NOVARTIS

AFINITOR

(everolimus)

5 and 10 mg Tablets

Professional Information

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

AFINITOR 5 mg tablets

AFINITOR 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AFINITOR 5 mg tablets

Each tablet contains 5 mg everolimus.

Excipient with known effect:

Each tablet contains 149 mg lactose.

AFINITOR 10 mg tablets

Each tablet contains 10 mg everolimus.

Excipient with known effect:

Each tablet contains 297 mg lactose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AFINITOR is indicated for

- The palliative treatment of patients with advanced renal cell carcinoma, who failed prior treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFTR-TKI) therapy.
- In combination with exemestane for palliative treatment of postmenopausal women with oestrogen receptor positive, HER2/neu negative advanced breast cancer with recurrence or progression after prior treatment with a non-steroidal aromatase inhibitor.
- Treatment of advanced neuroendocrine tumours of gastrointestinal, lung or pancreatic origin.
- Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

4.2 Posology and method of administration

Treatment with AFINITOR should be initiated by a medical practitioner experienced in the use of anticancer therapies.

Posology

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

General target population:

Adults

- Dosing in advanced neuroendocrine tumours of gastrointestinal, lung or pancreatic origin, advanced renal cell carcinoma, advanced breast cancer and tuberous sclerosis complex (TSC) with renal angiomyolipoma.

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

Management of severe and/or intolerable suspected adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is 5 mg daily (see section 4.4).

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, the dose should be reduced to 5 mg daily. Further dose reduction to 5 mg every other day may be required to manage adverse reactions (see sections 4.4 and 4.5).

If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) should be allowed before the AFINITOR dose is increased. The AFINITOR dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor (see sections 4.4 and 4.5).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. If patients require co- administration of a strong CYP3A4 inducer, consider doubling the daily dose of AFINITOR (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, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before AFINITOR dose is resumed to the dose used prior to initiation of the strong CYP3A4 inducer (see sections 4.4 and 4.5).

Dose adjustment recommendations for specific adverse drug reactions

Table 1 summarises recommendations for dose reduction, interruption, or discontinuation of AFINITOR in the management of ADRs. General management recommendations are also provided as applicable.

Clinical judgment of the treating medical practitioner should guide the management plan of each patient based on individual benefit/risk assessment.

Table 1: AFINITOR dose adjustment and management recommendations for adverse drug reactions:

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
Non-infectious interstitial pneumonitis	Grade 1 Asymptomatic, clinical, or diagnostic observations only; intervention not indicated	No dose-adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated, limiting instrumental ADL[C]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms Improve to Grade < 1 Re-initiate treatment at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.

	Grade 3 Severe symptoms; limiting self-care ADL[C] oxygen indicated	Interrupt treatment until symptoms resolve to Grade < 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)	Discontinue treatment, rule out infection and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms; intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0,9 %) mouthwash several times a day.

	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade < 1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade < 1. Re-initiate treatment at 5 mg daily. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl amino benzoate, tetracaine hydrochloride. menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade < 1. Re-initiate treatment at 5 mg daily.

		Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Life- threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.

	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.

Metabolic events (e.g. hyper-glycaemia, dys-lipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate treatment at 5 mg daily. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 (<LLN[e] - 75,000/mm^3; <LLN[e] - 75.0 x 10^9/L)	No dose adjustment required.
	Grade 2 (<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose.

	Grade 3 (<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9/L) **OR** Grade 4 (<25,000/mm^3; <25.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN[e] – 1,500/mm^3; <LLN[e] – 1.5 x 10^9/L) **OR** Grade 2 (<1,500 – 1,000/mm^3; <1.5 – 1.0 x 10^9/L)	No dose adjustment required.
	Grade 3 (<1,000 - 500/mm^3; <1.0 - 0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at same dose.
	Grade 4 (<500/ mm^3; <0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at 5 mg daily.

