right away. If you do not take the dose within 60 minutes after it has been prepared, throw away the dose and prepare a new dose of AFINITOR DISPERZ.

#### **Instructions for use and handling of AFINITOR DISPERZ**

Caregivers are advised to avoid contact with suspensions of AFINITOR DISPERZ. As AFINITOR DISPERZ can cause harm to an unborn baby, the suspension should be prepared, when possible, by an adult who is not pregnant or planning to become pregnant. Wash hands thoroughly before and after preparation of the suspension.

**Preparation of suspension**


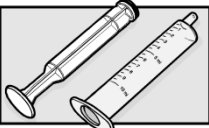
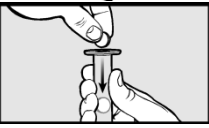

**Supplies needed to prepare the suspension in an oral syringe**





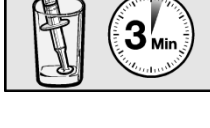
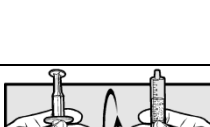
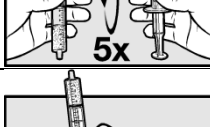




- Blister card with AFINITOR DISPERZ tablets for oral suspension
- Scissors to open the blister card
- 2 clean drinking glasses
- Approximately 30 mL of water
- 10 mL oral syringe (for one time use)



**Supplies needed to prepare the suspension in a small drinking glass**



- Blister card with AFINITOR DISPERZ tablets for oral suspension
- Scissors to open the blister card
- 30 mL dose cup for measuring water (you can ask your pharmacist for this)
- 1 clean drinking glass (maximum size 100 mL)
- Water to prepare the suspension
- Spoon for stirring

**Preparing a dose of AFINITOR DISPERZ suspension using an oral syringe**

	1. Wash and dry your hands before preparing the medication.
	2. Take a 10 mL oral syringe and pull back on the plunger. Remove the plunger from the barrel of the syringe.
	3. Use scissors to open the blister card along the dotted lines. Remove the prescribed number of tablets for oral suspension from the blister card. Place the tablets for oral suspension (maximum of five 2 mg tablets, three 3 mg tablets, or two 5 mg tablets) into the oral syringe immediately.
	4. Re-insert the plunger into the barrel of the oral syringe and push the plunger until it comes into contact with the tablets for oral suspension.


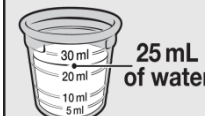
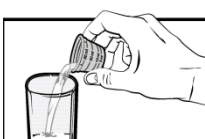






	5. Fill a drinking glass with water and pull up about 5 mL of water into the oral syringe by slowly pulling back on the plunger. <b>Note:</b> The amount of water in the syringe does not need to be accurate. All tablets for oral suspension should be covered by water. In case tablets for oral suspension remain in the dry upper part of the syringe, make them move into the water by gentle tapping.
	6. Hold the oral syringe with the tip pointing up. Pull back on the plunger to draw back about 4 mL of air.
	7. Place the filled oral syringe in the clean, empty glass with the tip pointing up. Allow the tablets for oral suspension <b>3 minutes</b> to break apart. Make sure to proceed further only when the 3 minutes are over and when the tablets for oral suspension have completely broken apart.
	8. Slowly turn the oral syringe up and down five times just before giving the dose. Do not shake the oral syringe.
	9. Hold the oral syringe in an upright position (with the tip up). Carefully remove most of the air by pushing up gently on the plunger.
	10. Give the full contents of the oral syringe slowly and gently into the mouth right away, within 60 minutes of preparing it.
	11. Carefully remove the oral syringe from patient's mouth.
	12. Insert the tip of the oral syringe into the drinking glass that is filled with water and pull up about 5 mL of water by slowly pulling back on the plunger.
	13. Hold the oral syringe with the tip pointing up and use the plunger to draw back about 4 mL of air.
	14. With the tip of the oral syringe still pointing up, swirl the contents by gently rotating the syringe in a circular manner to suspend any remaining particles of the medication.
	15. While holding the oral syringe in an upright position (with the tip up), carefully remove most of the air by pushing up gently on the plunger.

