**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 2.5 mg tablets
Afinitor 5 mg tablets
Afinitor 10 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Afinitor 2.5 mg tablets

Each tablet contains 2.5 mg everolimus.

*Excipient with known effect*
Each tablet contains 74 mg lactose.

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 the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

Afinitor 2.5 mg tablets

White to slightly yellow, elongated tablets of approximately 10.1 mm in length and 4.1 mm in width, with a bevelled edge and no score, engraved with “LCL” on one side and “NVR” on the other.

Afinitor 5 mg tablets

White to slightly yellow, elongated tablets of approximately 12.1 mm in length and 4.9 mm in width, with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other.

Afinitor 10 mg tablets

White to slightly yellow, elongated tablets of approximately 15.1 mm in length and 6.0 mm in width, with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hormone receptor-positive advanced breast cancer

Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

Neuroendocrine tumours of pancreatic origin

Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Neuroendocrine tumours of gastrointestinal or lung origin

Afinitor is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease (see sections 4.4 and 5.1).

Renal cell carcinoma

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

### 4.2 Posology and method of administration

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

Posology

For the different dose regimens Afinitor is available as 2.5 mg, 5 mg and 10 mg tablets.

The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

If a dose is missed, the patient should not take an additional dose, but take the next prescribed dose as usual.

*Dose adjustment due to adverse reactions*
Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of Afinitor therapy. For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily.

Table 1 summarises the dose adjustment recommendations for specific adverse reactions (see also section 4.4).

**Table 1 Afinitor dose adjustment recommendations**

| Adverse reaction | Severity[1] | Afinitor dose adjustment |
|---|---|---|
| Non-infectious pneumonitis | Grade 2 | Consider interruption of therapy until symptoms improve to Grade ≤1.<br>Re-initiate treatment at 5 mg daily.<br>Discontinue treatment if failure to recover within 4 weeks. |
| | Grade 3 | Interrupt treatment until symptoms resolve to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation. |
| | Grade 4 | Discontinue treatment. |
| Stomatitis | Grade 2 | Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose.<br>If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily. |
| | Grade 3 | Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily. |
| | Grade 4 | Discontinue treatment. |
| Other non-haematological toxicities (excluding metabolic events) | Grade 2 | If toxicity is tolerable, no dose adjustment required.<br>If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose.<br>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. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation. |
| | Grade 4 | Discontinue treatment. |
| Metabolic events (e.g. hyperglycaemia, dyslipidaemia) | Grade 2 | No dose adjustment required. |
| | Grade 3 | Temporary dose interruption.<br>Re-initiate treatment at 5 mg daily. |
| | Grade 4 | Discontinue treatment. |
| Thrombocytopenia | Grade 2 ($<75, \geq 50 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤1 ($\geq 75 \times 10^9$/l). Re-initiate treatment at same dose. |
| | Grade 3 & 4 ($<50 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤1 ($\geq 75 \times 10^9$/l). Re-initiate treatment at 5 mg daily. |
| Neutropenia | Grade 2 ($\geq 1 \times 10^9$/l) | No dose adjustment required. |
| | Grade 3 ($<1, \geq 0.5 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤2 ($\geq 1 \times 10^9$/l). Re-initiate treatment at same dose. |
| | Grade 4 ($<0.5 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤2 ($\geq 1 \times 10^9$/l). Re-initiate treatment at 5 mg daily. |
| Febrile neutropenia | Grade 3 | Temporary dose interruption until recovery to Grade ≤2 ($\geq 1.25 \times 10^9$/l) and no fever.<br>Re-initiate treatment at 5 mg daily. |
| | Grade 4 | Discontinue treatment. |

[1] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0

*Special populations*
*Elderly patients (≥65 years)*
No dose adjustment is required (see section 5.2).

*Renal impairment*
No dose adjustment is required (see section 5.2).

*Hepatic impairment*
- 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 daily.
- Severe hepatic impairment (Child-Pugh C) – Afinitor is only recommended if the desired benefit outweighs the risk. In this case, a dose of 2.5 mg daily must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment (see also sections 4.4 and 5.2).

*Paediatric population*
The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Afinitor should be administered orally once daily at the same time every day, consistently either with or without food (see section 5.2). Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

## 4.3 Contraindications

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) has been frequently reported in patients taking Afinitor (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as *pneumocystis jirovecii (carinii)* pneumonia (PJP/PCP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see "Infections" below). 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 adjustments. If symptoms are moderate (Grade 2) or severe (Grade 3) the use of corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP/PCP may be considered.

Infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis or 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, respiratory or hepatic failure) and occasionally fatal.

Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor.

If a diagnosis of invasive systemic fungal infection is made, the Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Cases of 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 everolimus (see section 4.3).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Stomatitis

Stomatitis, including mouth ulcerations and oral mucositis, is the most commonly reported adverse reaction in patients treated with Afinitor (see section 4.8). Stomatitis mostly occurs within the first 8 weeks of treatment. A single-arm study in postmenopausal breast cancer patients treated with Afinitor plus exemestane suggested that an alcohol-free corticosteroid oral solution, administered as a mouthwash during the initial 8 weeks of treatment, may decrease the incidence and severity of stomatitis (see section 5.1). Management of stomatitis may therefore include prophylactic and/or therapeutic use of topical treatments, such as an alcohol-free corticosteroid oral solution as a mouthwash. However products containing alcohol, hydrogen peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medicinal products. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5).

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor (see section 4.8). Renal function should be monitored particularly where patients have additional risk factors that may further impair renal function.

Laboratory tests and monitoring

*Renal function*
Elevations of serum creatinine, usually mild, and proteinuria have been reported (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter.

*Blood glucose*
Hyperglycaemia has been reported (see section 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 medicinal products that may induce hyperglycaemia. When possible optimal glycaemic control should be achieved before starting a patient on Afinitor.

*Blood lipids*
Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. 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 (see section 4.8). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

Functional carcinoid tumours

In a randomised, double-blind, multi-centre trial in patients with functional carcinoid tumours, Afinitor plus depot octreotide was compared to placebo plus depot octreotide. The study did not meet the primary efficacy endpoint (progression-free-survival [PFS]) and the overall survival (OS) interim analysis numerically favoured the placebo plus depot octreotide arm. Therefore, the safety and efficacy of Afinitor in patients with functional carcinoid tumours have not been established.

Prognostic factors in neuroendocrine tumours of gastrointestinal or lung origin

In patients with non-functional gastrointestinal or lung neuroendocrine tumours and good prognostic baseline factors, e.g. ileum as primary tumour origin and normal chromogranin A values or without bone involvement, an individual benefit-risk assessment should be performed prior to the start of Afinitor therapy. Limited evidence of PFS benefit was reported in the subgroup of patients with ileum as primary tumour origin (see section 5.1).

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a moderate CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, the clinical condition of the patient should be monitored closely. Dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5).

Concomitant treatment with potent CYP3A4/PgP inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and potent inhibitors is not recommended.

Caution should be exercised when Afinitor is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Afinitor is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), 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

Exposure to everolimus was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment (see section 5.2).

Afinitor is only recommended for use in patients with severe hepatic impairment (Child-Pugh C) if the potential benefit outweighs the risk (see sections 4.2 and 5.2).

No clinical safety or efficacy data are currently available to support dose adjustment recommendations for the management of adverse reactions in patients with hepatic impairment.

Vaccinations

The use of live vaccines should be avoided during treatment with Afinitor (see section 4.5).

Lactose

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

Wound healing complications

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

Radiation therapy complications

Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin injury), including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. Caution should therefore be exercised for the potentiation of radiotherapy toxicity in patients taking everolimus in close temporal relationship with radiation therapy.

Additionally, radiation recall syndrome (RRS) has been reported in patients taking everolimus who had received radiation therapy in the past. In the event of RRS, interrupting or stopping everolimus treatment should be considered.

## 4.5 Interaction with other medicinal products and other forms of interaction

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of 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.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 2 below.

CYP3A4 and PgP inhibitors increasing everolimus concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus 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.