Febrile neutropenia	Grade 3 ANC[f] <1,000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than one hour.	Temporary dose interruption until recovery to Grade ≤2 and no fever. Re-initiate treatment at 5 mg daily.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

[a] *Severity Grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.*

Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

[b] *If dose reduction is required, the suggested dose is approximately 50 % lower than the dose previously administered.*

[c] *Activities of daily living (ADL)*

[d] *Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.*

[e] *Lower limit of normal (LLN)*

[f] *Absolute Neutrophil Count (ANC)*

Dosing in special populations

Paediatric patients (below 18 years)

AFINITOR is not recommended for use in paediatric cancer patients with advanced renal cell carcinoma.

Elderly patients (≥ 65 years)

No dosage adjustment is required (see section 5).

Renal impairment

No dosage adjustment is required (see section 5).

Hepatic impairment

Hormone receptor-positive advance breast cancer, advanced neuroendocrine tumours of gastrointestinal, lung, or pancreatic origin, advanced renal cell carcinoma and TSC with renal angiomyolipoma

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7,5 mg daily
- Moderate hepatic impairment (Child-Pugh B) - the recommended dose is 5 mg
- Severe hepatic impairment (Child-Pugh C) - not recommended
- Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Method of administration

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

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

For patients unable to swallow tablets, AFINITOR tablet(s) should be dispersed completely in a glass of water (containing approximately 30 ml) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered (see section 5).

4.3 Contraindications

Hypersensitivity to everolimus, to other rapamycin derivatives or to any of the excipients of AFINITOR (see section 4.4).

Concomitant use of live vaccines.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Non-infectious interstitial pneumonitis

Non-infectious interstitial pneumonitis is a class effect of rapamycin derivatives, including everolimus. Cases of non-infectious interstitial pneumonitis (including interstitial lung disease) have been described in patients taking AFINITOR (see section 4.8). Some of these have been severe and fatalities have occurred.

A diagnosis of non-infectious interstitial pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnoea, and in whom infectious, neoplastic, and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as *pneumocystis jirovecii (carinii) pneumonia (PJP/PCP)* should be ruled out in the differential diagnosis of non- infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms. Patients who develop radiological changes suggestive of non-infectious interstitial 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 a daily dose approximately 50 % lower than the dose previously administered.

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

Infections

AFINITOR has immunosuppressive properties and may predispose patients to infections; especially infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, and invasive fungal infections, such as aspergillosis, candidiasis, or *pneumocystis jirovecii (carinii) pneumonia (PJP/PCP)* and viral infections including reactivation of hepatitis B virus have been described in patients taking AFINITOR. Some of these infections have been severe (e.g. leading to sepsis [including septic shock] or respiratory failure) and occasionally have had a fatal outcome. Medical practitioners and patients should be aware of the increased

risk of infection with AFINITOR, be vigilant for symptoms and signs of infection, and institute appropriate treatment promptly.

Pre-existing invasive fungal infections should be treated prior to starting treatment with AFINITOR. If a diagnosis of invasive systemic fungal infection is made, AFINITOR should be discontinued and treat with appropriate antifungal therapy.

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

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 AFINITOR (see section 4.3).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

Stomatitis

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

In a single arm study in 92 postmenopausal breast cancer patients, a topical alcohol-free corticosteroid oral solution was administered as a mouthwash during the initial 8 weeks of starting treatment with AFINITOR plus exemestane. In this study, a clinically meaningful reduction in the incidence and severity of stomatitis was observed.

Renal failure events

Cases of renal failure (including acute renal failure), some with fatal outcome, have been observed in patients treated with AFINITOR (see section 4.8).

Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function (see sections 4.4 and 4.8).

Laboratory tests monitoring

Renal function

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

Blood glucose

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

Blood lipids

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported in patients taking AFINITOR. Monitoring of blood cholesterol and triglycerides prior to the start of AFINITOR therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Haematological parameters

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

Interactions

Co-administration with strong inhibitors of CYP3A4 or P-glycoprotein (PgP) should be avoided (see sections 4.2 and 4.5). If AFINITOR must be co-administered with a strong CYP3A4 or PgP inhibitor, the patient should be carefully monitored for undesirable effects.

