

PRESCRIBING INFORMATION

^{Pr}**AFINITOR***

(everolimus tablets)

5 mg and 10 mg

Antineoplastic Agent
(mTOR kinase inhibitor)

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Dorval, Quebec
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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	7
DRUG INTERACTIONS.....	11
DOSAGE AND ADMINISTRATION	14
OVERDOSAGE	15
ACTION AND CLINICAL PHARMACOLOGY	15
STORAGE AND STABILITY.....	18
SPECIAL HANDLING INSTRUCTIONS	18
DOSAGE FORMS, COMPOSITION AND PACKAGING	18
PART II: SCIENTIFIC INFORMATION.....	20
PHARMACEUTICAL INFORMATION.....	20
CLINICAL TRIALS.....	21
DETAILED PHARMACOLOGY	24
TOXICOLOGY	28
REFERENCES	37

Pr **AFINITOR***
(everolimus)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 5 mg and 10 mg	Butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

AFINITOR* (everolimus) 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 TKIs¹ sunitinib or sorafenib.

Approval of AFINITOR* is based on progression-free survival (PFS). Prolongation of overall survival 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 **PART II: CLINICAL TRIALS**).

Geriatrics (≥ 65 years of age):

No differences in safety or efficacy were observed between older and younger patients (see **PART II: CLINICAL TRIALS**).

Paediatrics (< 18 years of age):

AFINITOR* is not recommended for use in paediatric cancer patients.

¹ VEGF receptor TKIs = vascular endothelial growth factor receptor tyrosine kinase inhibitors

CONTRAINDICATIONS

AFINITOR* is 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** section of the Product Monograph (see also **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

AFINITOR* has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

The following are clinically significant adverse events:

- Non-infectious pneumonitis (see “**Respiratory**” section below)
- Infections (see “**Immune**” section below)

General

Drug-Drug Interactions

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

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

Co-administration with strong inducers of CYP3A4 or PgP should be avoided due to the risk of reduced effectiveness of the drug.

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 4.3 and 0.2 times the estimated clinical exposure.

Endocrine and Metabolism

Hyperlipidaemia: Hypercholesterolaemia and hypertriglyceridaemia have been reported in clinical trials (see **Clinical Trial Adverse Reactions**). Monitoring of fasting lipid profile is recommended prior to the start of AFINITOR* therapy and periodically thereafter (see **Monitoring and Laboratory Tests**).

Hyperglycaemia: Hyperglycaemia has been reported in clinical trials (see **Clinical Trial Adverse Reactions**). Monitoring of fasting serum glucose is recommended prior to the start of AFINITOR* therapy and periodically thereafter (see **Monitoring and Laboratory Tests**). Optimal glycaemic control should be achieved before starting a patient on AFINITOR*. New onset type 2 diabetes has occurred with AFINITOR* treatment (see **Clinical Trial Adverse Reactions**).

Gastrointestinal

Mucositis (including stomatitis, aphthous stomatitis) is a common adverse event in patients treated with AFINITOR*. Approximately half of the patients receiving AFINITOR* experienced mucositis in the pivotal phase III trial.

For mouth ulcers, stomatitis and oral mucositis 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 **DRUG INTERACTIONS**).

Haematologic

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

Immune

Infections: AFINITOR* 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 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*. Pre-existing infections should be treated and fully resolved prior to starting treatment with AFINITOR*. 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*.

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

Vaccinations: The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR* (see **DRUG INTERACTIONS**).

Peri-Operative Considerations

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

Renal

Elevations of serum creatinine, usually mild, have been reported in clinical trials (see **ADVERSE REACTIONS**). Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR* therapy and periodically thereafter.

Respiratory

Non-infectious pneumonitis: Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR*. Cases of non-infectious pneumonitis (including interstitial lung disease) were reported in 14% 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. 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.

Sensitivity/Resistance

Hypersensitivity reactions: Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angio-oedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see **CONTRAINDICATIONS**).

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 **DETAILED PHARMACOLOGY, 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* 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 **DETAILED PHARMACOLOGY, Toxicology**).

Hepatic impairment: AFINITOR* is not recommended in patients with severe hepatic impairment, (Child-Pugh class C) (see **DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

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 ≥ 4 months. The median age of patients was 61 years (range 27 to 85). 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.

