

# NEW ZEALAND DATA SHEET

## 1 Trade name

**AFINITOR<sup>®</sup>**

**(everolimus)**

5 mg and 10 mg tablets

## 2 Description and Composition

### Pharmaceutical form

Tablet.

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

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

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

### Active substance

#### 5 mg tablets

Each tablet contains 5 mg everolimus.

#### 10 mg tablets

Each tablet contains 10 mg everolimus.

### Excipients

Butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.

## 3 Indications

Afinitor is indicated for the treatment of advanced renal cell carcinoma in patients who have received prior VEGF-targeted therapy.

## 4 Dosage and administration

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

Afinitor should be administered orally once daily at the same time every day, either with or without food (see section 11 Clinical Pharmacology).

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

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

### **General target population:**

#### **Adults**

The recommended dose of Afinitor for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily.

Management of severe and/or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of Afinitor therapy. If dose reduction is required, the suggested dose is 5 mg daily (see section 6 Warnings and precautions).

*Moderate CYP3A4 or Pgp inhibitors:* Use caution when administered in combination with moderate CYP3A4 inhibitors or Pgp inhibitors. If patients require co-administration of a moderate CYP3A4 or Pgp inhibitor, reduce the dose to 5 mg daily. Further dose reduction to 5 mg every other day may be required to manage adverse reactions (see section 6 Warnings and Precautions and section 8 Interactions).

*Strong CYP3A4 inducers:* Avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration of a strong CYP3A4 inducer, an Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered (based on pharmacokinetic data), using 5 mg increments. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer (see section 6 Warnings and Precautions and section 8 Interactions).

### **Dosing in special populations:**

#### **Paediatric population**

Afinitor is not recommended for use in paediatric cancer patients.

#### **Elderly patients (≥ 65 years)**

No dosage adjustment is required (see section 11 Clinical Pharmacology).

#### **Patients with renal impairment**

No dosage adjustment is required (see section 11 Clinical Pharmacology).

#### **Patients with hepatic impairment**

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population (see section 6 Warnings and precautions and section 11 Clinical Pharmacology).

## **5 Contraindications**

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients (see section 6 Warnings and Precautions).

## **6 Warnings and precautions**

### **Non-infectious pneumonitis**

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see section 7 Adverse drug 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. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration. If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reintroduced at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

### **Infections**

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens (see section 7 Adverse drug reactions). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

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

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

### **Hypersensitivity reactions**

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 5 Contraindications).

### **Oral ulceration**

Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with Afinitor (see section 7 Adverse drug reactions). In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate

the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 8 Interactions).

### **Renal failure events**

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor (see section 7 Adverse drug reactions, see also Laboratory tests and monitoring).

### **Laboratory tests and monitoring**

#### **Renal function**

Elevations of serum creatinine, usually mild, and proteinuria have been reported in clinical trials (see section 7 Adverse drug 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 therapy and periodically thereafter.

#### **Blood glucose**

Hyperglycaemia has been reported in clinical trials (see section 7 Adverse drug reactions). Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. Optimal glycaemic control should be achieved before starting a patient on Afinitor.

#### **Haematological parameters**

Decreased haemoglobin, lymphocytes, platelets and neutrophils have been reported in clinical trials (see section 7 Adverse drug reactions). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

### **Drug-Drug Interactions**

Co-administration with strong inhibitors of CYP3A4 or P-glycoprotein (PgP) should be avoided (see section 8 Interactions).

Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If Afinitor must be co-administered with a moderate CYP3A4 or PgP inhibitor, the patient should be carefully monitored for adverse effects and the dose reduced if necessary (see section 4 Dosage and Administration and section 8 Interactions).

Co-administration with strong inducers of CYP3A4 or PgP should be avoided (see section 8 Interactions). If Afinitor must be co-administered with a strong CYP3A4 or PgP inducer, the patient should be carefully monitored for clinical response. Consider a dose increase of Afinitor when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment is not possible (see Section 4 Dosage and Administration and section 8 Interactions).

### **Hepatic impairment**

Afinitor is not recommended in patients with severe hepatic impairment, (Child-Pugh class C) (see section 4 Dosage and administration and section 11 Clinical pharmacology).

## Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor (see section 8 Interactions).

## 7 Adverse drug reactions

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).

The most common adverse reactions (incidence  $\geq 10\%$ ) were stomatitis, rash, fatigue, asthenia, diarrhoea, anorexia, nausea, mucosal inflammation, vomiting, cough, peripheral oedema, infections, dry skin, epistaxis, pruritus, and dyspnoea. The most common grade 3-4 adverse reactions (incidence  $\geq 2\%$ ) were infections, stomatitis, fatigue, and pneumonitis.