**Table 2 Effects of other active substances on everolimus**

| **Active substance by interaction** | **Interaction – Change in Everolimus AUC/$C_{max}$ Geometric mean ratio (observed range)** | **Recommendations concerning co-administration** |
|---|---|---|
| ***Potent* CYP3A4/PgP inhibitors** | | |
| **Ketoconazole** | AUC ↑15.3-fold (range 11.2-22.5)<br>$C_{max}$ ↑4.1-fold (range 2.6-7.0) | Concomitant treatment of Afinitor and potent inhibitors is not recommended. |
| **Itraconazole, posaconazole, voriconazole** | Not studied. Large increase in everolimus concentration is expected. | |
| **Telithromycin, clarithromycin** | | |
| **Nefazodone** | | |
| **Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir** | | |

| | | |
|---|---|---|
| ***Moderate* CYP3A4/PgP inhibitors** | | |
| **Erythromycin** | AUC ↑4.4-fold<br>(range 2.0-12.6)<br>$C_{max}$ ↑2.0-fold<br>(range 0.9-3.5) | Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended (see sections 4.2 and 4.4). If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration. |
| **Imatinib** | AUC ↑ 3.7-fold<br>$C_{max}$ ↑ 2.2-fold | |
| **Verapamil** | AUC ↑3.5-fold<br>(range 2.2-6.3)<br>$C_{max}$ ↑2.3-fold<br>(range1.3-3.8) | |
| **Ciclosporin oral** | AUC ↑2.7-fold<br>(range 1.5-4.7)<br>$C_{max}$ ↑1.8-fold<br>(range 1.3-2.6) | |
| **Cannabidiol (PgP inhibitor)** | AUC ↑2.5-fold<br>$C_{max}$ ↑2.5-fold | |
| **Fluconazole** | Not studied. Increased exposure expected. | |
| **Diltiazem** | | |
| **Dronedarone** | Not studied. Increased exposure expected. | |
| **Amprenavir, fosamprenavir** | Not studied. Increased exposure expected. | |
| **Grapefruit juice or other food affecting CYP3A4/PgP** | Not studied. Increased exposure expected (the effect varies widely). | Combination should be avoided. |
| | | |
| ***Potent and moderate* CYP3A4 inducers** | | |
| **Rifampicin** | AUC ↓63%<br>(range 0-80%)<br>$C_{max}$ ↓58%<br>(range 10-70%) | Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following start of the inducer. 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. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose used prior to initiation of the co-administration. |
| **Dexamethasone** | Not studied. Decreased exposure expected. | |
| **Carbamazepine, phenobarbital, phenytoin** | Not studied. Decreased exposure expected. | |
| **Efavirenz, nevirapine** | Not studied. Decreased exposure expected. | |
| **St John's Wort (*Hypericum perforatum*)** | Not studied. Large decrease in exposure expected. | Preparations containing St John's Wort should not be used during treatment with everolimus |

Agents whose plasma concentration may be altered by everolimus

Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded. An interaction study in healthy subjects demonstrated that co-administration of an oral dose of midazolam, a sensitive CYP3A substrate probe, with everolimus resulted in a 25% increase in midazolam $C_{max}$ and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$. The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Hence everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates is not expected (see section 4.4).

Co-administration of everolimus and depot octreotide increased octreotide $C_{min}$ with a geometric mean ratio (everolimus/placebo) of 1.47. A clinically significant effect on the efficacy response to everolimus in patients with advanced neuroendocrine tumours could not be established.

Co-administration of everolimus and exemestane increased exemestane $C_{min}$ and $C_{2h}$ by 45% and 64%, respectively. However, the corresponding oestradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (see section 4.4).

Vaccinations

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with Afinitor. The use of live vaccines should be avoided during treatment with Afinitor (see section 4.4). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

Radiation treatment

Potentiation of radiation treatment toxicity has been reported in patients receiving everolimus (see sections 4.4 and 4.8).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment. Male patients should not be prohibited from attempting to father children.

Pregnancy

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity (see section 5.3). The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether everolimus is excreted in human breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk (see section 5.3). Therefore, women taking everolimus should not breast-feed during treatment and for 2 weeks after the last dose.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown, however amenorrhoea (secondary amenorrhoea and other menstrual irregularities) and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed in female patients. Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Afinitor has minor or moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Afinitor.

## 4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 2,879 patients treated with Afinitor in eleven clinical studies, consisting of five randomised, double-blind, placebo controlled phase III studies and six open-label phase I and phase II studies, related to the approved indications.

The most common adverse reactions (incidence ≥1/10) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, oedema peripheral, hyperglycaemia, asthenia, pruritus, weight decreased, hypercholesterolaemia, epistaxis, cough and headache.

The most frequent Grade 3-4 adverse reactions (incidence ≥1/100 to <1/10) were stomatitis, anaemia, hyperglycaemia, infections, fatigue, diarrhoea, pneumonitis, asthenia, thrombocytopenia, neutropenia, dyspnoea, proteinuria, lymphopenia, haemorrhage, hypophosphataemia, rash, hypertension, pneumonia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased and diabetes mellitus. The grades follow CTCAE Version 3.0 and 4.03.

Tabulated list of adverse reactions

Table 3 presents the frequency category of adverse reactions reported in the pooled analysis considered for the safety pooling. Adverse reactions are listed according to MedDRA system organ class and frequency category. 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, adverse reactions are presented in order of decreasing seriousness.

**Table 3 Adverse reactions reported in clinical studies**

| | |
|---|---|
| **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, hypocalcaemia |
| **Psychiatric disorders** | |
| Common | Insomnia |
| **Nervous system disorders** | |
| Very common | Dysgeusia, headache |
| Uncommon | Ageusia |
| **Eye disorders** | |
| Common | Eyelid oedema |
| Uncommon | Conjunctivitis |
| **Cardiac disorders** | |
| Uncommon | Congestive cardiac failure |
| **Vascular disorders** | |
| Common | Haemorrhage [b], hypertension, lymphoedema[g] |
| Uncommon | Flushing, 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, mucosal inflammation, oral pain, dyspepsia, dysphagia |
| **Hepatobiliary disorders** | |
| Common | Aspartate aminotransferase increased, alanine aminotransferase increased |
| **Skin and subcutaneous tissue disorders** | |
| Very common | Rash, pruritus |
| Common | Dry skin, nail disorders, mild alopecia, acne, erythema, onychoclasis, palmar-plantar erythrodysaesthesia syndrome, skin exfoliation, skin lesion |
| Rare | Angioedema* |
| **Musculoskeletal and connective tissue disorders** | |
| Common | Arthralgia |
| **Renal and urinary disorders** | |
| Common | Proteinuria*, blood creatinine increased, renal failure* |
| Uncommon | Increased daytime urination, acute renal failure* |
| **Reproductive system and breast disorders** | |
| Common | Menstruation irregular [e] |
| Uncommon | Amenorrhoea [e]* |

| | |
|---|---|
| **General disorders and administration site conditions** | |
| Very common | Fatigue, asthenia, oedema peripheral |
| Common | Pyrexia |
| Uncommon | Non-cardiac chest pain, impaired wound healing |
| **Investigations** | |
| Very common | Weight decreased |
| **Injury, poisoning and procedural complications** | |
| Not known[f] | Radiation recall syndrome, potentiation of radiation reaction |

* See also subsection "Description of selected adverse reactions"

[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, PJP/PCP and hepatitis B (see also section 4.4)] and (rare) viral myocarditis

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

[c] Includes (very common) pneumonitis, (common) interstitial lung disease, lung infiltration and (rare) pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

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

[e] Frequency based upon number of women from 10 to 55 years of age in the pooled data

[f] Adverse reaction identified in the post-marketing setting

[g] Adverse reaction was determined based on post-marketing reports. Frequency was determined based on oncology studies safety pool.

Description of selected adverse reactions

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome) and proteinuria. Monitoring of renal function is recommended (see section 4.4).

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhoea (secondary amenorrhoea and other menstrual irregularities).

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of PJP/PCP, some with fatal outcome (see section 4.4).

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

Elderly patients

In the safety pooling, 37% of the Afinitor-treated patients were ≥65 years of age. The number of patients with an adverse reaction leading to discontinuation of the medicinal product was higher in patients ≥65 years of age (20% *vs.* 13%). The most common adverse reactions leading to discontinuation were pneumonitis (including interstitial lung disease), stomatitis, fatigue and dyspnoea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability. General supportive measures should be initiated in all cases of overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EG02

Mechanism of action

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. S6K1is thought to phosphorylate the activation function domain 1 of the oestrogen receptor, which is responsible for ligand-independent receptor activation. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

Clinical efficacy and safety

*Hormone receptor-positive advanced breast cancer*
BOLERO-2 (study CRAD001Y2301), a randomised, double-blind, multicentre phase III study of Afinitor + exemestane versus placebo + exemestane, was conducted in postmenopausal women with oestrogen receptor-positive, HER2/neu negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomisation was stratified by documented sensitivity to prior hormonal therapy and by the presence of visceral metastasis. Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥24 weeks) from at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

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

Secondary endpoints included overall survival (OS), objective response rate, clinical benefit rate, safety, change in quality of life (QoL) and time to ECOG PS (Eastern Cooperative Oncology Group performance status) deterioration.