Table 1 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 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.

Clinical Trial Adverse Reactions

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					
	AFINITOR* 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any Adverse Event	97	52	13	93	23	5
Gastrointestinal Disorders						
Stomatitis ^a	44	4	<1	8	0	0
Diarrhoea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Blood and Lymphatic System Disorders						
Anaemia	38	9	<1	15	4	<1
Infections and Infestations^b	37	7	3	18	1	0
General Disorders and Administration Site Conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Oedema peripheral	25	<1	0	8	<1	0

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					
	AFINITOR* 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	30	<1	0	16	0	0
Dyspnoea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis ^c	14	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and Nutrition Disorders						
Anorexia	25	1	0	14	<1	0
Hypercholesterolaemia	20	3	0	2	0	0
Hypertriglyceridaemia	15	1	0	2	0	0
Hyperglycaemia	12	6	0	2	1	0
Nervous System Disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	10	1	0	7	0	0
Median Duration of Treatment (d)	141			60		
CTCAE Version 3.0						
^a Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.						
^b Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).						
^c Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis.						

Other notable treatment-emergent adverse events occurring more frequently with AFINITOR* than with placebo, but with an incidence of <10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), haemorrhoids (5%), dysphagia (4%)

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%)

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%)

Metabolism and nutrition disorders: 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%)

Eye disorders: Eyelid oedema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%)

Renal and urinary disorders: Renal failure (3%)

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

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

Haematologic disorders: Haemorrhage (3%)

Abnormal Haematological and Clinical Chemistry Findings

Key treatment-emergent 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
	%	%	%	%	%	%
Haematology^a						
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
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

^a Includes reports of 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.

DRUG INTERACTIONS

Overview

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.

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 or PgP (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin) should be avoided.

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

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

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.

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).

Potential pharmacokinetic interactions between everolimus and agents which are CYP3A4 substrates:

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*. 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.

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 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 **WARNINGS AND PRECAUTIONS**). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21, a typhoid vaccine.

Drug-Food Interactions

Grapefruit, grapefruit juice and other foods that are known to affect cytochrome P450 and Pgp activity 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.

Drug-Laboratory Interactions

Interactions between AFINITOR* and laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose for treatment of metastatic renal cell carcinoma is 10 mg.

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

Dosing Considerations

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 **WARNINGS AND PRECAUTIONS**).

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4 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 **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Strong CYP3A4 or PgP inducers: Avoid the use of concomitant strong CYP3A4 or PgP inducers, due to the risk of reduced effectiveness of the drug.

Elderly patients (≥ 65 years):

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

Patients with 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 Insufficiency**).

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

WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

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.

OVERDOSAGE

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

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* 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 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 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.

Pharmacodynamics

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-BP1). 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 cell cycle progression and expression of hypoxia-inducible factors (e.g. HIF-1 transcription factor); the latter resulting in reduced expression of factors involved in the potentiation of tumour angiogenic processes (e.g. the vascular endothelial growth factor [VEGF] and platelet derived growth factor [PDGF]).

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.

QT/QTc Interval Prolongation: A thorough QT study conducted in humans indicated that single doses of everolimus up to 50 mg had minimal effects on QTc prolongation (maximal mean changes from baselines were 4.1 ms for 20 mg and 4.3 ms for 50 mg) that are acceptable according to the current guidelines. The effect of multiple dosing in humans on QTc prolongation was not studied.

Pharmacokinetics

Absorption: In patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack. C_{\max} is dose-proportional between 5 and 10 mg 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. Steady-state was achieved within two 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 3 - 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 ²)
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: Based on data in healthy subjects taking 1 mg everolimus tablets, a high-fat meal reduced C_{\max} and AUC by 60% and 16%, respectively. No data are available with AFINITOR* 5 and 10 mg tablets, which have a different formulation from the 1 mg everolimus tablets used in this study.

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 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: There is no indication for use of AFINITOR* in the paediatric population (see INDICATIONS AND CLINICAL USE).

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 Insufficiency: The average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

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

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

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

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.