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 rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the Afinitor and placebo treatment groups, respectively. Most treatment-emergent adverse reactions were grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 39% versus 7% of patients receiving Afinitor and placebo, respectively.

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of  $\geq 5\%$  for patients receiving Afinitor 10 mg/day versus placebo. Adverse reactions in Table 1 are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/100$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), including isolated reports.

**Table 1 Adverse reactions reported in at least 5% of patients and at a higher rate in the Afinitor arm than in the placebo arm**

	Frequency	Afinitor 10 mg/day N=274			Placebo N=137		
		All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
		%	%	%	%	%	%
<b>Any adverse reaction</b>		<b>89</b>	<b>35</b>	<b>3.3</b>	<b>58</b>	<b>6.6</b>	<b>0</b>
<b>Infections and infestations</b>							
Infections <sup>a</sup>	Very common	13	2.2	2.2	2.2	0	0
<b>Metabolism and nutrition disorders</b>							
Anorexia	Very common	19	<1	0	5.8	0	0
<b>Nervous system disorders</b>							
Dysgeusia	Very common	9.9	0	0	1.5	0	0
Headache	Common	8.8	0	0	5.1	0	0

		Frequency	Afinitor 10 mg/day N=274			Placebo N=137		
			All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
<b>Respiratory, thoracic and mediastinal disorders</b>								
Cough	Very common	14	0	0	4.4	0	0	
Pneumonitis <sup>b</sup>	Very common	12	3.3	0	0	0	0	
Epistaxis	Very common	12	0	0	0	0	0	
Dyspnoea	Very common	10	1.8	0	2.9	0	0	
<b>Gastrointestinal disorders</b>								
Stomatitis <sup>c</sup>	Very common	42	3.3	0	8.0	0	0	
Diarrhoea	Very common	21	1.5	0	3.6	0	0	
Nausea	Very common	18	<1	0	8.0	0	0	
Vomiting	Very common	15	<1	0	3.6	0	0	
Dry mouth	Common	6.2	0	0	4.4	0	0	
<b>Skin and subcutaneous tissue disorders</b>								
Rash	Very common	28	1.1	0	5.1	0	0	
Dry skin	Very common	12	<1	0	4.4	0	0	
Pruritus	Very common	12	<1	0	2.9	0	0	
<b>General disorders and administration site conditions</b>								
Fatigue	Very common	23	3.3	0	17	<1	0	
Asthenia	Very common	22	1.8	0	9.5	<1	0	
Mucosal inflammation	Very common	17	1.1	0	1.5	0	0	
Oedema peripheral	Very common	13	<1	0	3.6	0	0	
Pyrexia	Common	5.5	0	0	2.2	0	0	
<b>Investigations</b>								
Weight decreased	Common	5.5	0	0	<1	0	0	
<b>Median Duration of Treatment (d)</b>			<b>141</b>			<b>60</b>		

CTCAE Version 3.0

<sup>a</sup> All infections reported including pneumonia, aspergillosis, candidiasis and sepsis.

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

<sup>c</sup> Stomatitis (including aphthous stomatitis) and mouth and tongue ulceration

Other notable adverse reactions occurring more frequently with Afinitor than with placebo, but with an incidence of <5% include:

***Metabolism and nutrition disorders***

Common: dehydration (1.5%), exacerbation of pre-existing diabetes mellitus (1.1%)

Uncommon: new onset of diabetes mellitus (<1%)

***Psychiatric disorders***

Common: insomnia (3.3%)

***Nervous system disorders***

Uncommon: ageusia (<1%)

***Cardiac disorders***

Uncommon: congestive cardiac failure (<1 %)

***Vascular disorders***

Common: hypertension (1.8 %)

***Respiratory, thoracic and mediastinal disorders***

Common: haemoptysis (1.1 %)

***Gastrointestinal disorders***

Common: abdominal pain (3.6%), dysphagia (2.6%), dyspepsia (2.6%)

***Skin and subcutaneous tissue disorders***

Common: hand-foot syndrome (4.7%), erythema (3.6%)

***Renal and urinary disorders***

Common: renal failure (1.1), increased daytime urination (1.8%)

***General disorders and administration site conditions***

Common: chest pain (1.1%)

Uncommon: impaired wound healing (<1%)

Single cases of grade 1 haemorrhages in a variety of locations were observed.

Key observed laboratory abnormalities are presented in Table 2.