A total of 724 patients were randomised in a 2:1 ratio to the combination everolimus (10 mg daily) + exemestane (25 mg daily) (n=485) or to the placebo + exemestane arm (25 mg daily) (n=239). At the time of the final OS analysis, the median duration of everolimus treatment was 24.0 weeks (range 1.0-199.1 weeks). The median duration of exemestane treatment was longer in the everolimus + exemestane group at 29.5 weeks (1.0-199.1) compared to 14.1 weeks (1.0-156.0) in the placebo + exemestane group.

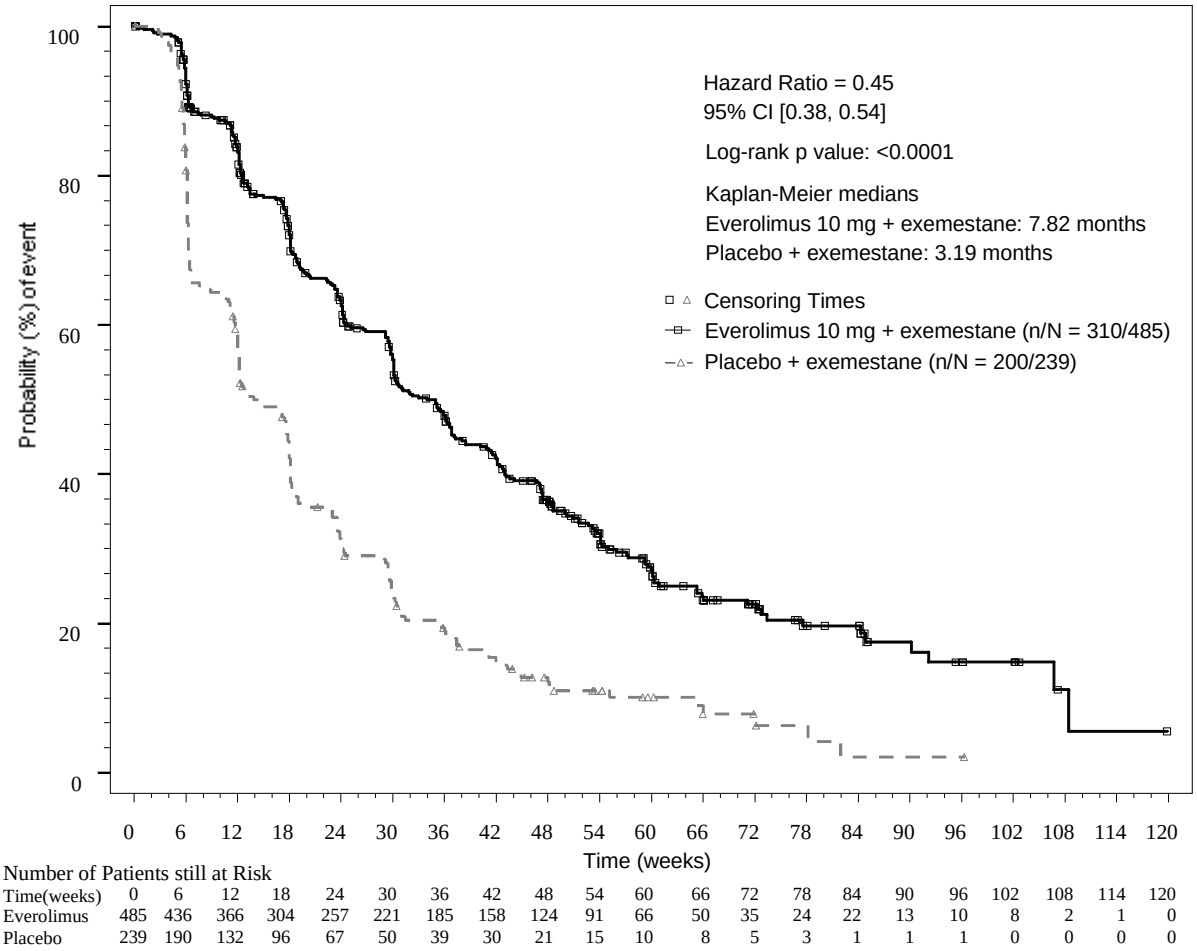
The efficacy results for the primary endpoint were obtained from the final PFS analysis (see Table 4 and Figure 1). Patients in the placebo + exemestane arm did not cross over to everolimus at the time of progression.

**Table 4 BOLERO-2 efficacy results**

| Analysis | Afinitor[a] n=485 | Placebo[a] n=239 | Hazard ratio | p value |
|---|---|---|---|---|
| **Median progression-free survival (months) (95% CI)** | | | | |
| Investigator radiological review | 7.8 (6.9 to 8.5) | 3.2 (2.8 to 4.1) | 0.45 (0.38 to 0.54) | <0.0001 |
| Independent radiological review | 11.0 (9.7 to 15.0) | 4.1 (2.9 to 5.6) | 0.38 (0.31 to 0.48) | <0.0001 |
| **Median overall survival (months) (95% CI)** | | | | |
| Median overall survival | 31.0 (28.0 – 34.6) | 26.6 (22.6 – 33.1) | 0.89 (0.73 – 1.10) | 0.1426 |
| **Best overall response (%) (95% CI)** | | | | |
| Objective response rate[b] | 12.6% (9.8 to 15.9) | 1.7% (0.5 to 4.2) | n/a[d] | <0.0001[e] |
| | | | | |
| Clinical benefit rate[c] | 51.3% (46.8 to 55.9) | 26.4% (20.9 to 32.4) | n/a[d] | <0.0001[e] |

[a] Plus exemestane
[b] Objective response rate = proportion of patients with complete or partial response
[c] Clinical benefit rate = proportion of patients with complete or partial response or stable disease ≥24 weeks
[d] Not applicable
[e] p value is obtained from the exact Cochran-Mantel-Haenszel test using a stratified version of the Cochran-Armitage permutation test.

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




Number of Patients still at Risk

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

The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analysed subgroups (age, sensitivity to prior hormonal therapy, number of organs involved, status of bone-only lesions at baseline and presence of visceral metastasis, and across major demographic and prognostic subgroups) a positive treatment effect was seen with everolimus + exemestane with an estimated hazard ratio (HR) versus placebo + exemestane ranging from 0.25 to 0.60.

No differences in the time to ≥5% deterioration in the global and functional domain scores of QLQ-C30 were observed in the two arms.

BOLERO-6 (Study CRAD001Y2201), a three-arm, randomised, open-label, phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with oestrogen receptor-positive, HER2/neu negative, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole.

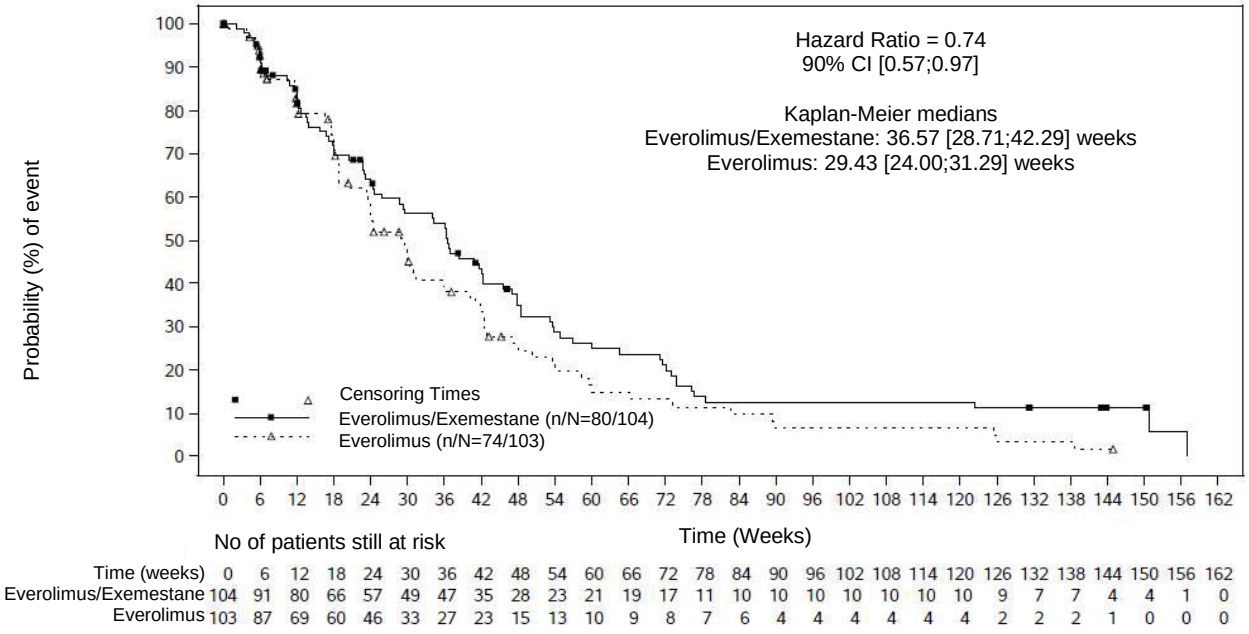
The primary objective of the study was to estimate the HR of PFS for everolimus + exemestane versus everolimus alone. The key secondary objective was to estimate the HR of PFS for everolimus + exemestane versus capecitabine.