	<p>16. Dispense the full contents of the oral syringe slowly and gently into the mouth of the patient.</p> <p>17. Carefully remove the syringe from the patient's mouth. <b>If the total prescribed dose is more than 10 mg, repeat steps 2 to 17 to finish giving the dose.</b></p> <p>18. Throw away the original syringe in your household trash.</p>
	<p>19. Wash your hands.</p>

<b>finish taking the dose.</b>	
	<p>11. Wash the glass and the spoon thoroughly with water. Wipe the glass and spoon with a clean paper towel and store them in a dry and clean place until your next dose.</p>
	<p>12. Wash your hands.</p>

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

**Preparing a dose of AFINITOR DISPERZ suspension using a small drinking glass**

	<p>1. Wash and dry your hands before preparing the medication.</p>
	<p>2. Add about 25 mL of water to the 30 mL dose cup. The amount of water added does not need to be exact.</p>
	<p>3. Pour the water from the dose cup into a small drinking glass (maximum size 100 mL).</p>
	<p>4. Use scissors to open the blister card along the dotted line and remove the prescribed number of tablets for oral suspension from the blister card.</p> <p>5. Add the prescribed number of tablets for oral suspension into the water (maximum of five 2 mg tablets, three 3-mg tablets, or two 5 mg tablets).</p>
	<p>6. Wait 3 minutes to allow the tablets for oral suspension to break apart.</p>
	<p>7. Gently stir the contents of the glass with a spoon.</p>
	<p>8. Drink the full amount of the suspension right away, within 60 minutes of preparing it.</p>
	<p>9. Refill the glass with the same amount of water (about 25 mL). Stir the contents with the same spoon.</p>
	<p>10. Drink the full amount right away so that you take any remaining medicine. <b>If the total prescribed dose is more than 10 mg, repeat steps 2 to 10 to</b></p>

Continue taking AFINITOR or AFINITOR DISPERZ as long as your doctor tells you.

**Usual dose:**

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

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

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

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

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

Your doctor might need to reduce your dose of AFINITOR DISPERZ, or to interrupt or discontinue your treatment with AFINITOR DISPERZ for a variety of reasons. For example, if you have lung or breathing problems, mouth sores/ulcers, etc.

**Overdose:**

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

**Missed Dose:**

If you forget to take AFINITOR or AFINITOR DISPERZ, you may still take it up to 6 hours after the time you normally take it.

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

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, AFINITOR and AFINITOR DISPERZ can cause side effects.

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

**Very common side effects:**

*These side effects may affect more than 1 in 10 patients.*

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

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

**Common side effects:**

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

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

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

**Uncommon side effects:**

*These side effects may affect between 1 and 10 in every 1,000 patients.*

- A type of anaemia called pure red cell aplasia
- Onset of diabetes
- Abnormal wound healing
- Absence of menstrual periods (amenorrhoea)
- Loss of hearing

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

**Treatment of angiomyolipoma of the kidney associated with TSC**

**Very common side effects:**

*These side effects may affect more than 1 in 10 patients.*

- Low level of red blood cells (anaemia)
- Low level of white blood cells (leukopenia)
- High level of cholesterol in the blood (hypercholesterolaemia)
- Mouth ulcers. AFINITOR® can cause mouth ulcers and sores. **Tell your doctor** if you have pain, discomfort, or open sores in your mouth. You might need treatment with a mouthwash or gel. Some mouthwashes and gels can make ulcers worse, so do not try anything without checking with your doctor first.
- Middle ear infection
- Stomach upsets like feeling sick (nausea)
- Being sick (vomiting)
- Diarrhoea
- Abdominal pain
- Swelling of arms, hands, feet, ankles or other part of the body (signs of oedema)
- Upper respiratory tract infection
- Acne
- Skin rash
- Itchy rash (eczema)
- High level of an enzyme, called blood lactate dehydrogenase, in the blood that gives information about the health of certain organs
- Low level of phosphate in the blood (hypophosphatemia)
- Joint pain
- Headache
- Cough
- Menstruation disorders such as absence of periods (amenorrhoea), irregular periods, heavy periods (menorrhagia)