**Table 2 Key laboratory abnormalities reported at a higher rate in the Afinitor arm than in the placebo arm**

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	1.1	79	5.1	<1
Lymphocytes decreased	51	16	2.2	28	5.1	0
Platelets decreased	23	1.1	0	2.2	0	<1
Neutrophils decreased	14	0	<1	3.6	0	0
<b>Clinical chemistry</b>						
Cholesterol increased	77	4.4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1.5	0
Creatinine increased	50	1.5	0	34	0	0
Phosphate decreased	37	6.2	0	8.0	0	0
Aspartate transaminase (AST) increased	25	<1	<1	6.6	0	0
Alanine transaminase (ALT) increased	21	1.1	0	3.6	0	0
Bilirubin increased	2.9	<1	<1	2.2	0	0

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

### Information from further clinical trials

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

Pulmonary embolism has been reported in clinical trials.

### Adverse Reactions of special interest

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal ones) and proteinuria. Monitoring of renal function is recommended (see section 6 Warnings and precautions).

## 8 Interactions

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

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

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

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

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

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

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

Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, ciclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and PgP inhibitors requires caution. Reduce the Afinitor dose if co-administered with moderate CYP3A4/PgP inhibitors (see section 4 Dosage and Administration and section 6 Warnings and Precautions).

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

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

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

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

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

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

Concurrent treatment with strong inducers of CYP3A4 or PgP should be avoided. If Afinitor must be co-administered with a strong CYP3A4 or PgP inducer (e.g. rifampicin and rifabutin), it may be necessary to adjust the dose (see section 4 Dosage and Administration and section 6 Warnings and Precautions).

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

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

#### **Agents whose plasma concentration may be altered by everolimus:**

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

*In vitro*, everolimus competitively inhibited the metabolism of the CYP3A4 substrate ciclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus  $C_{\max}$  with an oral dose of 10 mg daily or 70 mg weekly is more

than 12- to 36-fold below the  $K_i$ -values of the *in vitro* inhibition. An effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is therefore unlikely.

## **Vaccinations**

Immunosuppressants may affect the response to vaccination and vaccination during treatment with Afinitor may therefore be less effective. The use of live vaccines should be avoided during treatment with Afinitor (see section 6 Warnings and precautions). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

## **9 Pregnancy and Breast-feeding**

### **Pregnancy**

There are no adequate data from the use of Afinitor in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity (see section 13 Non-clinical safety data). The potential risk for humans is unknown. Afinitor should not be given to pregnant women unless the potential benefit outweighs the potential risk to the foetus.

### **Breast-feeding**

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 should therefore not breast-feed.

### **Women of childbearing potential**

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

### **Fertility**

Based on non-clinical findings, male fertility may be compromised by treatment with Afinitor (see section 13 Non-clinical safety data).

## **10 Overdosage**

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

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

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

## **11 Clinical pharmacology**

### **ATC code**

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

## Mechanism of action

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

## Pharmacodynamic properties

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

## Pharmacokinetic properties

### Absorption

In patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack.  $C_{max}$  is dose-proportional between 5 and 10 mg in the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in  $C_{max}$  is less than dose-proportional, however AUC shows dose-proportionality over the 5 to 70 mg dose range.

### Food effect:

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

## Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given 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.

## 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.

## Excretion

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

## Steady-state pharmacokinetics

After daily or weekly administration of everolimus in patients with advanced solid tumours, steady-state  $AUC_{0-\tau}$  was dose-proportional over the range of 5 to 10 mg in the daily dosing regimen and 5 to 70 mg on the weekly regimen. Steady-state was achieved within two weeks with the daily dosing regimen.  $C_{max}$  is dose-proportional between 5 and 10 mg on the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in  $C_{max}$  is less than dose-proportional.  $t_{max}$  occurs at 1 to 2 hours post-dose. There was a significant correlation between  $AUC_{0-\tau}$  and pre-dose trough concentration at steady-state on the daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

## Patients with hepatic impairment

The average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed (see section 4 Dosage and administration and section 6 Warnings and precautions).

## Patients with renal impairment

In a population pharmacokinetic analysis of 170 patients with advanced cancer, no significant influence of creatinine clearance (25 to 178 mL/min) was detected on CL/F of everolimus.

Post-transplant renal impairment (creatinine clearance range 11 to 107 mL/min) did not affect the pharmacokinetics of everolimus in transplant patients.

### **Paediatric patients**

There is no indication for use of Afinitor in the paediatric cancer population (see section 4 Dosage and administration).

### **Elderly patients**

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

### **Ethnicity**

Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black transplant patients.