Other secondary objectives included the evaluation of OS, objective response rate, clinical benefit rate, safety, time to ECOG performance deterioration, time to QoL deterioration, and treatment satisfaction (TSQM). No formal statistical comparisons were planned.

A total of 309 patients were randomised in a 1:1:1 ratio to the combination of everolimus (10 mg daily) + exemestane (25 mg daily) (n=104), everolimus alone (10 mg daily) (n=103), or capecitabine (1250 mg/m$^2$ dose twice daily for 2 weeks followed by one week rest, 3-week cycle) (n=102). At the time of data cut-off, the median duration of treatment was 27.5 weeks (range 2.0-165.7) in the everolimus + exemestane arm, 20 weeks (1.3-145.0) in the everolimus arm, and 26.7 weeks (1.4-177.1) in the capecitabine arm.

The result of the final PFS analysis with 154 PFS events observed based on local investigator assessment showed an estimated HR of 0.74 (90% CI: 0.57, 0.97) in favour of the everolimus + exemestane arm relative to everolimus arm. The median PFS was 8.4 months (90% CI: 6.6, 9.7) and 6.8 months (90% CI: 5.5, 7.2), respectively.

**Figure 2 BOLERO-6 Kaplan-Meier progression-free survival curves (investigator radiological review)**




For the key secondary endpoint PFS the estimated HR was 1.26 (90% CI: 0.96, 1.66) in favour of capecitabine over the everolimus + exemestane combination arm based on a total of 148 PFS events observed.

Results of the secondary endpoint OS were not consistent with the primary endpoint PFS, with a trend observed favouring the everolimus alone arm. The estimated HR was 1.27 (90% CI: 0.95, 1.70) for the comparison of OS in the everolimus alone arm relative to the everolimus + exemestane arm. The estimated HR for the comparison of OS in the everolimus + exemestane combination arm relative to capecitabine arm was 1.33 (90% CI: 0.99, 1.79).

*Advanced neuroendocrine tumours of pancreatic origin (pNET)*
RADIANT-3 (study CRAD001C2324), a phase III, multicentre, randomised, double-blind study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pNET, demonstrated a statistically significant clinical benefit of Afinitor over placebo by a 2.4-fold prolongation of median progression-free-survival (PFS) (11.04 months versus 4.6 months), (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001) (see Table 5 and Figure 3).

RADIANT-3 involved patients with well- and moderately-differentiated advanced pNET whose disease had progressed within the prior 12 months. Treatment with somatostatin analogues was allowed as part of BSC.

The primary endpoint for the study was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumors). Following documented radiological progression, patients could be unblinded by the investigator. Those randomised to placebo were then able to receive open-label Afinitor.

Secondary endpoints included safety, objective response rate, response duration and overall survival (OS).

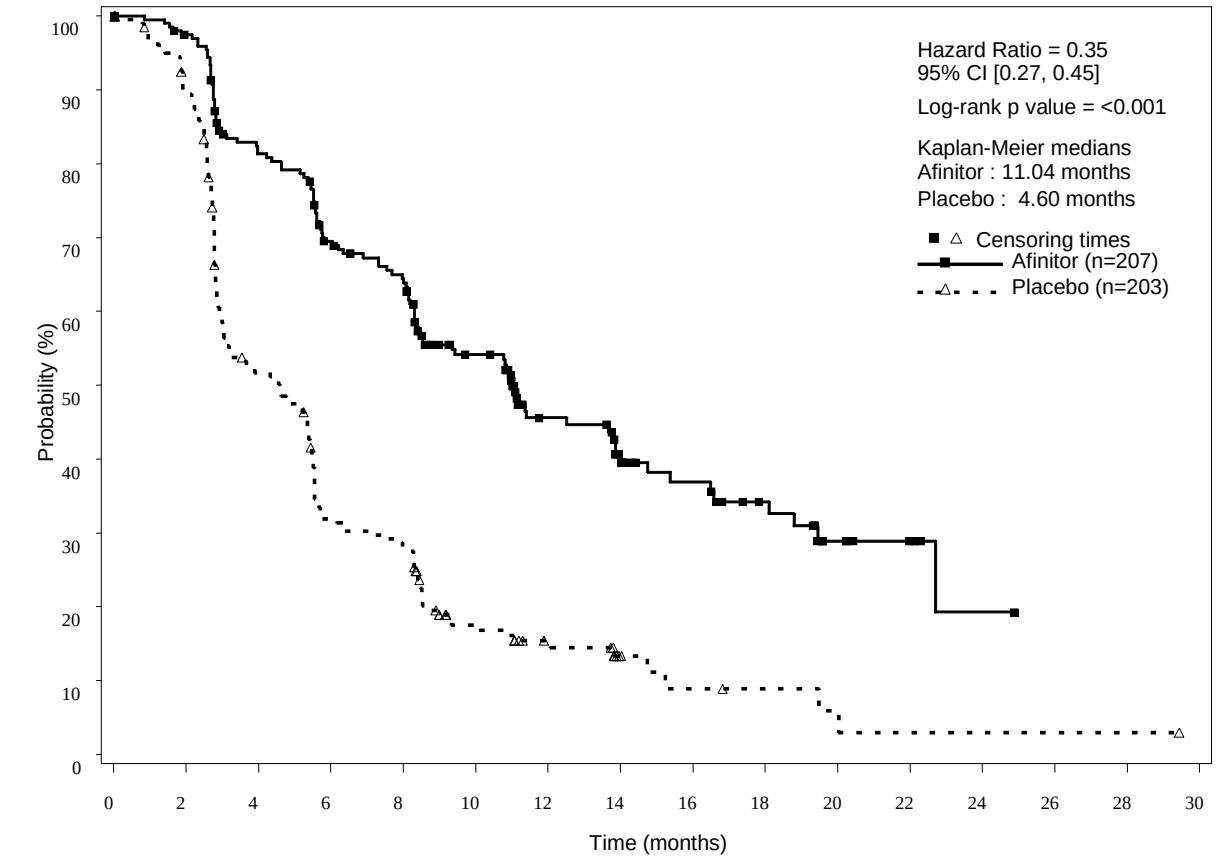
In total, 410 patients were randomised 1:1 to receive either Afinitor 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 78.5% Caucasian). Fifty-eight percent of the patients in both arms received prior systemic therapy. The median duration of blinded study treatment was 37.8 weeks (range 1.1-129.9 weeks) for patients receiving everolimus and 16.1 weeks (range 0.4-147.0 weeks) for those receiving placebo.

Following disease progression or after study unblinding, 172 of the 203 patients (84.7%) initially randomised to placebo crossed over to open-label Afinitor. The median duration of open-label treatment was 47.7 weeks among all patients; 67.1 weeks in the 53 patients randomised to everolimus who switched to open-label everolimus and 44.1 weeks in the 172 patients randomised to placebo who switched to open-label everolimus.

**Table 5 RADIANT-3 – efficacy results**

| **Population** | **Afinitor n=207** | **Placebo n=203** | **Hazard ratio (95% CI)** | **p-value** |
|---|---|---|---|---|
| **Median progression-free survival (months) (95% CI)** | | | | |
| Investigator radiological review | 11.04 (8.41, 13.86) | 4.60 (3.06, 5.39) | 0.35 (0.27, 0.45) | <0.0001 |
| Independent radiological review | 13.67 (11.17, 18.79) | 5.68 (5.39, 8.31) | 0.38 (0.28, 0.51) | <0.0001 |
| **Median overall survival (months) (95% CI)** | | | | |
| Median overall survival | 44.02 (35.61, 51.75) | 37.68 (29.14, 45.77) | 0.94 (0.73, 1.20) | 0.300 |

**Figure 3 RADIANT-3 – Kaplan-Meier progression-free survival curves (investigator radiological review)**




*Advanced neuroendocrine tumours of gastrointestinal or lung origin*

RADIANT-4 (study CRAD001T2302), a randomised, double-blind, multicentre, phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with advanced, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours 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 Tumors (RECIST), based on independent radiology assessment. Supportive PFS analysis was based on local investigator review. Secondary endpoints included overall survival (OS), overall response rate, disease control rate, safety, change in quality of life (FACT-G) and time to World Health Organisation performance status (WHO PS) deterioration.