Non-medicinal Ingredients

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

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

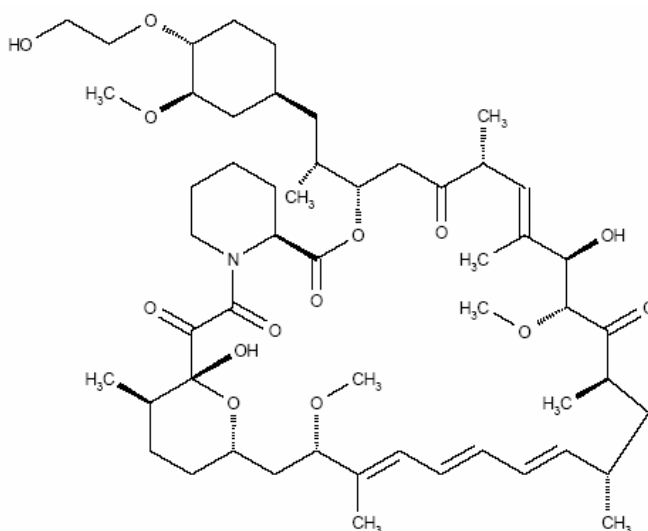
Common name: Everolimus

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 [30.3.1.04,9]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

Molecular formula: $C_{53}H_{83}NO_{14}$

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_3 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

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 4).

Table 4 Demographic and Disease Characteristics

Demographic or disease characteristic	AFINITOR N=277	Placebo N=139
Age (years)		
Median (range)	61.0 (27 to 85)	60.0 (29 to 79)
Age group (years) (n [%])		

Demographic or disease characteristic	AFINITOR N=277		Placebo N=139	
< 65 years	165	(59.6)	98	(70.5)
≥ 65 years	112	(40.4)	41	(29.5)
Gender (n [%])				
Male	216	(78.0)	106	(76.3)
Female	61	(22.0)	33	(23.7)
Race (n [%])				
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)
MSKCC prognostic score [n (%)]				
Favourable risk	81	(29.2)	39	(28.1)
Intermediate risk	156	(56.3)	79	(56.8)
Poor risk	40	(14.4)	21	(15.1)
Prior VEGF-receptor TKI therapy [n (%)]				
One prior VEGF-receptor TKI	205	(74.0)	103	(74.1)
Two prior VEGF-receptor TKIs	72	(26.0)	36	(25.9)
Prior immunotherapy (n [%])	179	(64.6)	93	(66.9)

Results from a planned interim analysis showed that 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 5 and Figure 1).

Table 5 Progression Free Survival results

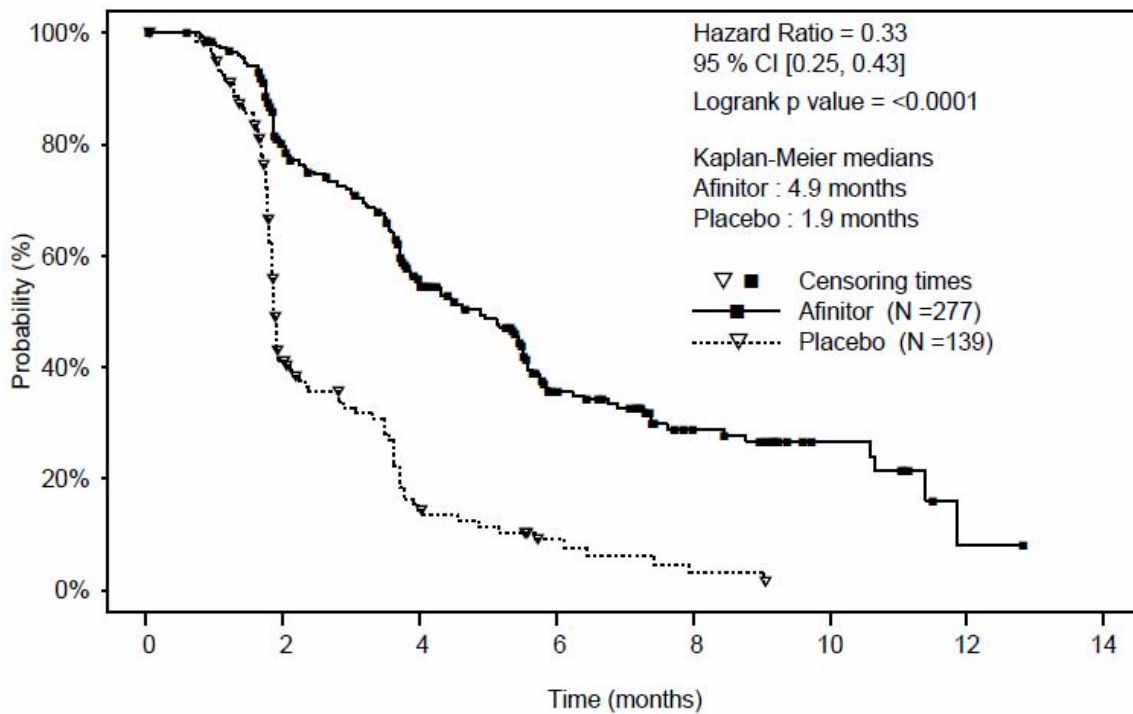
Population	N	AFINITOR* N=277	Placebo N=139	Hazard Ratio (95% CI)	p-value^a
Median progression-free survival (months) (95% CI)					
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 ^a
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6 to 5.8)	1.9 (1.8 to 2.2)	0.32 (0.25 to 0.41)	<0.001 ^a
MSKCC prognostic score					
Favourable risk	120	5.8	1.9	0.31	<0.001 ^b