Use caution when administering AFINITOR 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 undesirable effects and the dose reduced if necessary (see sections 4.2 and 4.5).

Co-administration with strong CYP3A4 or PgP inducers should be avoided (see section 4.5). 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 sections 4.2 and 4.5). Exercise caution when AFINITOR is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index, due to the potential for medicine interactions. If AFINITOR is taken with orally administered CYP3A4 substrates with a narrow therapeutic index, the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section 4.5).

Hepatic impairment

AFINITOR is not recommended in patients ≥18 years of age with severe hepatic impairment, (Child-Pugh class C) (see sections 4.2 and 5).

Vaccinations

The use of live vaccines is contraindicated during treatment with AFINITOR and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR (see sections 4.3 and 4.5). Examples of live vaccines are intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

Wound healing complications

Impaired wound healing is a class effect of rapamycin derivatives such as everolimus, as in AFINITOR. Caution is advised with the use of AFINITOR in the peri-surgical period (see section 4.8).

Lactose

Patients with hereditary galactose intolerance (galactosaemia). Lapp lactase deficiency or glucose-galactose malabsorption should not use AFINITOR.

Radiation therapy complications

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

Additionally, radiation recall syndrome (RRS) has been reported in patients on everolimus who have received prior radiotherapy. In the event of RRS, interrupting or stopping everolimus treatment should be considered.

4.5 Interaction with other medicines and other forms of interaction

Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with AFINITOR may therefore be less effective. The use of live vaccines is contraindicated during treatment with AFINITOR (see sections 4.3 and 4.4). Examples of live vaccines are intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines (see section 4.4).

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multi-medicine efflux pump P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by medicines that affect CYP3A4 and/or PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Medicines that may increase everolimus blood concentrations:

Everolimus blood concentrations may be increased by medicines 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 AFINITOR and 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, 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 sections 4.2 and 4.4).

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)
- cannabidiol (PgP inhibitor; C_{max} and AUC increased by 2,5- and 2.5-fold, respectively)

Other moderate inhibitors of CYP3A4 and PgP that may increase everolimus blood concentrations include certain antifungal medicines (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 with AFINITOR.

No difference in everolimus C_{min} was apparent when administered in the presence or absence of substrates of CYP3A4 and/or PgP following treatment with the 10 mg or 5 mg daily dose.

Co-administration of weak inhibitors of CYP3A4 with or without PgP inhibitors had no apparent impact on everolimus C_{min} following treatment with 10 mg or 5 mg daily dose regimen.

Medicines 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 sections 4.2 and 4.4).

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 inducers of CYP3A4 that may increase the metabolism of everolimus and decrease everolimus blood levels include St. John's Wort (*Hypericum perforatum*), anticonvulsants (e.g. carbamazepine, phenobarbitone, phenytoin,) and anti-HIV medicines (e.g. efavirenz, nevirapine). Concomitant treatment with moderate inducers of CYP3A4 or PgP requires caution.

Medicines of which the plasma concentration may be altered by AFINITOR:

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a

CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

In vitro, everolimus competitively inhibited the metabolism of the CYP3A4 substrate ciclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus C_{max} with an oral dose of 10 mg daily or 70 mg weekly is more than 12- to 36-fold below the Ki-values of the in vitro inhibition. An effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is therefore unlikely. Co-administration of weak inhibitors of CYP3A4 with or without PgP inhibitors had no apparent impact on everolimus C_{min} following treatment with 10 mg or 5 mg daily dose regimen.

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

Co-administration of an oral dose of midazolam with AFINITOR resulted in a 25 % increase in midazolam C_{max} and a 30 % increase in midazolam $AUC_{0\text{-}int}$, whereas the

metabolic $AUC_{0\text{-}int}$ ratio (1-hydroxy- midazolam/midazolam) and the terminal $t_{1/2}$ of midazolam were not affected. This suggests that increased exposure to midazolam is due to effects of AFINITOR in the gastrointestinal system when both medicines are taken at the same time. Therefore, AFINITOR may affect the bioavailability of orally administered medicines which are CYP3A4 substrate medicines which are administered by non-oral routes such as intravenous, subcutaneous, and transdermal administrations (see section 4.4).