**Common side effects:**

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

- Rash, itching, hives, difficulty breathing or swallowing, dizziness, signs of serious allergic reaction (hypersensitivity)
- Menstruation disorders such as vaginal bleeds, delayed periods, or infrequent periods (oligomenorrhoea)
- Rash with pus-filled blister
- Rash with small, fluid-filled blisters on the mouth (mouth herpes)
- Fever, coughing, difficulty breathing, wheezing, signs of inflammation of the lung (pneumonia)
- Inflammation of the sinuses and nasal passages (sinusitis). Symptoms may include headache, pressure in the eyes, nose or cheek area
- Low level of platelets (thrombocytopenia)
- A special lung functional test result decreased (carbon monoxide test)

- High level of an enzyme called blood alkaline phosphatase, in the blood that gives information about the health of certain organs
- High level of an enzyme, called blood gamma-glutamyltransferase, in the blood that gives information about the health of your liver
- High level of lipids in the blood (hyperlipidaemia)
- Decreased appetite
- Low level of iron (iron deficiency)
- Severe headache often accompanied by nausea, vomiting and sensitivity to light (migraine)
- Disturbed taste (dysgeusia)
- Loss of taste (ageusia)
- Nose bleeds (epistaxis)
- Excess amount of gas in the bowels (flatulence)
- An inflammatory condition of the skin characterized by redness, itching, and oozing liquid-filled cysts which become scaly, crusted, or hardened (dermatitis acneiform)
- Dry skin
- Fever, coughing, difficulty breathing, wheezing, signs of inflammation of the lung (pneumonitis)
- Feeling depressed
- Sudden, severe increase in blood pressure
- Inability to sleep (insomnia)
- Aggression
- Mouth pain
- Higher level of ovulation triggering hormone (blood luteinising hormone increased)
- Higher level of female reproductive hormone (blood follicle stimulating hormone increased)
- Swollen, bleeding gums, signs of gum inflammation (gingivitis)
- Bad pain in the lower abdomen and pelvic area that may be sharp, with menstrual irregularities (ovarian cyst)

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

**Treatment of SEGA associated with TSC**

**Very common side effects:**

*These side effects may affect more than 1 in 10 patients.*

- Infections, such as inflammation of the sinuses and nasal passages (sinusitis), middle or outer ear infection, gastric infection, sore throat and runny nose, skin infections, ringworm (a fungus infection of the skin), infections of the hair follicle, urinary tract infection, conjunctivitis, upper respiratory tract infection, pneumonia.
- Mouth ulcers: AFINITOR® can cause mouth ulcers and sores. **Tell your doctor** if you have pain, discomfort, or open sores in the mouth. Your doctor may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- High level of cholesterol in the blood
- High levels of fats in the blood (raised triglycerides)
- Cough
- Diarrhoea and constipation
- Skin problems (such as rash, acne, dry skin or scratching of the skin)



- Fever
- Low white blood cells (a type of blood cell that fights infections; your doctor will check periodically)
- Vomiting
- Stomach pain
- Seizure
- Headache
- Dizziness
- Stuffy or runny nose
- Change in personality
- Loss of appetite
- High level of sugar in the blood (hyperglycemia)
- High blood pressure (hypertension)
- Sore throat and runny nose (nasopharyngitis)