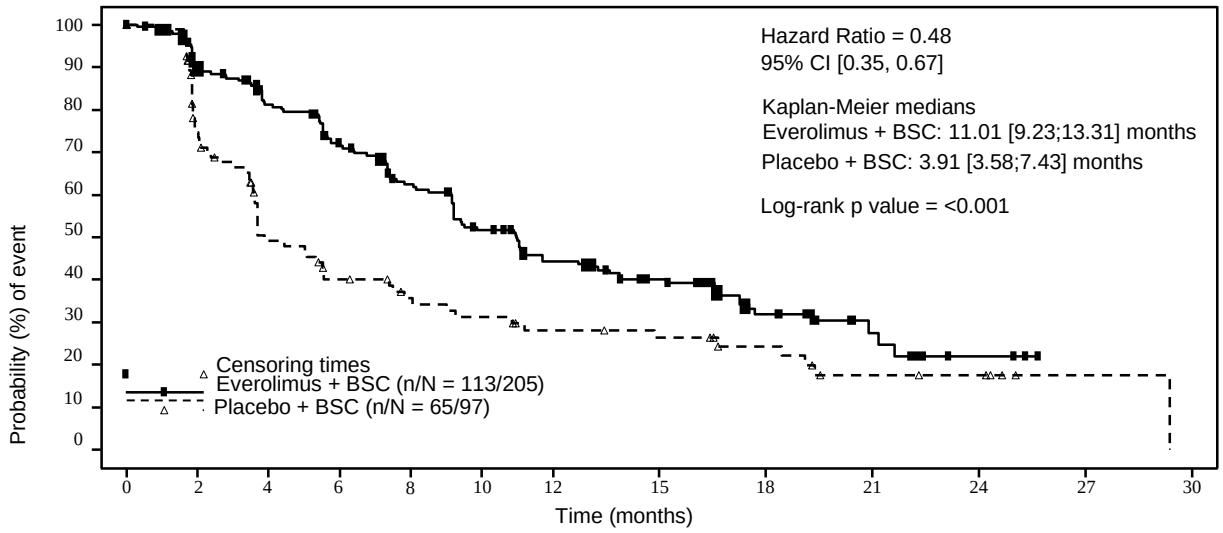
A total of 302 patients were randomised in a 2:1 ratio to receive either everolimus (10 mg daily) (n=205) or placebo (n=97). Demographics and disease characteristics were generally balanced (median age 63 years [range 22 to 86], 76% Caucasian, history of prior somatostatin analogue [SSA] use). The median duration of blinded treatment was 40.4 weeks for patients receiving Afinitor and 19.6 weeks for those receiving placebo. After primary PFS analysis, 6 patients from the placebo arm crossed over to open-label everolimus.

The efficacy results for the primary endpoint PFS (independent radiological review) were obtained from the final PFS analysis (see Table 6 and Figure 4). The efficacy results for PFS (investigator radiological review) were obtained from the final OS analysis (see Table 6).

**Table 6 RADIANT-4 – Progression-free survival results**

| Population | Afinitor n=205 | Placebo n=97 | Hazard ratio (95% CI) | p-value[a] |
|---|---|---|---|---|
| **Median progression-free survival (months) (95% CI)** | | | | |
| Independent radiological review | 11.01 (9.2, 13.3) | 3.91 (3.6, 7.4) | 0.48 (0.35, 0.67) | <0.001 |
| Investigator radiological review | 14.39 (11.24, 17.97) | 5.45 (3.71, 7.39) | 0.40 (0.29, 0.55) | <0.001 |
| [a] One-sided p-value from a stratified log-rank test | | | | |

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

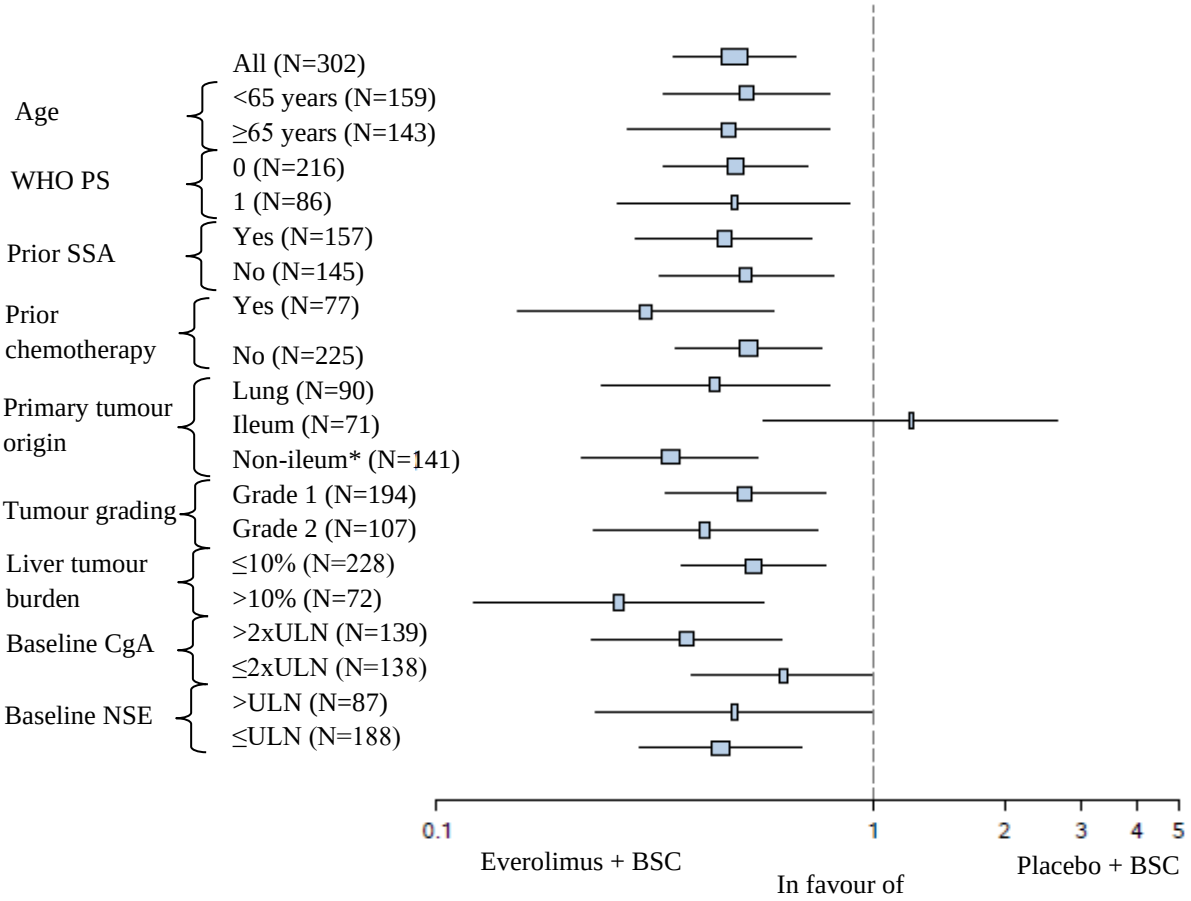



Number of Patients still at Risk

| Time(months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 15 | 18 | 21 | 24 | 27 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Everolimus | 205 | 168 | 145 | 124 | 101 | 81 | 65 | 52 | 26 | 10 | 3 | 0 | 0 |
| Placebo | 97 | 65 | 39 | 30 | 24 | 21 | 17 | 15 | 11 | 6 | 5 | 1 | 0 |

In supportive analyses, positive treatment effect has been observed in all subgroups with the exception of the subgroup of patients with ileum as primary site of tumour origin (Ileum: HR=1.22 [95% CI: 0.56 to 2.65]; Non-ileum: HR=0.34 [95% CI: 0.22 to 0.54]; Lung: HR=0.43 [95% CI: 0.24 to 0.79]) (see Figure 5).

**Figure 5 RADIANT-4 – Progression free survival results by pre-specified patient subgroup (independent radiological review)**




*Non-ileum: stomach, colon, rectum, appendix, caecum, duodenum, jejunum, carcinoma of unknown primary origin and other gastrointestinal origin
ULN: Upper limit of normal
CgA: Chromogranin A
NSE: Neuron specific enolase
Hazard ratio (95% CI) from stratified Cox model

The final overall survival (OS) analysis did not show a 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 1.22]).