AFINITOR increased pre-dose concentrations of the antiepileptic medicines (AEMs) carbamazepine, clobazam, and the clobazam metabolite N-desmethylclobazam by about 10 %. The increase in the pre-dose concentrations of these AEMs may not be clinically significant and dose adjustments for AEMs with a narrow therapeutic index, e.g. carbamazepine, may be considered. AFINITOR had no impact on pre-dose concentrations of AEMs that are substrates of CYP3A4 (clonazepam, diazepam, felbamate and zonisamide). AFINITOR had no impact on the pre-dose concentration of other AEMs, including valproic acid, topiramate, oxcarbazepine, phenobarbital, phenytoin, and primidone.

Co-administration of AFINITOR containing everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus /placebo) of 1,47 (90 % CI: 1,32 to 1,64) which was unlikely to have clinically significant effects on the efficacy response to everolimus in patients with advanced neuroendocrine tumours.

4.6 Fertility, pregnancy, and lactation

Pregnancy

AFINITOR should not be given to pregnant women (see section 4.3). AFINITOR is contraindicated in pregnancy.

Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown.

Breastfeeding

There are no reported cases of exposure to everolimus during breast-feeding in humans. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Women taking AFINITOR should therefore not breastfeed their infants during treatment and for 2 weeks after the last dose. (see section 4.3).

Women of childbearing potential

Women of childbearing potential should be advised that animal studies have been performed showing AFINITOR to be harmful to the developing foetus. Sexually active women of childbearing potential should use highly effective contraception (one that results in an annual pregnancy rate <1% when used correctly) while receiving AFINITOR, and for up to 8 weeks after ending treatment.

Fertility

Both male and female fertility may be compromised by treatment with AFINITOR.

4.7 Effects on ability to drive and use machines

Caution is advised when driving and using machines, until the effect of AFINITOR on the individual patient has been established.

4.8 Undesirable effects

Oncology - Summary of the safety profile

Adverse drug reaction (ADR, suspected to be related to treatment by the investigator) information is based on pooled safety data in patients receiving AFINITOR (N=2672) in clinical studies including randomised, double-blind, placebo- or active comparator-controlled phase Ill trials and phase-II related to the approved indications in oncology (see section 4.1).

The most common ADRs (incidence > 1/10 and suspected to be related to treatment by the investigator) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, peripheral oedema, hyperglycaemia asthenia, pruritus, decreased weight hypercholesterolaemia, epistaxis cough, headache.

The most common grade 3-4 ADRs (incidence > 1/100 to < 1/10 and suspected to be related to treatment by the investigator) were stomatitis, anaemia, hyperglycaemia, fatigue, infections, pneumonitis, diarrhoea, aesthaenia, thrombocytopenia, neutropenia, dyspnoea, lymphopenia, proteinuria, haemorrhage, hypophosphataemia, rash, hypertension, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), pneumonia and diabetes mellitus.

Tabulated summary of adverse drug reactions from clinical trials in Oncology

Table 2 presents the frequency category of ADRs reported in the pooled, safety analysis. ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥ 1 /10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/10 000)

Table 2. Adverse drug reactions from oncology trials

Infections and infestations	
Very common	Infections[a]
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia

Uncommon	Pancytopenia
Rare	Pure red cell aplasia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration
Psychiatric disorders	
Common	Insomnia, anxiety, somnolence
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage[b], hypertension, lymphoedema[g]
Uncommon	Deep vein thrombosis
Respiratory, thoracic, and mediastinal disorders	
Very common	Pneumonitis[c], epistaxis, cough
Common	Dyspnoea

Uncommon	Haemoptysis, pulmonary embolism
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis[d], diarrhoea, nausea
Common	Vomiting, dry mouth, abdominal pain, oral pain, mouth ulcers, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, acne, erythema, hand-foot syndrome[e], pityriasis rosea
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria, renal failure
Uncommon	Increased daytime urination, acute renal failure
Reproductive system and breast disorders	
Common	Irregular menstruation[f]
Uncommon	Amenorrhoea[f]
General disorders and administration site conditions	
Very common	Fatigue, aesthaenia, peripheral oedema
Common	Pyrexia, mucosal inflammation

Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood creatinine increased

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

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

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

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

[e] reported as palmar-plantar erythrodysaesthesia syndrome

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

[g] ADR was determined based on post-marketing reports. Frequency was determined based on oncology trials safety pool

Laboratory Abnormalities

In the pooled double-blind phase Ill safety database, the following new or worsening clinically relevant laboratory abnormalities were reported with an incidence of ≥ 10 % (Very common, listed in decreasing frequency):

Haematology: decreased haemoglobin, decreased lymphocytes, decreased white blood cells; decreased platelets, and decreased neutrophils (or collectively as pancytopenia).

Clinical chemistry: increased glucose (fasting), increased cholesterol, increased triglycerides, increased aspartate transaminases, decreased phosphate, increased alanine transaminases, increased creatinine and decreased potassium and decreased albumin.

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

Haematology: Decreased Iymphocytes, decreased haemoglobin (very common) decreased neutrophils, decreased platelet count, decreased white blood cells (all common).

Clinical chemistry: increased glucose (fasting) (very common); decreased phosphate, decreased potassium, increased AST, increased ALT, increased creatinine, increased cholesterol (total), albumin decreased (all common), increased triglycerides (uncommon).

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

Adverse drug reaction (ADR) information is based on pooled data from patients with TSC receiving AFINITOR (N=612, including 409 patients <18 years of age) in three randomised, double blind, placebo-controlled, phase Ill studies including blinded and open-label treatment periods, and one non-randomised, open-label, single-arm phase II study which serve as the basis for the listed indications.

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

The most frequent grade 3/4 adverse reactions (incidence > 1/100 to < 1/10 were pneumonia, stomatitis, amenorrhoea, neutropenia, pyrexia, menstruation irregular, hypophosphataemia, diarrhoea and cellulitis.

Tuberous sclerosis complex (TSC)

Tabulated summary of adverse reactions from clinical trials in TSC

Table 3 shows the incidence of ADRs based on pooled data in patients receiving everolimus in the TSC studies (including both the double-blind and open-label study and extension periods) covering a duration of exposure of approximately 47 months in TSC-renal angiomyolipoma study. ADRs are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥ 1 /10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

Table 3 Adverse drug reactions from clinical trials in TSC reported at a higher rate in the AFINITOR arm than in the placebo arm in TSC studies.

Infections and infestations	
Very common	Nasopharyngitis, upper respiratory tract infection, pneumonia, urinary tract infection, sinusitis, pharyngitis
Common	Otitis media, cellulitis, streptococcal pharyngitis, viral gastroenteritis, gingivitis
Uncommon	Herpes zoster, sepsis, viral bronchitis
Blood and lymphatic system disorders	
Common	Anaemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypercholesterolaemia
Common	Hypertriglyceridaemia, hyperlipidaemia, hypophosphataemia, hyperglycaemia
Psychiatric disorders	
Common	Insomnia, aggression, irritability
Nervous system disorders	
Very common	Headache
Uncommon	Dysgeusia
Vascular disorders	

Common	Hypertension, lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Epistaxis, pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis[a], diarrhoea, vomiting
Common	Constipation, nausea, abdominal pain, flatulence, oral pain, gastritis
Skin and subcutaneous tissue disorders	
Very common	Rash[b], acne
Common	Dry skin, acneiform, dermatitis
Uncommon	Angioedema
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very common	Amenorrhoea[c], irregular menstruation[c]
Common	Menorrhagia, ovarian cyst, vaginal haemorrhage
Uncommon	Delayed menstruation[c]
General disorders and administration site conditions	
Very common	Pyrexia, fatigue
Investigations	
Common	Increased blood lactate dehydrogenase, increased blood luteinising hormone