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

**Common side effects:**

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

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

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

**Treatment of seizures associated with TSC:**

**Very common side effects:**

- Mouth ulcers. AFINITOR® can cause mouth ulcers and sores. Tell your doctor if you have pain, discomfort, or open sores in your mouth. You might need treatment with a mouthwash or gel. Some mouthwashes and gels can make ulcers worse, so do not try anything without checking with your doctor first
- Diarrhoea
- Throwing up (vomiting)
- Sore throat and runny nose (nasopharyngitis)
- Upper respiratory tract infection
- Fever
- Cough
- Low level of white blood cells which help fight infections (leukopenia, lymphopenia, neutropenia). This could increase chances of contracting different types of infection.
- Low level of red blood cells (anaemia)
- Low level of blood cells called platelets (thrombocytopenia) which are responsible to control bleeding. This could increase risk of bleeding.
- High level of fat called cholesterol in the blood (hypercholesterolaemia)
- High level of fats in the blood called triglycerides (Hypertriglyceridemia)
- Increased levels of enzymes liver enzymes in the blood which give information about health of liver.
- High level of sugar in the blood (hyperglycemia)
- High level of an enzyme called alkaline phosphatase, in the blood that gives information about the health of certain organs mainly liver and bones.

**Common side effects:**

- Rash
- Constipation
- Feeling sick (nausea)
- Gas in the stomach and bowels (flatulence)
- Inflammation of the stomach lining (gastritis)
- Abdominal pain
- Feeling tired
- Sore throat (pharyngitis)
- Inflammation of the tissue in one or both lungs (pneumonia), with cough, fever and difficulty in breathing
- Inflammation of the lining of the sinuses (hollow spaces in the bones of the face around nose) (sinusitis)
- Urinary tract infection
- Infection of stomach and intestines by a virus (gastroenteritis and intestinal flu)
- Inflammation and swelling of gums(gingivitis)
- Ear infection
- Skin inflammation (cellulitis)
- High level of an enzyme, called blood lactate dehydrogenase, in the blood that gives information about the health of certain organs

- Higher level of ovulation triggering hormone (blood luteinising hormone increased)
- Decreased appetite
- Headache
- Irritability
- Aggression
- Inability to sleep (insomnia)
- Protein in the urine
- Absence of periods (amenorrhoea) or irregular periods or heavy periods (menorrhagia)
- Nose bleeds (epistaxis)
- Fever, coughing, difficulty breathing, wheezing, signs of inflammation of the lung (pneumonitis)
- Acne
- Dry skin
- High blood pressure (hypertension)
- Low level of a chemical called phosphate in the blood (hypophosphatemia), which is responsible for health of bones, teeth and muscles.

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	Pain, discomfort or sores in the mouth		√	
Common	Lung or breathing problems (pneumonitis, pulmonary embolism, acute respiratory syndrome) (cough, chest pain, shortness of breath)		√	
	Fever or chills or other signs of an infection as you might need urgent treatment		√	
	Increased frequency in urination; kidney failure		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Rash, itching, hives, difficulty breathing or swallowing, dizziness, signs of serious allergic reaction (swelling of the face, lips, tongue or throat) (hypersensitivity)			√
Coughing up blood			√
Uncommon	Swelling and/or pain, and redness or warm skin in your leg, usually affecting the calf (deep vein thrombosis)		√
	Blood in urine		√
	Unexpected vaginal bleeding		√
	Severe abdominal pain, vomiting blood, black or bloody stools, swelling of the abdomen, constipation (gastrointestinal bleeding)		√
	<b>Hepatitis B reactivation</b> with symptoms of fever, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, yellowing of the skin, pain in the upper abdomen, pale stool or dark urine		√
	Swelling of the airways or tongue, with or without respiratory impairment (angioedema)		√

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Fever, chills, rapid breathing and heart rate, rash, and possibly confusion and disorientation (signs of serious infection, also known as sepsis)		√	
Reported from post-marketing with unknown frequency			√
Severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness (bleeding in the brain)			
Muscle pain, tenderness and weakness that you cannot explain		√	
Brownish or discoloured urine			√

*This is not a complete list of side effects. For any unexpected effects while taking AFINITOR or AFINITOR DISPERZ, contact your doctor or pharmacist.*

**HOW TO STORE IT**

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

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

Keep out of the reach and sight of children and pets.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program

Health Canada  
Postal Locator 1908C  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.novartis.ca>

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc. at: 1-800-363-8883

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