Table 5 Progression Free Survival results

Population	N	AFINITOR* N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value ^a
Intermediate risk	235	4.5 (3.8 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.001 ^b
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.013 ^b

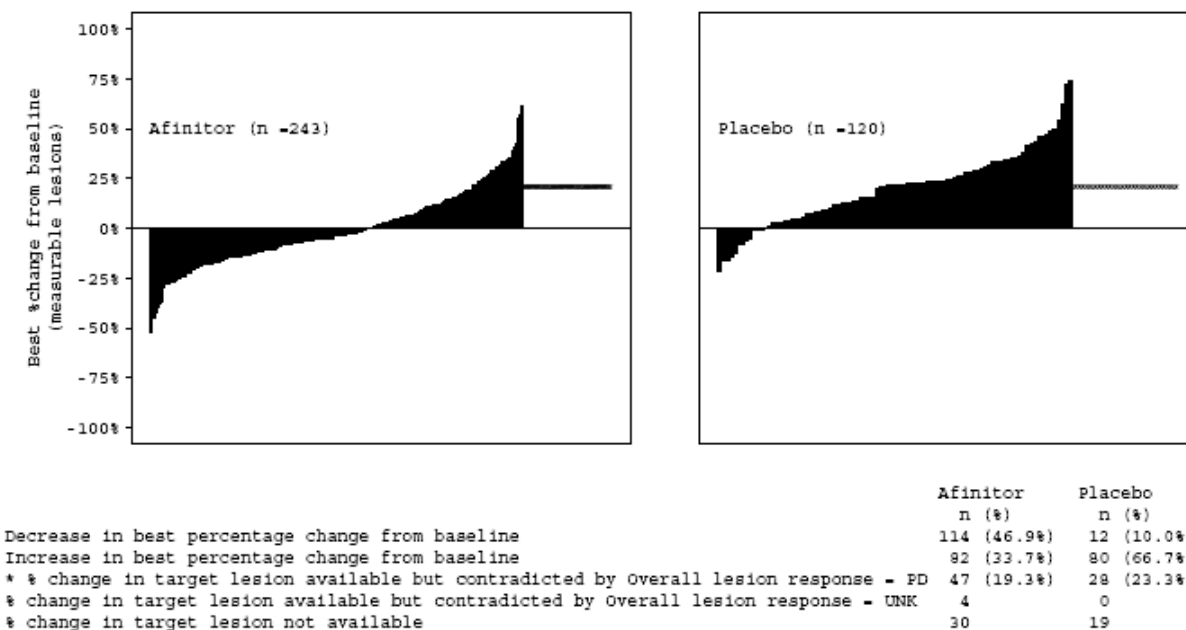
^aLog-rank test stratified by prognostic score

^bUnstratified, two-sided log-rank test

Figure 1 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 2).