No difference in the time to definitive deterioration of WHO PS (HR=1.02; [95% CI: 0.65, 1.61]) and time to definitive deterioration in quality of life (FACT-G total score HR=0.74; [95% CI: 0.50, 1.10]) was observed between the two arms.

*Advanced renal cell carcinoma*

RECORD-1 (study CRAD001C2240), a phase III, international, multicentre, randomised, double-blind study comparing everolimus 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed on or after treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-α was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- *vs.* intermediate- *vs.* poor-risk groups) and prior anticancer therapy (1 *vs.* 2 prior VEGFR-TKIs).

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

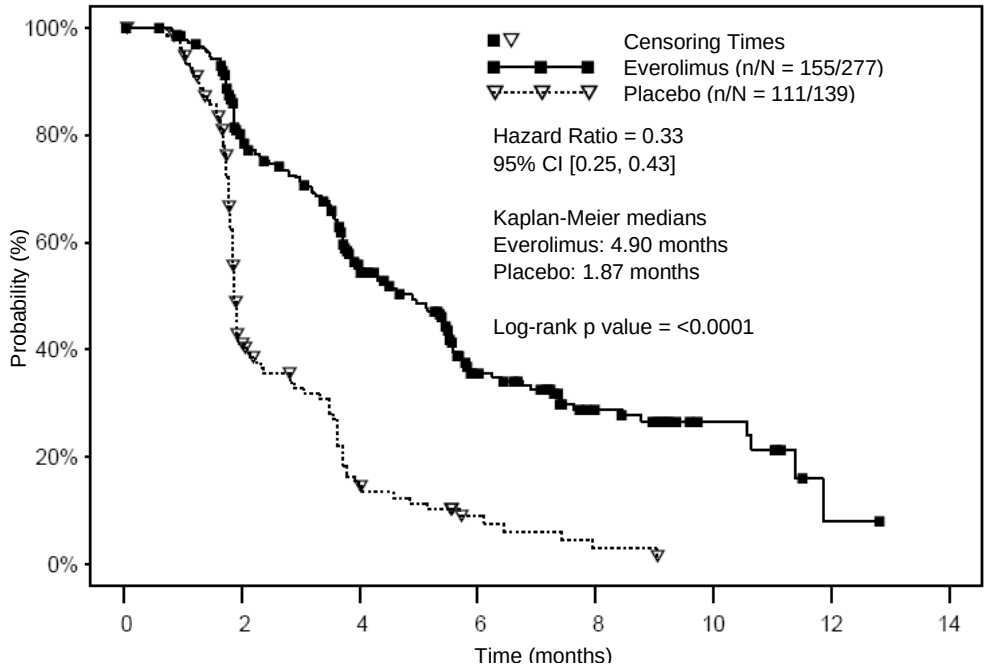
In total, 416 patients were randomised 2:1 to receive Afinitor (n=277) or placebo (n=139). Demographics were well balanced (pooled median age [61 years; range 27-85], 78% male, 88% Caucasian, number of prior VEGFR-TKI therapies [1-74%, 2-26%]). The median duration of blinded study treatment was 141 days (range 19-451 days) for patients receiving everolimus and 60 days (range 21-295 days) for those receiving placebo.

Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 7 and Figure 6).

**Table 7 RECORD-1 – Progression-free survival results**

| **Population** | **n** | **Afinitor n=277** | **Placebo n=139** | **Hazard ratio (95%CI)** | **p-value** |
|---|---|---|---|---|---|
| | | **Median progression-free survival (months) (95% CI)** | | | |
| **Primary analysis** | | | | | |
| All (blinded independent central review) | 416 | 4.9 (4.0-5.5) | 1.9 (1.8-1.9) | 0.33 (0.25-0.43) | <0.0001[a] |
| **Supportive/sensitivity analyses** | | | | | |
| All (local review by investigator) | 416 | 5.5 (4.6-5.8) | 1.9 (1.8-2.2) | 0.32 (0.25-0.41) | <0.0001[a] |
| *MSKCC prognostic score (blinded independent central review)* | | | | | |
| Favourable risk | 120 | 5.8 (4.0-7.4) | 1.9 (1.9-2.8) | 0.31 (0.19-0.50) | <0.0001 |
| Intermediate risk | 235 | 4.5 (3.8-5.5) | 1.8 (1.8-1.9) | 0.32 (0.22-0.44) | <0.0001 |
| Poor risk | 61 | 3.6 (1.9-4.6) | 1.8 (1.8-3.6) | 0.44 (0.22-0.85) | 0.007 |
| [a] Stratified log-rank test | | | | | |

**Figure 6 RECORD-1 – Kaplan-Meier progression-free survival curves (independent central review)**




No. of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 |
|---|---|---|---|---|---|---|---|---|
| Afinitor | 277 | 192 | 115 | 51 | 26 | 10 | 1 | 0 |
| Placebo | 139 | 47 | 15 | 6 | 2 | 0 | 0 | 0 |

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

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

No statistically significant treatment-related difference in overall survival was noted (hazard ratio 0.87; confidence interval: 0.65-1.17; p=0.177). Crossover to open-label Afinitor following disease progression for patients allocated to placebo confounded the detection of any treatment-related difference in overall survival.

*Other studies*

Stomatitis is the most commonly reported adverse reaction in patients treated with Afinitor (see sections 4.4 and 4.8). In a post-marketing single-arm study in postmenopausal women with advanced breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 ml alcohol-free oral solution was administered as a mouthwash (4 times daily for the initial 8 weeks of treatment) 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. The incidence of Grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than historically reported. The incidence of Grade 1 stomatitis was 18.8% (n=16/85) and no cases of 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 tuberous sclerosis complex (TSC) settings, with the exception of a slightly increased frequency of oral candidiasis which was reported in 2.2% (n=2/92) of patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Afinitor in all subsets of the paediatric population in neuroendocrine tumours of pancreatic origin, thoracic neuroendocrine tumours and in renal cell carcinoma (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

In patients with advanced solid tumours, peak everolimus concentrations ($C_{max}$) are reached at a median time of 1 hour after daily administration of 5 and 10 mg everolimus under fasting conditions or with a light fat-free snack. $C_{max}$ is dose-proportional between 5 and 10 mg. Everolimus is a substrate and moderate inhibitor of PgP.

*Food effect*
In healthy subjects, high fat meals reduced systemic exposure to everolimus 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%. Approximately 20% of the everolimus concentration in whole blood is confined to plasma 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. In patients with advanced solid tumours, $V_d$ was 191 l for the apparent central compartment and 517 l for the apparent peripheral compartment.

Biotransformation

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus 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, everolimus is considered to contribute the majority of the overall pharmacological activity.

Elimination

Mean oral clearance (CL/F) of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24.5 l/h. The mean elimination half-life of everolimus is approximately 30 hours.

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

Steady-state pharmacokinetics

After 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 daily dose. Steady-state was achieved within 2 weeks. $C_{max}$ is dose-proportional between 5 and 10 mg. $t_{max}$ 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.

Special populations

*Hepatic impairment*
The safety, tolerability and pharmacokinetics of everolimus were evaluated in two single oral dose studies of Afinitor tablets in 8 and 34 subjects with impaired hepatic function relative to subjects with normal hepatic function.

In the first study, the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh B) was twice that found in 8 subjects with normal hepatic function.

In the second study of 34 subjects with different impaired hepatic function compared to normal subjects, there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure (i.e. $AUC_{0\text{-}inf}$) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively.

Simulations of multiple dose pharmacokinetics support the dosing recommendations in subjects with hepatic impairment based on their Child-Pugh status.

Based on the results of the two studies, dose adjustment is recommended for patients with hepatic impairment (see sections 4.2 and 4.4).

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

*Elderly patients*
In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27-85 years) on oral clearance 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, CL/F is on average 20% higher in black transplant patients.

## 5.3 Preclinical safety data

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

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

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

In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% of the $AUC_{0-24h}$ in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss.

Everolimus crossed the placenta and was toxic to the foetus. In rats, everolimus caused embryo/foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Butylhydroxytoluene
Magnesium stearate
Lactose monohydrate
Hypromellose
Crospovidone type A
Lactose anhydrous

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 25°C.

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

### 6.5 Nature and contents of container

Aluminium/polyamide/aluminium/PVC blister containing 10 tablets.

Afinitor 2.5 mg tablets

Packs containing 30 or 90 tablets.

Afinitor 5 mg tablets

Packs containing 10, 30 or 90 tablets.