Uncommon	Increased blood follicle stimulating hormone
[a] Includes very common: stomatitis, mouth ulceration, aphthous ulcer; common: tongue ulceration, lip ulceration; uncommon: gingival pain, glossitis. *[b] Includes very common: rash; common: rash erythematous, erythema; uncommon: rash generalized, rash maculo-papular, rash macular.* *[c] frequency is based upon number of women aged 10 to 55 years of age while on treatment in the safety pool*	

Clinically relevant laboratory abnormalities

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

Haematology: increased partial thromboplastin time, decreased neutrophils, decreased haemoglobin, decreased white blood cells, decreased platelet count and decreased lymphocytes.

Clinical chemistry: increased cholesterol, increased triglycerides, increased AST, decreased phosphatase, increased ALT, increased alkaline phosphatase and glucose (fasting) increased.

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

Haematology: decreased neutrophils, increased partial thromboplastin time, haemoglobin decreased (common); lymphocytes decreased, platelet count decreased, and white blood cells decreased (uncommon).

Clinical chemistry: decreased phosphate, triglycerides increased, increased alkaline phosphatase, increased ALT, increased AST, increased cholesterol (common); and glucose (fasting) increased (uncommon).

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

The following adverse drug reactions have been derived from post-marketing experience with Afinitor via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 4. Adverse drug reactions from spontaneous reports and literature in Oncology and TSC (frequency not known)

Injury poisoning and procedural complications	
Frequency unknown	Radiation recall syndrome

Description of selected adverse drug reactions

AFINITOR has been associated with:

Serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression (see section 4.4).

Renal failure events (including fatal ones) and proteinuria. Monitoring of renal function is recommended (see section 4.4).

- Cases of amenorrhoea (including secondary amenorrhoea).

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with *pneumocystis jirovecii (carinii) pneumonia* (PJP/PCP), some with fatal outcome (see section 4.4).

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors (see section 4.4).

In a post-marketing single arm study in postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 mL alcohol-free oral solution (10 mL swished in the mouth for 2 minutes and then spat out, to be repeated 4 times daily for 8 weeks) was administered as a mouthwash to patients at the time of initiating treatment with AFINITOR (10 mg/day) plus exemestane (25 mg/day) to reduce the incidence and severity of stomatitis. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone oral solution. The incidence of grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than historically reported at 27.4% (n=132/482) in the phase III study in this patient population (BOLERO-2). The incidence of grade 1 stomatitis was 18.8% (n=16/85) and no grade 3 or 4 stomatitis were reported. The overall safety profile in this study was consistent with that established for everolimus

in the oncology and TSC settings, with the exception of oral candidiasis which was reported in 2.2% (n=2/92) of patients in this study compared to 0.2% (n=1/482) of patients in BOLERO-2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

General symptomatic and supportive measures should be initiated in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 34 Other: selective immunosuppressive agents

Everolimus is an inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). It exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The

FKBP12/ everolimus complex binds to mTORC1, inhibiting its signalling capacity. mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. Inhibition of mTORC1 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.

mTORC1 signalling is affected through modulation of the phosphorylation of downstream effectors, the best characterized of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic initiation 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) in multiple tumours such as RCC and angiomyolipoma).

Two primary regulators of mTORC1 signalling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (TSC1, TSC2). Loss or inactivation of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signalling cascade, including activation of the S6K1. A substrate of mTOR complex

1(mTORC1), S6K1 phosphorylates the oestrogen receptor, which is responsible for ligand-independent receptor activation. In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

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 antitumor cell activity and inhibition of the tumour stromal compartment.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the P13K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (A1)-resistant and long- term oestrogen deprived breast cancer cells. In breast cancer cells, resistance due to A1s due to Akt activation can be reversed by co-administration with everolimus.

There was a moderate correlation between the decrease in the phosphorylation of 4E-BP1 (P4-EBP1) in tumour tissue and the average everolimus C_{min} at steady state in blood after daily administration of 5 or 10 mg everolimus. Further data suggest that the inhibition of phosphorylation of the S6 kinase is very sensitive to the mTOR inhibition by everolimus.

Inhibition of phosphorylation of elF-4G was complete at all C_{min} values after the 10 mg daily dose.

Clinical Studies

RADIANT-4

RADIANT-4 (Study CRAD001T2302), a randomized, double-blind, multicentre phase III study of Afinitor plus best supportive care (BSC) versus placebo plus best supportive care was conducted in patients with advanced non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome. The primary endpoint for the study was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumours (modified RECIST version 1.0), based on independent radiological assessment. Supportive PFS analysis was based on local investigator review. Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Disease Control Rate (DCR = proportion of patients with a best overall response of complete response, partial response or stable disease), Safety, change in Quality of Life (QoL) via FACT-G and time to WHO PS deterioration. A total of 302 patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) (n=205) or placebo (n=97). The two treatment groups were generally balanced with respect to the baseline demographics, disease characteristics and history of prior somatostatin analogue (SSA) use. The efficacy results were obtained from the final analysis of PFS after 178 PFS events were observed per independent radiological review.

The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 2.8-fold prolongation in median PFS (11.01 months versus 3.91 months), resulting in a 52% risk reduction of progression or death (HR 0.48; 95% CI: 0.35, 0.67; one-sided stratified log-rank test p-value <0.001) per independent assessment. The analysis of PFS based on local investigator assessment was supportive and showed a 2.6-fold prolongation in median progression-free-survival (14.39 months versus 5.45 months), resulting in a 60% risk reduction of progression or death (HR 0.40; 95% CI: 0.29, 0.55; one-sided stratified log-rank test p-value<0.001). The overall response rate as per independent assessment was 2% in the everolimus arm vs. 1% in the placebo arm. Disease control rate (CR or PR or SD) for everolimus was 82.4% vs. 64.9% in the placebo arm. Results also indicate that 63.6% of patients in the everolimus arm experienced tumour shrinkage versus 25.9% for placebo.

The final overall survival (OS) analysis did not show statistically significant difference between those patients who received Afinitor or placebo during the blinded treatment period of the study [HR= 0.90 (95% CI: 0.66 to 1.24)]

5.2 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 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg.

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 everolimus 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 ciclosporine, 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 safety, tolerability and pharmacokinetics were evaluated in a single oral dose study of everolimus in 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1,6-fold, 3,3-fold and 3,6-fold increase in exposure (i.e. AUC_{0-inf} for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively. Simulation of multiple dose pharmacokinetics supports the dosing recommendations in hepatic impaired patients based on their Child-Pugh status. Dose adjustment is recommended for patients with hepatic impairment (see sections 4.2 and 4.4).

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:

Everolimus has not been studied in children with renal carcinoma.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Pack size 30: 3 years

Pack size 60 and 90: 2 years

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Store in original package.

6.5 Nature and contents of container

Clear colourless thermoformed PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with silver aluminium foil backing.

Pack size of 30, 60, and 90.

Not all pack sizes may be marketed.

The blister foil is imprinted with the proprietary name, company name, batch number and expiry date. The blisters are packed into a white cardboard carton

6.6 Special precautions for disposal other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

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8. REGISTRATION NUMBERS

AFINITOR 5 mg tablets: 43/34/1010

AFINITOR 10 mg tablets: 43/34/1133

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine:

AFINITOR 5 mg tablets: 30 September 2011

AFINITOR 10 mg tablets: 30 September 2011

10. DATE OF REVISION OF THE TEXT

31 March 2026

	Namibia		Botswana	
AFINITOR 5 mg	14/26/0654	NS2	BOT 1502710	S2
AFINITOR 10 mg	14/26/0655	NS2	BOT 1502711	S2

2020-PSB/GLC-1147-s and 2021-PSB/GLC-1183-s