Figure 2 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.

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) ($IC_{50} < 1$ nM) and insensitivity in others ($IC_{50} > 1$ μ M), although the majority of cell lines tested (80%) had IC_{50} 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_{50} s in the low/sub nM range, while two renal cell lines were insensitive ($IC_{50} > 2500$ 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_{50} 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.

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. Everolimus had minimal influence on QT interval prolongation both *in vitro* and in animal models as shown with isolated sheep cardiac Purkinje fibres, in stable transfected HEK293 cells (hERG currents) and with conventional ECG monitoring in minipigs and monkeys. The study in minipigs 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

[³H]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 [³H]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. [³H]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-medications that are strong CYP3A4 inducers 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_{\max} . In patients with advanced solid tumours, the steady-state $AUC_{0-\tau}$ 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_{\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_{\max} is less than dose-proportional. Pre-dose trough blood concentrations (C_{\min}) correlate well with $AUC_{0-\tau}$ 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 PgP-like mediated efflux systems. After an oral ^{14}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 two-fold in patients with moderate hepatic impairment (Child-Pugh class B, score 7 to 9). The impact of severe hepatic impairment (Child-Pugh class C, score 10 to 15) has not been assessed and the use of everolimus is not recommended in these patients. The strong CYP3A4 inhibitor and PgP inhibitor ketoconazole increases everolimus $AUC_{0-\infty}$ 15.0-fold. The moderate CYP3A4 and PgP inhibitors erythromycin and verapamil increase everolimus $AUC_{0-\infty}$ 4.4-fold and 3.5-fold, respectively. The CYP3A4 substrate and PgP inhibitor cyclosporine (NEORAL*) 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-∞} 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*² 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 6. 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 6 – 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"> • ≥ 0.15 mg/kg: higher incidence of swollen spleen • ≥ 0.5 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 • ≥ 1.5 mg/kg: higher liver weight (m),

² NEORAL* and SANDOSTATIN* LAR* are registered trademarks.

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					<p>slightly higher cholesterol (m), skin lesions (+m), foamy alveolar macrophages (f), reduced ovarian follicular development and atrophy of uterus (f)</p> <ul style="list-style-type: none"> • ≥ 5 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) • 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) • NTEL=0.15 (m), and 0.5 (f)
Rat	2 weeks	Oral, gavage	4m, 4f	0, 2.5, 10, 40 (everolimus), 40 (rapamycin)	<ul style="list-style-type: none"> • ≥ 2.5 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 macrophages in lungs • ≥ 10 mg/kg: reduced body weight gain, food intake (+f); increased cholesterol (m); skin lesions; bone marrow depletion (m) • 40 mg/kg: increased WBC/neutrophils; degenerative changes in testes; increased incidence of dioestrus stage. No major differences in toxicity profile compared with rapamycin • NTEL < 2.5 mg/kg

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
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"> No relevant differences in toxicity profile and exposure between microemulsion and solid dispersion
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"> ≥ 0.5 mg/kg: reduced body weight gain, food intake (m); haemo-concentration; low platelets; increased cholesterol (m); chronic myocarditis (m) ≥ 1.5 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 ≥ 5 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 15 mg/kg: Reduced sperm counts in testes; reduced contents in epididymides. Recovery of changes except for lungs, heart, eyes and testes NTEL approx. 0.5 mg/kg
Rat	4 weeks (with 2 week recovery)	Oral, gavage	10m, 10f, additional 6m, 6f in recovery	0, 0.1, 0.25, 0.5, 1.5, Recovery: 0, 15	<ul style="list-style-type: none"> ≥ 0.5 mg/kg: Medullary atrophy of thymus 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