### **Exposure-response relationships**

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

## **12 Clinical studies**

A phase III, international, multicentre, randomised, double-blind study comparing Afinitor 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-alpha was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- vs intermediate- vs poor-risk groups) and prior anticancer therapy (1 vs 2 prior VEGFR-TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms, and quality of life. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label Afinitor 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

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

Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 3 and Figure 1).

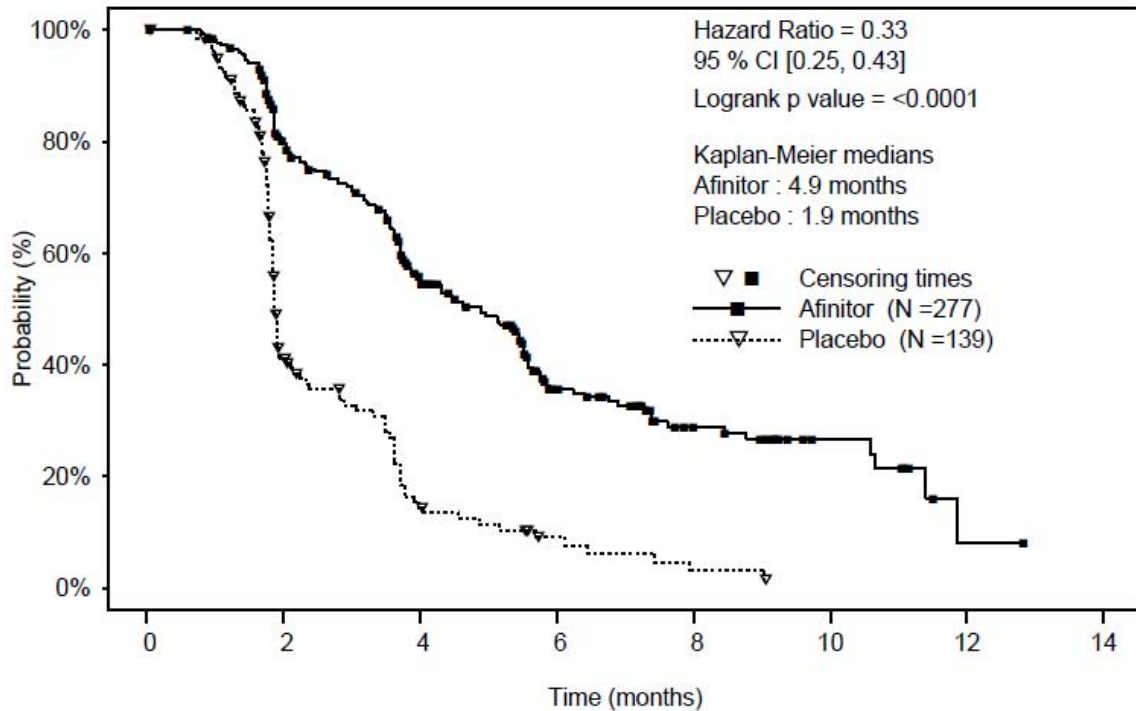
**Table 3 Progression Free Survival results**

Population	N	Afinitor N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value
Median progression-free survival (months) (95% CI)					
<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>					
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)	0.007 <sup>b</sup>
Prior VEGFR-TKI therapy					
Sunitinib only	184	3.9 (3.6 to 5.6)	1.8 (1.8 to 1.9)	0.34 (0.23 to 0.51)	<0.001 <sup>b</sup>
Sorafenib only	124	5.9 (4.9 to 11.4)	2.8 (1.9 to 3.6)	0.25 (0.16 to 0.42)	<0.001 <sup>b</sup>
Sunitinib and sorafenib	108	4.0 (3.6 to 5.4)	1.8 (1.8 to 2.0)	0.32 (0.19 to 0.54)	<0.001 <sup>b</sup>

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

<sup>b</sup> Unstratified one-sided log-rank test

**Figure 1 Kaplan-Meier progression-free survival curves**



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

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

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

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

### 13 Non-clinical safety data

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

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

above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution.

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and which caused a reduction in male fertility. There was evidence of reversibility. 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.

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 4.2 and 0.2 times the estimated clinical exposure.

## **14            Pharmaceutical information**

### **Incompatibilities**

Not applicable.

### **Shelf life**

36 months.

### **Special precautions for storage**

Do not store above 30°C

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

Keep out of the reach and sight of children.

### **Instructions for use and handling**

No special requirements.

### **Nature and contents of container**

Blister packs containing 30 tablets. Each blister strip contains 10 tablets.

### **Medicine classification**

Prescription Medicine

### **Name and address**

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