Afinitor 10 mg tablets

Packs containing 10, 30 or 90 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

Afinitor 2.5 mg tablets

EU/1/09/538/009
EU/1/09/538/010

Afinitor 5 mg tablets

EU/1/09/538/001
EU/1/09/538/003
EU/1/09/538/007

Afinitor 10 mg tablets

EU/1/09/538/004
EU/1/09/538/006
EU/1/09/538/008

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 August 2009
Date of latest renewal: 02 April 2019

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 2.5 mg tablets
everolimus

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg everolimus.

## 3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/09/538/009 | 30 tablets |
| EU/1/09/538/010 | 90 tablets |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Afinitor 2.5 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 2.5 mg tablets
everolimus

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 5 mg tablets
everolimus

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg everolimus.

## 3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
90 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/09/538/007 | 10 tablets |
| EU/1/09/538/001 | 30 tablets |
| EU/1/09/538/003 | 90 tablets |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Afinitor 5 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 5 mg tablets
everolimus

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 10 mg tablets
everolimus

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg everolimus.

## 3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
90 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/09/538/008 | 10 tablets |
| EU/1/09/538/004 | 30 tablets |
| EU/1/09/538/006 | 90 tablets |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Afinitor 10 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Afinitor 10 mg tablets
everolimus

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Afinitor 2.5 mg tablets**
**Afinitor 5 mg tablets**
**Afinitor 10 mg tablets**
everolimus

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Afinitor is and what it is used for

Afinitor is an anticancer medicine containing the active substance everolimus. Everolimus reduces the blood supply to the tumour and slows down the growth and spread of cancer cells.

Afinitor is used to treat adult patients with:
- hormone receptor-positive advanced breast cancer in postmenopausal women, in whom other treatments (so called “non-steroidal aromatase inhibitors”) no longer keep the disease under control. It is given together with a medicine called exemestane, a steroidal aromatase inhibitor, which is used for hormonal anticancer therapy.
- advanced tumours called neuroendocrine tumours that originate from the stomach, bowels, lung or pancreas. It is given if the tumours are inoperable and do not overproduce specific hormones or other related natural substances.
- advanced kidney cancer (advanced renal cell carcinoma), where other treatments (so-called “VEGF-targeted therapy”) have not helped stop your disease.

## 2. What you need to know before you take Afinitor

Afinitor will only be prescribed for you by a doctor with experience in cancer treatment. Follow all the doctor’s instructions carefully. They may differ from the general information contained in this leaflet. If you have any questions about Afinitor or why it has been prescribed for you, ask your doctor.

**Do not take Afinitor**
- **if you are allergic** to everolimus, to related substances such as sirolimus or temsirolimus, or to any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic, ask your doctor for advice.

**Warnings and precautions**
**Talk to your doctor before taking Afinitor:**

- if you have any problems with your liver or if you have ever had any disease which may have affected your liver. If this is the case, your doctor may need to prescribe a different dose of Afinitor.
- if you have diabetes (high level of sugar in your blood). Afinitor may increase blood sugar levels and worsen diabetes mellitus. This may result in the need for insulin and/or oral antidiabetic agent therapy. Tell your doctor if you experience any excessive thirst or increased frequency of urination.
- if you need to receive a vaccine while taking Afinitor.
- if you have high cholesterol. Afinitor may elevate cholesterol and/or other blood fats.
- if you have had recent major surgery, or if you still have an unhealed wound following surgery. Afinitor may increase the risk of problems with wound healing.
- if you have an infection. It may be necessary to treat your infection before starting Afinitor.
- if you have previously had hepatitis B, because this may be reactivated during treatment with Afinitor (see section 4 'Possible side effects').
- if you have received or are about to receive radiation therapy.

Afinitor may also:

- weaken your immune system. Therefore, you may be at risk of getting an infection while you are taking Afinitor. If you have fever or other signs of an infection, consult with your doctor. Some infections may be severe and may have fatal consequences.
- impact your kidney function. Therefore, your doctor will monitor your kidney function while you are taking Afinitor.
- cause shortness of breath, cough and fever.
- cause mouth ulcers and sores to develop. Your doctor might need to interrupt or discontinue your treatment with Afinitor. You might need treatment with a mouthwash, gel or other products. Some mouthwashes and gels can make ulcers worse, so do not try anything without checking with your doctor first. Your doctor might restart treatment with Afinitor at the same dose or at a lower dose.
- cause complications of radiation therapy. Severe complications of radiotherapy (such as shortness of breath, nausea, diarrhoea, skin rashes and soreness in mouth, gums and throat), including fatal cases, have been observed in some patients who were taking everolimus at the same time as radiation therapy or who were taking everolimus shortly after they had radiation therapy. In addition, so-called radiation recall syndrome (comprising skin redness or lung inflammation at the site of previous radiation therapy) has been reported in patients who had radiation therapy in the past.
  Tell your doctor if you are planning to have radiation therapy in the near future, or if you have had radiation therapy before.

**Tell your doctor** if you experience these symptoms.

You will have regular blood tests during treatment. These will check the amount of blood cells (white blood cells, red blood cells and platelets) in your body to see if Afinitor is having an unwanted effect on these cells. Blood tests will also be carried out to check your kidney function (level of creatinine) and liver function (level of transaminases) and your blood sugar and cholesterol levels. This is because these can also be affected by Afinitor.

**Children and adolescents**
Afinitor is not to be used in children or adolescents (age below 18 years).

**Other medicines and Afinitor**
Afinitor may affect the way some other medicines work. If you are taking other medicines at the same time as Afinitor, your doctor may need to change the dose of Afinitor or the other medicines.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following may increase the risk of side effects with Afinitor:
- ketoconazole, itraconazole, voriconazole, or fluconazole and other antifungals used to treat fungal infections.
- clarithromycin, telithromycin or erythromycin, antibiotics used to treat bacterial infections.
- ritonavir and other medicines used to treat HIV infection/AIDS.
- verapamil or diltiazem, used to treat heart conditions or high blood pressure.
- dronedarone, a medicine used to help regulate your heart beat.
- ciclosporin, a medicine used to stop the body from rejecting organ transplants.
- imatinib, used to inhibit the growth of abnormal cells.
- angiotensin-converting enzyme (ACE) inhibitors (such as ramipril) used to treat high blood pressure or other cardiovascular problems.
- nefazodone, used to treat depression.
- cannabidiol (uses amongst others include treatment of seizures).

The following may reduce the effectiveness of Afinitor:
- rifampicin, used to treat tuberculosis (TB).
- efavirenz or nevirapine, used to treat HIV infection/AIDS.
- St. John's wort (*Hypericum perforatum*), a herbal product used to treat depression and other conditions.
- dexamethasone, a corticosteroid used to treat a wide variety of conditions including inflammatory or immune problems.
- phenytoin, carbamazepine or phenobarbital and other anti-epileptics used to stop seizures or fits.

These medicines should be avoided during your treatment with Afinitor. If you are taking any of them, your doctor may switch you to a different medicine, or may change your dose of Afinitor.

**Afinitor with food and drink**
Avoid grapefruit and grapefruit juice while you are on Afinitor. It may increase the amount of Afinitor in the blood, possibly to a harmful level.

**Pregnancy, breast-feeding and fertility**

Pregnancy
Afinitor could harm your unborn baby and is not recommended during pregnancy. Tell your doctor if you are pregnant or think that you may be pregnant. Your doctor will discuss with you whether you should take this medicine during your pregnancy.

Women who could potentially become pregnant should use highly effective contraception during treatment and for up to 8 weeks after ending treatment. If, despite these measures, you think you may have become pregnant, ask your doctor for advice **before** taking any more Afinitor.

Breast-feeding
Afinitor could harm your breast-fed baby. You should not breast-feed during treatment and for 2 weeks after the last dose of Afinitor. Tell your doctor if you are breast-feeding.

Female fertility
Absence of menstrual periods (amenorrhoea) has been observed in some female patients receiving Afinitor.

Afinitor may have an impact on female fertility. Talk to your doctor if you wish to have children.

Male fertility
Afinitor may affect male fertility. Talk to your doctor if you wish to father a child.

**Driving and using machines**
If you feel unusually tired (fatigue is a very common side effect), take special care when driving or using machines.

**Afinitor contains lactose**
Afinitor contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Afinitor

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 10 mg, taken once a day. Your doctor will tell you how many tablets of Afinitor to take.

If you have liver problems, your doctor may start you on a lower dose of Afinitor (2.5, 5 or 7.5 mg per day).

If you experience certain side effects while you are taking Afinitor (see section 4), your doctor may lower your dose or stop treatment, either for a short time or permanently.

Take Afinitor once a day, at about the same time every day, consistently either with or without food.