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					<ul style="list-style-type: none"> EM: Alveolar macrophages in lungs with vacuoles and multi-lamellar bodies NTEL = 0.5 mg/kg
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"> ≥ 0.15 mg/kg: reduced body weight gain (f); medullary atrophy of thymus (f) ≥ 0.5 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) 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 Special investigations on the liver drug metabolizing enzyme levels and on the overall metabolism: Minor increase in total metabolite formation and reduction of P450 2B1/2 NTEL = 0.15 mg/kg
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"> ≥ 2 mg/kg: quietness (f) ≥ 20 mg/kg: increased WBC ≥ 40 mg/kg: quietness (m), piloerection and huddled posture (f) 60 mg/kg: piloerection and huddled posture (+m); reduced lymphoid activity in thymus, spleen, LN
Monkey	2 weeks	Oral,	1m, 1f	0, 5, 15, 45	<ul style="list-style-type: none"> ≥ 5 mg/kg: piloerection, rash on

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
		gavage			<p>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)</p> <ul style="list-style-type: none"> • ≥ 15 mg/kg: quietness; increased fibrinogen (+f); subendocard./interstitial haemorrhage in heart (m) • 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) • NTEL < 5 mg/kg
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"> • ≥ 1.5 mg/kg: reduced food intake (f); increased fibrinogen; decreased phosphorus; splenic lymphoid atrophy • ≥ 5 mg/kg: increase in skin lesions; reduced food intake (+m); reduced RBC parameters; increased $\alpha 2/\beta$ globulins, decreased albumin and Alb/Glob ratio (m); thymic medullary atrophy; increased histiocytosis in small intestine (f) • 15 mg/kg: pilo-erection, reddening of abdomen (m); increased WBC, neutrophils, monocytes; increased alanine and aspartate aminotransferases; increased $\alpha 2/\beta$ globulins and decreased albumin and Alb/Glob ratio (+f); reduced urine sodium; increased histiocytosis in small intestine (+m) • NTEL = 1.5 mg/kg
Monkey	26 weeks	Oral, gavage	4m, 4f additional 4m, 4f in control and 2m,	0, 0.1, 0.5, 1.5, 5	<ul style="list-style-type: none"> • ≥ 0.5 mg/kg: increased skin lesions (m); reduced body weight gain; splenic lymphoid atrophy; lymphoid depletion in LN; macrophage aggregation in small

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
			2f at high-dose		<p>intestine</p> <ul style="list-style-type: none"> • ≥ 1.5 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 • 5 mg/kg: early termination in weeks 9/10 due to skin lesions, poor health, body weight loss; increased $\alpha 2/\beta$ 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 • Virology: coxsackievirus in plasma (including pretest) and heart tissue • NTEL = 0.5 mg/kg
Monkey	39/52 weeks	Oral, gavage	4m, 4f	0, 0.1, 0.3, 0.9	<ul style="list-style-type: none"> • ≥ 0.3 mg/kg: diarrhoea/soft faeces (m); reduced body weight/food intake (2m); increased neutrophils (f); inflammatory changes in GI tract; atrophy of testes • 0.9 mg/kg: termination after 39 weeks; 1m and 2f sacrificed early due to poor health condition consequent to diarrhoea/soft faeces and inflammation/ ulceration of large intestine; body weight loss and reduced food intake; increased fibrinogen (f) • NOAEL = 0.1 mg/kg
Minipig	2 weeks	Oral, gavage	1m, 1f	0, 0.5, 1.5, 5	<ul style="list-style-type: none"> • ≥ 0.5 mg/kg: decreased platelets and lymphocytes; increased creatinine (f); increased seminiferous tubular atrophy in testes; thymic cortical

Species (strain)	Duration	Route	No./ groups	Dose (mg/kg)	Major findings
					lymphocytolysis; decreased germinal centre activity in LN <ul style="list-style-type: none"> • ≥ 1.5 mg/kg: decreased albumin, γ-globulins and Alb/Glob ratio; increase in $\beta 1$ globulins • 5 mg/kg: early sacrifice (f) due to pneumonitis; increased creatinine (m)
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"> • ≥ 1.5 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 γ-globulins; increased $\alpha 2$ and $\beta 1$ globulins; increased percent. of β-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 • ≥ 5 mg/kg: lymphoid depletion of spleen (1f); necrotic follicles in uterus; microvacuolation of adrenals • 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 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. • NTEL < 1.5 mg/kg
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 4.3 and 0.2 times the estimated clinical exposure.

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 and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions. The effects of everolimus on the pre- and post-natal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥ 0.1 mg/kg, and did not indicate a specific toxic potential.

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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