Swallow the tablet(s) whole with a glass of water. Do not chew or crush the tablets.

**If you take more Afinitor than you should**
- If you have taken too much Afinitor, or if someone else accidentally takes your tablets, see a doctor or go to a hospital immediately. Urgent treatment may be necessary.
- Take the carton and this leaflet, so that the doctor knows what has been taken.

**If you forget to take Afinitor**
If you miss a dose, take your next dose as scheduled. Do not take a double dose to make up for the forgotten tablets.

**If you stop taking Afinitor**
Do not stop taking Afinitor unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Afinitor and seek medical help immediately if you experience any of the following signs of an allergic reaction:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

**Serious side effects of Afinitor include:**

**Very common** *(may affect more than 1 in 10 people)*
- Increased temperature, chills (signs of infection)
- Fever, coughing, difficulty breathing, wheezing (signs of inflammation of the lung, also known as pneumonitis)

**Common** *(may affect up to 1 in 10 people)*
- Excessive thirst, high urine output, increased appetite with weight loss, tiredness (signs of diabetes)
- Bleeding (haemorrhage), for example in the gut wall
- Severely decreased urine output (sign of kidney failure)

**Uncommon** *(may affect up to 1 in 100 people)*
- Fever, skin rash, joint pain and inflammation, as well as tiredness, loss of appetite, nausea, jaundice (yellowing of the skin), pain in the upper right abdomen, pale stools, dark urine (may be signs of hepatitis B reactivation)
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of heart failure)
- Swelling and/or pain in one of the legs, usually in the calf, redness or warm skin in the affected area (signs of blockade of a blood vessel (vein) in the legs caused by blood clotting)
- Sudden onset of shortness of breath, chest pain or coughing up blood (potential signs of pulmonary embolism, a condition that occurs when one or more arteries in your lungs become blocked)
- Severely decreased urine output, swelling in the legs, feeling confused, pain in the back (signs of sudden kidney failure)
- Rash, itching, hives, difficulty breathing or swallowing, dizziness (signs of serious allergic reaction, also known as hypersensitivity)

**Rare** (*may affect up to 1 in 1,000 people*)
- Shortness of breath or rapid breath (signs of acute respiratory distress syndrome)

**If you experience any of these side effects, tell your doctor immediately as this might have life-threatening consequences.**

**Other possible side effects of Afinitor include:**

**Very common** (*may affect more than 1 in 10 people)*
- High level of sugar in the blood (hyperglycaemia)
- Loss of appetite
- Disturbed taste (dysgeusia)
- Headache
- Nose bleeds (epistaxis)
- Cough
- Mouth ulcers
- Upset stomach including feeling sick (nausea) or diarrhoea
- Skin rash
- Itching (pruritus)
- Feeling weak or tired
- Tiredness, breathlessness, dizziness, pale skin, signs of low level of red blood cells (anaemia)
- Swelling of arms, hands, feet, ankles or other part of the body (signs of oedema)
- Weight loss
- High level of lipids (fats) in the blood (hypercholesterolaemia)

**Common** (*may affect up to 1 in 10 people)*

- Spontaneous bleeding or bruising (signs of low level of platelets, also known as thrombocytopenia)
- Breathlessness (dyspnoea)
- Thirst, low urine output, dark urine, dry flushed skin, irritability (signs of dehydration)
- Trouble sleeping (insomnia)
- Headache, dizziness (sign of high blood pressure, also known as hypertension)
- Swelling of part or all of your arm (including fingers) or leg (including toes), feeling of heaviness, restricted movement, discomfort (possible symptoms of lymphoedema)
- Fever, sore throat, mouth ulcers due to infections (signs of low level of white blood cells, leukopenia, lymphopenia and/or neutropenia)
- Fever
- Inflammation of the inner lining of the mouth, stomach, gut
- Dry mouth
- Heartburn (dyspepsia)
- Being sick (vomiting)
- Difficulty in swallowing (dysphagia)
- Abdominal pain
- Acne
- Rash and pain on the palms of your hands or soles of your feet (hand-foot syndrome)
- Reddening of the skin (erythema)
- Joint pain
- Pain in the mouth
- Menstruation disorders such as irregular periods
- High level of lipids (fats) in the blood (hyperlipidaemia, raised triglycerides)
- Low level of potassium in the blood (hypokalaemia)
- Low level of phosphate in the blood (hypophosphataemia)
- Low level of calcium in the blood (hypocalcaemia)
- Dry skin, skin exfoliation, skin lesions
- Nail disorders, breaking of your nails
- Mild loss of hair
- Abnormal results of liver blood tests (increased alanine and aspartate aminotransferase)
- Abnormal results of renal blood tests (increased creatinine)
- Swelling of the eyelid
- Protein in the urine

**Uncommon** (*may affect up to 1 in 100 people)*

- Weakness, spontaneous bleeding or bruising and frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of low level of blood cells, also known as pancytopenia)
- Loss of sense of taste (ageusia)
- Coughing up blood (haemoptysis)
- Menstruation disorders such as absence of periods (amenorrhoea)
- Passing urine more often during daytime
- Chest pain
- Abnormal wound healing
- Hot flushes
- Discharge from the eye with itching and redness, pink eye or red eye (conjunctivitis)

**Rare** *(may affect up to 1 in 1,000 people*)
- Tiredness, breathlessness, dizziness, pale skin (signs of low level of red blood cells, possibly due to a type of anaemia called pure red cell aplasia)
- Swelling of the face, around the eyes, mouth, and inside the mouth and/or throat, as well as the tongue and difficulty breathing or swallowing (also known as angioedema), may be signs of an allergic reaction

**Not known** *(frequency cannot be estimated from the available data)*
- Reaction at the site of previous radiation therapy, e.g. skin redness or lung inflammation (so-called radiation recall syndrome)
- Worsening of radiation treatment side effects

**If these side effects get severe please tell your doctor and/or pharmacist. Most of the side effects are mild to moderate and will generally disappear if your treatment is interrupted for a few days.**

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Afinitor

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and blister foil. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Store in the original package in order to protect from light and moisture.
- Open the blister just before taking the tablets.
- Do not use this medicine if any pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Afinitor contains**
- The active substance is everolimus.
  - Each tablet of Afinitor 2.5 mg contains 2.5 mg everolimus.
  - Each tablet of Afinitor 5 mg contains 5 mg everolimus.
  - Each tablet of Afinitor 10 mg contains 10 mg everolimus.
- The other ingredients are butylhydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone type A and lactose anhydrous.

**What Afinitor looks like and contents of the pack**
Afinitor 2.5 mg tablets are white to slightly yellowish, elongated tablets. They are engraved with "LCL" on one side and "NVR" on the other.
Afinitor 5 mg tablets are white to slightly yellowish, elongated tablets. They are engraved with "5" on one side and "NVR" on the other.
Afinitor 10 mg tablets are white to slightly yellowish, elongated tablets. They are engraved with "UHE" on one side and "NVR" on the other.

Afinitor 2.5 mg is available in blister packs containing 30 or 90 tablets.
Afinitor 5 mg and Afinitor 10 mg are available in blister packs containing 10, 30 or 90 tablets.
Not all pack sizes or strengths may be marketed in your country.

**Marketing Authorisation Holder**
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

**Manufacturer**
Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**България**
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

**Česká republika**
Novartis s.r.o.
Tel: +420 225 775 111

**Danmark**
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

**Deutschland**
Novartis Pharma GmbH
Tel: +49 911 273 0

**Eesti**
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

**Ελλάδα**
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

**España**
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

**Lietuva**
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

**Luxembourg/Luxemburg**
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

**Magyarország**
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

**Malta**
Novartis Pharma Services Inc.
Tel: +356 2122 2872

**Nederland**
Novartis Pharma B.V.
Tel: +31 88 04 52 555

**Norge**
Novartis Norge AS
Tlf: +47 23 05 20 00

**Österreich**
Novartis Pharma GmbH
Tel: +43 1 86 6570

**Polska**
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

**France**
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

**Hrvatska**
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

**Ireland**
Novartis Ireland Limited
Tel: +353 1 260 12 55

**Ísland**
Vistor hf.
Sími: +354 535 7000

**Italia**
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

**Κύπρος**
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

**Latvija**
SIA Novartis Baltics
Tel: +371 67 887 070

**Portugal**
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

**România**
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

**Slovenija**
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

**Slovenská republika**
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

**Suomi/Finland**
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

**Sverige**
Novartis Sverige AB
Tel: +46 8 732 32 00

**United Kingdom (Northern Ireland)**
Novartis Ireland Limited
Tel: +44 1276 698370

**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu