NOVARTIS

Regulatory Affairs

AFINITOR®

(everolimus)

Tablets: 2.5 mg, 5 mg and 10 mg
Dispersible Tablets: 2 mg, 3 mg and 5 mg

International Package Leaflet

(IPL with HR(+)BC+RCC+NET+TSC-AML+TSC-SEGA indications)

IPL Author:	Sree Lalitha Narayana
CDS Author(s):	Amrish Huddar
GLC approval:	18 May 2021
Effective date:	07 Jul 2021
Safety Label Change (SLC) Tracking Number:	NA
Document status:	Final
Number of pages:	49

Afinitor®

Protein kinase inhibitors

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Tablets

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

- **2.5 mg:** The tablets are engraved with "LCL" on one side and "NVR" on the other.
- **5 mg:** The tablets are engraved with "5" on one side and "NVR" on the other.
- **10 mg:** The tablets are engraved with "UHE" on one side and "NVR" on the other.

Dispersible Tablets

White to slightly yellowish, round, flat tablets with a bevelled edge and no score.

- **2 mg**: The tablets are engraved with "D2" on one side and "NVR" on the other.
- **3 mg:** The tablets are engraved with "D3" on one side and "NVR" on the other.
- **5 mg:** The tablets are engraved with "D5" on one side and "NVR" on the other.

Active substance

Tablets

- 2.5 mg: Each tablet contains 2.5 mg everolimus.
- 5 mg: Each tablet contains 5 mg everolimus.
- 10 mg: Each tablet contains 10 mg everolimus.

Dispersible Tablets

- 2 mg: Each dispersible tablet contains 2 mg everolimus.
- 3 mg: Each dispersible tablet contains 3 mg everolimus.
- 5 mg: Each dispersible tablet contains 5 mg everolimus.

Certain dosage strengths and dosage forms may not be available in all countries.

Excipients

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

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

Information might differ in some countries.

INDICATIONS

Afinitor Tablets are indicated for the treatment of:

- Postmenopausal women with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, after prior endocrine therapy.
- Patients with advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin
- Patients with advanced renal cell carcinoma
- Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery

Afinitor Tablets and Afinitor Dispersible Tablets are indicated for the treatment of:

- Patients with TSC who have subependymal giant cell astrocytoma (SEGA) not requiring immediate surgery.

DOSAGE REGIMEN AND ADMINISTRATION

Afinitor is available in two dosage forms, tablets (Afinitor Tablets) and dispersible tablets (Afinitor Dispersible Tablets).

Afinitor Tablets may be used in all oncology indications and in the TSC with SEGA and TSC with renal angiomyolipoma indications.

Afinitor Dispersible Tablets may be used for the treatment of patients with TSC who have SEGA in conjunction with therapeutic drug monitoring (see section Therapeutic drug monitoring and section CLINICAL PHARMACOLOGY).

Dosage regimen

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

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

General target population

Dosing in hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin, advanced renal cell carcinoma and TSC with renal angiomyolipoma

The recommended dose of Afinitor Tablets is 10 mg, to be taken once daily (see section METHOD OF ADMINISTRATION).

Dosing in TSC with SEGA:

Individualize dosing based on body surface area (BSA, in m^2) using the Dubois formula, where weight (W) is in kilograms and height (H) is in centimeters:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

Starting dose and target trough concentrations in TSC with SEGA

The recommended starting daily dose for Afinitor for the treatment of patients with TSC who have SEGA is 4.5 mg/m^2, rounded to the nearest strength of Afinitor Tablets or Afinitor Dispersible Tablets. Different strengths of Afinitor Tablets can be combined to attain the desired dose. Likewise, different strengths of Afinitor Dispersible Tablets can be combined to attain the desired dose. The two dosage forms should not be combined to achieve the desired dose. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL.

Dose monitoring

Therapeutic drug monitoring of everolimus blood concentrations is required for patients with TSC who have SEGA (see section Therapeutic drug monitoring). Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after commencing treatment or any change in dose.

Titration

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

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

For example, a patient's current dose based on BSA is 4 mg with a steady state concentration of 4 ng/mL. In order to achieve a target concentration above the lower C_{min} limit of 5 ng/mL, e.g. 8 ng/mL, the new everolimus dose would be 8 mg (an increase of 4 mg to the current daily dose). The trough concentration should then be assessed 1 to 2 weeks after this change in dose.

Long-term dose monitoring

For patients with TSC who have SEGA, evaluate SEGA volume approximately 3 months after commencing Afinitor therapy, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration, and tolerability (see section CLINICAL PHARMACOLOGY).

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

Dose Modifications

Adverse drug reactions:

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

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of Afinitor in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 1 Afinitor dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, clinical or diagnostic observations only; intervention not indicated	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated; limiting instrumental ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1. Re-initiate treatment at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self-care ADL[c]; oxygen indicated	Interrupt treatment until symptoms resolve to Grade ≤1, Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose.

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
		Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at a lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 (<LLN[e] - 75,000/mm^3; <LLN[e] - 75.0 x 10^9/L)	No dose adjustment required.
	Grade 2 (<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose.
	Grade 3 (<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9/L) **OR** Grade 4 (<25,000/mm^3; <25.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose.
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN[e] – 1,500/mm^3; <LLN[e] – 1.5 x 10^9/L) **OR**	No dose adjustment required.

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	Grade 2 (<1,500 – 1,000/mm^3; <1.5 – 1.0 x 10^9/L)	
	Grade 3 (<1,000 - 500/mm^3; <1.0 - 0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at the same dose.
	Grade 4 (<500/ mm^3; <0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at a lower dose.
Febrile neutropenia	Grade 3 ANC[f] <1,000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than one hour.	Temporary dose interruption until recovery to Grade ≤2 and no fever. Re-initiate treatment at a lower dose.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

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

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

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

[c] Activities of daily living (ADL)

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

[e] Lower limit of normal (LLN)

[f] Absolute Neutrophil Count (ANC)

Moderate CYP3A4/PgP inhibitors

Use caution when administering Afinitor in combination with moderate CYP3A4/PgP inhibitors. If patients require co-administration of a moderate CYP3A4/PgP inhibitor, reduce the Afinitor dose by approximately 50%. Further dose reduction may be required to manage ADRs. For dose reductions below the lowest available strength, alternate day dosing should be considered (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin, advanced renal cell carcinoma, and TSC with renal angiomyolipoma**: If the moderate CYP3A4/PgP inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) before the Afinitor dose is increased. The Afinitor dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).
- TSC with SEGA: Everolimus trough concentrations should be assessed approximately 1 to 2 weeks after the addition of a moderate CYP3A4/PgP inhibitor. If the inhibitor is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the inhibitor and the everolimus trough concentration should be re-assessed approximately

2 weeks later (see sections Therapeutic drug monitoring, WARNINGS AND PRECAUTIONS and INTERACTIONS).

Strong CYP3A4 inducers

Avoid the use of concomitant strong CYP3A4 inducers.

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin, advanced renal cell carcinoma, and TSC with renal angiomyolipoma**: If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of Afinitor (based on pharmacokinetic data), using increments of 5 mg or less. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).
- **TSC with SEGA:**
  - Patients with SEGA receiving concomitant strong CYP3A4 inducers (e.g., the enzyme inducing antiepileptic drugs carbamazepine, phenobarbital, and phenytoin) at the start of treatment may require an increased Afinitor dose to attain trough concentrations of 3 to 15 ng/mL. Double the daily dose of Afinitor and assess tolerability. Assess the everolimus trough level approximately two weeks after doubling the dose. Further adjust the dose by increments of 1 to 4 mg as necessary to maintain the target trough concentrations.
  - For SEGA patients not receiving concomitant strong inducers at the start of everolimus treatment, the addition of a strong inducer may require an increased Afinitor dose. Double the daily dose of Afinitor and assess tolerability. Assess the everolimus trough level approximately two weeks after doubling the dose. Further adjust the dose if necessary by increments of 1 to 4 mg as necessary to maintain the target trough concentration.
  - The addition of another concomitant strong CYP3A4 inducer may not require additional dose adjustment. Assess the everolimus trough level approximately two weeks after initiating the additional inducer. Adjust the dose in 1 to 4 mg increments as necessary to maintain the target trough concentration.
  - Discontinuation of one of multiple strong CYP3A4 inducers may not require additional dose adjustment. Assess the everolimus trough level approximately two weeks after discontinuation of one of multiple strong CYP3A4 inducers. If all strong inducers are discontinued consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction) before returning to the Afinitor dose used prior to initiation of the strong CYP3A4 inducers. Assess the everolimus trough concentration approximately two weeks later (see sections Therapeutic drug monitoring, WARNINGS AND PRECAUTIONS and INTERACTIONS).

Special populations

Pediatric patients (below 18 years)

- Afinitor is not recommended for use in pediatric cancer patients.
- Afinitor is not recommended for use in pediatric patients with TSC who have renal angiomyolipoma.
- Afinitor has not been studied in pediatric patients <1 year of age with TSC who have SEGA.
- Dosing recommendations for pediatric patients with TSC who have SEGA are consistent with those for the corresponding adult population with the exception of those patients with hepatic impairment.
- Afinitor is not recommended for patients <18 years of age with hepatic impairment and TSC with SEGA.

Geriatric patients (65 years of age or older)

No dosage adjustment is required (see section CLINICAL PHARMACOLOGY).

Renal impairment

No dosage adjustment is required (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

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

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

TSC with SEGA:

Patients ≥18 years of age

- Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B) – 50% of the dose calculated based on BSA (rounded to the nearest strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended. If the desired benefit outweighs the risk, 25% of the dose calculated based on BSA (rounded to the nearest strength) must not be exceeded.

Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after commencing treatment or after any change in hepatic (Child-Pugh) status. For patients with SEGA, dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL (see section Therapeutic drug monitoring). Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment (see section CLINICAL PHARMACOLOGY).

Patients <18 years of age

- Afinitor is not recommended for patients <18 years of age with TSC with SEGA and hepatic impairment.

Therapeutic drug monitoring

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA using a validated bioanalytical LC/MS method. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Trough concentrations should be assessed approximately 1 to 2 weeks after the initial dose, after any change in dosage form, after an initiation or change in co-administration of CYP3A4/PgP inhibitors (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS), or after any change in hepatic (Child-Pugh) status (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY). Trough concentrations should be assessed approximately 2 weeks after initiation or change in co-administration of CYP3A4/PgP inducers (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS). Dosing should be titrated with the objective of attaining everolimus trough concentrations of 3 to 15 ng/mL, for patients with TSC who have SEGA, subject to tolerability (see section CLINICAL PHARMACOLOGY). The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

Method of administration

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

Afinitor Tablets

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

For patients with TSC who have SEGA and are unable to swallow tablets whole, Afinitor Tablet(s) can be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered (see section CLINICAL PHARMACOLOGY).

Afinitor Dispersible Tablets

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

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

A complete and illustrated set of instructions for the dispersible tablet is provided in section INSTRUCTIONS FOR USE AND HANDLING.

Using an oral syringe:

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

Using a small drinking glass:

- Place the prescribed dose of Afinitor Dispersible Tablets into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg of Afinitor Dispersible Tablets per glass. If higher doses are required, prepare an additional glass. Do not break or crush tablets.
- Allow 3 minutes for suspension to occur.
- Stir the contents gently with a spoon, immediately prior to drinking.

After administration of the prepared suspension, add 25 mL of water and stir with the same spoon to re-suspend remaining particles. Administer the entire contents of the glass

Switching dosage forms:

The two dosage forms (Afinitor Tablets and Afinitor Dispersible Tablets) are not interchangeable. Do not combine the two dosage forms to achieve the desired dose. Consistently use the same dosage form as appropriate for the indication being treated.

When switching dosage forms, the dose should be adjusted to the closest milligram strength of the new dosage form and the everolimus trough concentration should be assessed approximately 1 to 2 weeks later (see section Therapeutic drug monitoring).

Missed dose

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

CONTRAINDICATIONS

Afinitor is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients (see section WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see section ADVERSE DRUG REACTIONS). Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jirovecii pneumonia (PJP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see sub-section Infections).

Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration (see section DOSAGE REGIMEN AND ADMINISTRATION, Table 1).

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt Afinitor until resolution to less than or equal to grade 1. Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances If toxicity recurs at grade 3, consider discontinuation of Afinitor. For cases of grade 4 non-infectious pneumonitis, Afinitor therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered.

The development of pneumonitis has also been reported at a reduced dose (see section DOSAGE REGIMEN AND ADMINISTRATION, Table 1).

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section ADVERSE DRUG REACTIONS). Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jirovecii pneumonia (PJP) and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to sepsis [including septic shock], respiratory or hepatic failure) and occasionally have had a fatal outcome in adult and pediatric patients (see section ADVERSE DRUG REACTIONS).

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

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

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

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, 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 CONTRAINDICATIONS).

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

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

Stomatitis

Stomatitis, including mouth ulceration and oral mucositis, is the most commonly reported adverse drug reaction in patients treated with Afinitor (see section ADVERSE DRUG REACTIONS). Stomatitis mostly occurs within the first 8 weeks of treatment. If stomatitis occurs, topical treatments are recommended, but alcohol-, hydrogen peroxide, iodine-, or thyme-containing products should be avoided as they may exacerbate the condition (see section DOSAGE REGIMEN AND ADMINISTRATION, Table 1). Antifungal agents should not be used unless fungal infection has been diagnosed (see section INTERACTIONS).

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

Renal failure events

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

Laboratory tests and monitoring

Renal function

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

Blood glucose

Hyperglycemia has been reported in patients taking Afinitor (see section ADVERSE DRUG REACTIONS). 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 drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on Afinitor.

Blood lipids

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking Afinitor. Monitoring of blood cholesterol and triglycerides prior to the start of Afinitor therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hematological parameters

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

Interactions

Co-administration with strong CYP3A4/ P-glycoprotein (PgP) inhibitors should be avoided (see section INTERACTIONS).

Use caution when administered in combination with moderate CYP3A4/PgP inhibitors. If Afinitor must be co-administered with a moderate CYP3A4/PgP inhibitor, the patient should be carefully monitored for undesirable effects and the Afinitor dose reduced if necessary (see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

Co-administration with strong CYP3A4/PgP inducers should be avoided (see section INTERACTIONS). If Afinitor must be co-administered with a strong CYP3A4/PgP inducer, the patient should be carefully monitored for clinical response. Consider a dose increase of Afinitor when co-administered with strong CYP3A4/PgP inducers if alternative treatment is not possible (see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

Exercise caution 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, the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section INTERACTIONS).

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 CLINICAL PHARMACOLOGY).

Afinitor is not recommended in patients ≥18 years of age with severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Afinitor is not recommended for use in patients < 18 years of age with TSC who have SEGA and concomitant hepatic impairment (Child-Pugh A, B or C) (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor (see section INTERACTIONS). For pediatric patients with TSC who have SEGA and do not require immediate treatment, complete the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines.

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

Severe radiation reactions (including radiation esophagitis, radiation pneumonitis and radiation skin injury) have been reported when everolimus was used during, or shortly after radiation

therapy. Caution should therefore be exercised for patients using everolimus in close temporal relationship with radiation therapy.

Additionally, radiation recall syndrome has been reported in patients on everolimus who have received prior radiotherapy.

ADVERSE DRUG REACTIONS

Oncology - Summary of the safety profile

Adverse drug reaction (ADR, suspected to be related to treatment by the investigator) information is based on pooled safety data in patients receiving Afinitor (N=2672) in clinical studies including randomized, double-blind, placebo- or active comparator-controlled phase III and phase-II studies related to the approved indications in oncology:

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

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

Tabulated summary of adverse drug reactions from clinical trials in oncology

Table 2 presents the frequency category of ADRs reported in the pooled safety analysis

ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing frequency. In addition, the corresponding frequency category using the following convention (CIOMS III) 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).

Table 2	**Adverse drug reactions from oncology trials**
Infections and infestations	
Very common	Infections[a]
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia
Uncommon	Pancytopenia
Rare	Pure red cell aplasia

Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage[b], hypertension, lymphoedema
Uncommon	Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis[c], epistaxis, cough
Common	Dyspnoea
Uncommon	Haemoptysis, pulmonary embolism,
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis[d], diarrhoea, nausea
Common	Vomiting, dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, acne, erythema, hand-foot syndrome[e]
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria, renal failure
Uncommon	Increased daytime urination, acute renal failure
Reproductive system and breast disorders	
Common	Menstruation irregular[f]
Uncommon	Amenorrhoea[f]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, oedema peripheral

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

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

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

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

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

[e] reported as palmar-plantar erythrodysaesthesia syndrome

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

Clinically relevant laboratory abnormalities

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

- Haematology: haemoglobin decreased, lymphocytes decreased, white blood cells decreased, platelet count decreased, and neutrophils decreased (or collectively as pancytopenia).
- Clinical chemistry: glucose (fasting) increased, cholesterol increased, triglycerides increased, AST increased, phosphate decreased, ALT increased, creatinine increased, potassium decreased and albumin decreased.

Most of the observed abnormalities (≥1/100) were mild (grade 1) or moderate (grade 2).

Grade 3/4 haematology and chemistry abnormalities include:

- Haematology: lymphocytes decreased, haemoglobin decreased, (very common); neutrophils decreased, platelet count decreased, white blood cells decreased (all common).
- Clinical chemistry: glucose (fasting) increased (very common); phosphate decreased, potassium decreased, AST increased, ALT increased, creatinine increased cholesterol (total) increased, triglycerides increased, albumin decreased (all common).

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

Adverse drug reaction (ADR) information is based on pooled data from patients with TSC receiving Afinitor (N=612, including 409 patients <18 years of age) in three randomized, double-blind, placebo-controlled, phase III studies including blinded and open label treatment periods, and one non-randomized, open-label, single-arm phase II study which serve as the basis for the listed indications (see Table 3 and section INDICATIONS):

Table 3 Afinitor TSC studies in the pooled safety data

Study name Indication	CRAD001C2485[a] TSC-SEGA	EXIST-1 (M2301) TSC-SEGA	EXIST-2 (M2302) TSC-renal angiomyolipoma	EXIST-3 (M2304) TSC-Seizures
Total number of patients receiving everolimus	28	111[b]	112[b]	361[c]
Median duration of exposure, months (range)	67.8 (4.7 to 83.2)	47.1(1.9 to 58.3)	46.9 (0.5 to 63.9)	30.4 (0.5 to 48.8)
Exposure in Patient-Years	146	391	391	833

[a] Open label single arm trial, no comparator or control arm

[b] Total number of patients receiving everolimus during the double blind and open label extension phases including patients from the placebo arm who crossed over to everolimus treatment

[c] Total number of patients receiving everolimus during the core, extension and post-extension phases, including patients from placebo arm who crossed over to everolimus treatment.

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

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

Tabulated summary of adverse drug reactions from clinical trials in TSC

Table 4 shows the incidence of ADRs based on pooled data in patients receiving everolimus in the TSC studies (including both the double-blind and open-label study and extension periods) covering a median duration of exposure of 36.8 months (with approximately 47 months in the TSC-SEGA and TSC-renal angiomyolipoma studies) . ADRs are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

Table 4 Adverse drug reactions from clinical trials in TSC

Infections and infestations	
Very common	Nasopharyngitis, upper respiratory tract infection, pneumonia, urinary tract infection sinusitis, pharyngitis
Common	Otitis media, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis
Uncommon	Herpes zoster, sepsis, bronchitis viral
Blood and lymphatic system disorders	

Common	Anaemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypercholesterolaemia
Common	Hypertriglyceridaemia, hyperlipidaemia, hypophosphataemia, hyperglycaemia
Psychiatric disorders	
Common	Insomnia, aggression, Irritability
Nervous system disorders	
Very common	Headache
Uncommon	Dysgeusia
Vascular disorders	
Very common	Hypertension,
Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Epistaxis, pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis[a], diarrhoea, vomiting
Common	Constipation, nausea, abdominal pain, flatulence, oral pain, gastritis
Skin and subcutaneous tissue disorders	
Very common	Rash[b] , acne
Common	Dry skin, dermatitis acneiform
Uncommon	Angioedema
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very common	Amenorrhoea[c], menstruation irregular[c]
Common	Menorrhagia, ovarian cyst, vaginal haemorrhage
Uncommon	Menstruation delayed[c]
General disorders and administration site conditions	
Very common	Pyrexia, fatigue
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased
Uncommon	Blood follicle stimulating hormone increased

[a] Includes very common: stomatitis, mouth ulceration, aphthous ulcer; common: tongue ulceration, lip ulceration; uncommon: gingival pain, glossitis.

[b] Includes very common: rash; common: rash erythematous; erythema; uncommon: rash generalized, rash maculo-papular,rash macular.

[c] frequency is based upon number of women 10 to 55 yrs of age while on treatment in the safety pool

Clinically relevant laboratory abnormalities

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

- Haematology: partial thromboplastin time increased, neutrophils decreased, haemoglobin decreased, white blood cells decreased, platelet count decreased, and lymphocytes decreased.
- Clinical chemistry: cholesterol increased, triglycerides increased, AST increased, ALT increased, phosphate decreased, alkaline phosphatase increased and glucose (fasting) increased.

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

- Haematology: neutrophils decreased, partial thromboplastin time increased, haemoglobin decreased, (common); lymphocytes decreased, platelet count decreased, and white blood cells decreased (uncommon).
- Clinical chemistry: phosphate decreased, triglycerides increased, alkaline phosphatase increased, ALT increased, AST increased, cholesterol increased (common); and glucose (fasting) increased (uncommon).

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

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

Table 5 Adverse drug reactions from spontaneous reports and literature in Oncology and TSC (frequency not known)

Injury, poisoning and procedural complications
Radiation recall syndrome

Description of selected adverse drug reactions

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression (see section WARNINGS AND PRECAUTIONS).

In clinical trials 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 WARNINGS AND PRECAUTIONS).

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhea (including secondary amenorrhea).

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with pneumocystis jirovecii pneumonia (PJP), some with fatal outcome (see section WARNINGS AND PRECAUTIONS).

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

In a post-marketing single arm study in postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 mL alcohol-free oral solution (10 mL swished in the mouth for 2 minutes and then spat out, to be repeated 4 times daily for 8 weeks) was administered as a mouthwash to patients at the time of initiating treatment with Afinitor (10 mg/day) plus exemestane (25 mg/day) to reduce the incidence and severity of stomatitis. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone oral solution. The incidence of grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than historically reported at 27.4% (n=132/482) in the phase III study in this patient population (BOLERO-2). The incidence of grade 1 stomatitis was 18.8% (n=16/85) and no grade 3 or 4 stomatitis were reported. The overall safety profile in this study was consistent with that established for everolimus in the oncology and TSC settings, with the exception of oral candidiasis which was reported in 2.2% (n=2/92) of patients in this study compared to 0.2% (n=1/482) of patients in BOLERO-2.

Special populations

Pediatric patients (below 18 years)

Pediatric use of Afinitor Tablets and Afinitor Dispersible Tablets is recommended for patients with TSC who have SEGA and do not require immediate surgery. The safety and effectiveness of Afinitor Tablets and Afinitor Dispersible Tablets have not been established in pediatric patients with renal angiomyolipoma with TSC or in pediatric cancer patients.

The safety of Afinitor in pediatric patients with TSC who have SEGA was demonstrated in two clinical trials.

The overall type, frequency and severity of ADRs across the age groups evaluated were similar, with the exception of infections, which were reported at a higher frequency and severity in patients below the age of 6 years. A total of 49 out of 137 patients (36%) <6 years had Grade 3/4 infections, compared to 53 out of 272 patients (19%) 6 to <18 years and 27 out of 203 patients (13%) ≥18 years. Two fatal cases due to infection were reported in 409 patients <18 years receiving everolimus.

Clinical trial results did not show an impact of Afinitor on growth and pubertal development.

A trend toward lower C_{min} normalized to dose (as mg/m^2) was observed in younger patients with TSC who have SEGA. Median C_{min} normalized to mg/m^2 was lower for the younger age groups, indicating that everolimus clearance (normalized to body surface area) was higher in younger patients (see section CLINICAL PHARMACOLOGY).

Geriatric patients (65 years of age or older)

In the pooled oncology safety database, 37% of the Afinitor-treated patients were ≥65 years of age.

The number of oncology patients with an ADR leading to discontinuation of Afinitor was higher in patients ≥65 years of age (20% vs. 13%). The most common ADRs (≥1/100) leading to discontinuation were pneumonitis (including interstitial lung disease), stomatitis, fatigue and dyspnea.

INTERACTIONS

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

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

Agents that may increase everolimus blood concentrations

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

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

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

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

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

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

- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.0- and 4.4-fold, respectively).

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

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

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

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

Agents that may decrease everolimus blood concentrations

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

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

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

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

Agents whose plasma concentration may be altered by everolimus

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

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

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$, whereas the metabolic $AUC_{(0\text{-}inf)}$ ratio (1-hydroxy-

midazolam/midazolam) and the terminal $t_{1/2}$ of midazolam were not affected. This suggests that increased exposure to midazolam is due to effects of everolimus in the gastrointestinal system when both drugs are taken at the same time. Therefore, everolimus may affect the bioavailability of orally co-administered drugs which are CYP3A4 substrates. Everolimus is unlikely to affect the exposure of other CYP3A4 substrate drugs which are administered by non-oral routes such as intravenous, subcutaneous, and transdermal administration. (see section WARNINGS AND PRECAUTIONS).

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

Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47 (90% CI: 1.32 to 1.64) which was unlikely to have clinically significant effects on the efficacy response to everolimus in patients with advanced neuroendocrine tumors.

Co-administration of everolimus and exemestane increased exemestane Cmin and C2h by 45% and 71%, respectively. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

Vaccinations

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There are no adequate data from the use of Afinitor in pregnant women. The potential risk for humans is unknown. Studies in animals have shown reproductive toxicity effects including

embryo-toxicity and feto-toxicity. Afinitor should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

Animal Data

Oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increased incidence of pre-implantation loss. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/feto-toxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced fetal 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 via an increase in late resorptions that occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose in adults or the median dose administered to SEGA patients, and 1.3 times the median dose for patients with TSC and refractory seizures, on a body surface area basis. In rats, there was no evidence of adverse effects by treating males with everolimus on embryo-fetal parameters.

Human data

There have been reports of exposure to everolimus during pregnancy, some due to exposure via the mother and some via the father (pregnancy in a female partner of a male patient while under treatment with everolimus). There were no reports of congenital abnormalities. In some cases the pregnancies progressed uneventfully with delivery of healthy, normal babies.

Lactation

Risk Summary

It is not known whether everolimus is transferred in human breast milk. There are no reported cases of exposure to everolimus during breast-feeding in humans. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum.

Women taking Afinitor should therefore not breast-feed during treatment and for 2 weeks after the last dose.

Females and males of reproductive potential

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing Afinitor to be harmful to the developing fetus. Sexually-active females of reproductive potential should use effective contraception (one that results in an annual pregnancy rate <1% when used correctly) while receiving Afinitor, and for up to 8 weeks after ending treatment. Male patients taking Afinitor should not be prohibited from attempting to father children (see section NON-CLINICAL SAFETY DATA).

Infertility

Females and Males

Animal data

In animal reproductive studies, female fertility was not affected. However, pre-implantation losses were observed. In male rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure (52 ng.hr/mL and 414 ng.hr/mL respectively compared to 560 ng.hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility. There was evidence of reversibility.

Human data

Both male and female fertility may be compromised by treatment with everolimus (see section NON-CLINICAL SAFETY DATA). Menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance have been observed in female patients receiving everolimus. Blood levels of FSH and LH increased, blood levels of testosterone decreased, and azoospermia have been observed in male patients receiving everolimus.

OVERDOSAGE

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

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

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Everolimus is an inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). It exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signaling capacity. mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signaling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream on the PI3K/AKT pathway, which is dysregulated in the majority of human cancers as well as genetic diseases such as TSC.

mTORC1 signaling is effected through modulation of the phosphorylation of downstream effectors, the best characterized of which are the translational regulators S6 ribosomal protein

kinase (S6K1) and eukaryotic initiation factor 4E-binding protein (4E-BP1). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumor growth and expression of hypoxia-inducible factors (e.g. HIF-1 transcription factors); the latter resulting in reduced expression of factors involved in the potentiation of tumor angiogenic processes (e.g. the vascular endothelial growth factor VEGF) in multiple tumors such as RCC and angiomyolipoma). Two primary regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (TSC1, TSC2). Loss or inactivation of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signaling cascade, including activation of the S6K1. A substrate of mTOR complex 1 (mTORC1), S6K1 phosphorylates the estrogen receptor, which is responsible for ligand-independent receptor activation.

Everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells. Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumor cell proliferation, glycolysis and angiogenesis in solid tumors *in vivo*, and thus provides two independent mechanisms for inhibiting tumor growth: direct antitumor cell activity and inhibition of the tumor stromal compartment.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the PI3K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (AI)-resistant and long-term estrogen-deprived breast cancer cells. *In vitro* studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner. In breast cancer cells, resistance to AIs due to Akt activation can be reversed by co-administration with everolimus.

In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body. The mTOR regulates protein synthesis and multiple downstream cellular functions that may influence neuronal excitability and epileptogenesis. Overactivation of mTOR results in neuronal dysplasia, aberrant axonogenesis and dendrite formation, increased excitatory synaptic currents, reduced myelination, and disruption of the cortical laminar structure causing abnormalities in neuronal development and function. Preclinical studies in models of mTOR dysregulation in the brain demonstrated that treatment with an mTOR inhibitor such as everolimus could prolong survival, suppress seizures, prevent the development of new-onset seizures, and prevent premature death. In summary, everolimus is highly active in this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 inhibition.

Pharmacodynamics (PD)

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

A trend suggestive of longer progression-free survival with higher time-normalized everolimus C_{min} (defined as (area under the C_{min}-time curve from study start to the time of the event)/(time from study start to the event)) was evident in patients with advanced pancreatic neuroendocrine tumors (pNET, risk ratio 0.73; 95% CI: 0.50 to 1.08) and in patients with advanced carcinoid tumor (risk ratio 0.66; 95% CI: 0.40 to 1.08). Everolimus C_{min} impacted the probability of tumor size reduction ($p<0.001$) with the odds ratios of 1.62 and 1.46, respectively, for a change in exposure from 5 ng/mL to 10 ng/mL in patients with advanced pNET and in patients with advanced carcinoid tumor.

In patients with TSC who have SEGA, a model based analysis indicated that a 2-fold C_{min} increase led to a 13% (95% CI: -18.2%, -7.5%) tumor size reduction from baseline, which was statistically significant at a 5% level.

Pharmacokinetics (PK)

Absorption

After administration of Afinitor Tablets in patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional with daily dosing between 5 and 10 mg. With single doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 to 70 mg dose range.

Food effect:

In healthy subjects, high fat meals reduced systemic exposure to 10 mg Afinitor Tablets (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Low-fat meals reduced AUC by 32% and C_{max} by 42%.

In healthy subjects taking a single 9 mg dose (3 x 3 mg) of Afinitor Dispersible Tablets, high fat meals reduced AUC by 11.7% and C_{max} by 59.8%. Low-fat meals reduced AUC by 29.5% and C_{max} by 50.2%. Food, however, had no apparent effect on the post absorption phase concentration-time profile 24 h post-dose of either dosage form.

Relative bioavailability of dispersible tablets:

The $AUC_{0-\infty}$ of the Afinitor Dispersible Tablets when administered as a suspension in water was equivalent to that of Afinitor Tablets. The predicted trough concentrations of everolimus at steady-state after daily administration were similar for both dosage forms. The C_{max} of

everolimus associated with Afinitor Dispersible Tablets was, however, somewhat lower (64% to 80% relative to that associated with Afinitor Tablets).

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given Afinitor 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Following intravenous administration in a rat model, everolimus was shown to cross the blood-brain barrier in a non-linear dose-dependent manner, suggesting saturation of an efflux pump at the blood-brain barrier. Brain penetration of everolimus has also been demonstrated in rats receiving oral doses of everolimus.

Biotransformation/metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, it is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself. Hence, the parent substance is considered to contribute the majority of the overall pharmacological activity of everolimus.

Elimination

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

Steady-state pharmacokinetics

After administration of Afinitor Tablets in patients with advanced solid tumors, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg with a daily dosing regimen. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg daily. T_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on a daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Special populations

Hepatic impairment

The safety, tolerability and pharmacokinetics of Afinitor were evaluated in two single oral dose studies of Afinitor Tablets in subjects with impaired hepatic function relative to subjects with normal hepatic function. In one study the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. In a 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 hepatic impaired subjects based on their Child Pugh status.

Based on a meta-analysis of the two studies, dose adjustment is recommended for patients with hepatic impairment (see sections WARNINGS AND PRECAUTIONS and DOSAGE REGIMEN AND ADMINISTRATION).

Renal impairment

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

Pediatric patients (below 18 years)

- There is no indication for use of Afinitor in the pediatric cancer population (see section DOSAGE REGIMEN AND ADMINISTRATION) or in pediatric patients with TSC who have renal angiomyolipoma.
- In patients with TSC who have SEGA receiving Afinitor Tablets, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.
- In patients with TSC who have SEGA receiving Afinitor Tablets, the everolimus geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10-18 years were statistically lower than those observed in adults (> 18 years of age), suggesting that everolimus clearance was higher in younger patients.

Geriatric patients (65 years of age or older)

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

Race/Ethnicity

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

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

CLINICAL STUDIES

Hormone receptor-positive advanced breast cancer

BOLERO-2 (Study CRAD001Y2301), a randomized, double-blind, multicenter phase III study of Afinitor + exemestane versus placebo + exemestane was conducted in postmenopausal women with estrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole.

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

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Clinical Benefit Rate (CBR), Safety, change in Quality of Life (QoL) and time to ECOG PS deterioration. Additional endpoints included changes in bone turnover markers at 6 and 12 weeks.

A total of 724 patients were randomized in 2:1 ratio to the combination everolimus (10 mg daily) + exemestane (25 mg daily) (n = 485) or placebo + exemestane arm (25 mg daily) (n = 239). The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics and history of prior anti-neoplastic usages. The median age of patients was 61 years (range 28 to 93) and 75% were Caucasian. The median duration of blinded treatment was 24 weeks for patients receiving Afinitor plus exemestane and 13.4 weeks for those receiving placebo plus exemestane.

The efficacy results were obtained from the final analysis of PFS after 510 local PFS events and 320 central PFS events were observed. Patients in the placebo + exemestane arm did not cross-over to everolimus at the time of progression.

The study demonstrated a statistically significant clinical benefit of everolimus + exemestane over placebo + exemestane by a 2.5-fold prolongation in median PFS (see Table 6).

Table 6 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	7.82 (6.93 to 8.48)	3.19 (2.76 to 4.14)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.01 (9.66 to 15.01)	4.14 (2.89 to 5.55)	0.38 (0.31 to 0.48)	<0.0001
Best overall response (%, 95% CI)				
Objective response rate (ORR)[b]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[d]	<0.0001[e]
Clinical benefit rate (CBR) [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 CR or PR

[c] Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

[d] not applicable

[e] p-value is obtained from the exact CMH test using a stratified version of the Cochran-Armitage permutation test

At the time of the final overall survival (OS) analysis, the median duration of OS was 31 months versus 26.6 months for the everolimus + exemestane arm versus the placebo + exemestane arm, respectively [HR= 0.89 (95% CI: 0.73 to 1.10; p=0.1426)] (see Figure 2).

Twelve-month PFS rates were 33% of patients receiving everolimus + exemestane compared with 11% in the placebo + exemestane arm.

Tumor reduction was also evident in 70.8% of patients in the everolimus + exemestane arm versus 29.7% for placebo + exemestane.

Clinically or statistically significant differences were not observed between the two treatment arms in terms of time to deterioration of ECOG PS (≥1 point) and median times to deterioration (≥5%) of QLQ-C30 domain scores.

Effects on bone

There are no long-term data on the effect of everolimus on bone. Comparative data from BOLERO-2 showed marked improvement in serum bone-turnover markers during the first 12 weeks of therapy, suggesting a favorable effect on bone turnover.

Advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin

RADIANT-3 (Study CRAD001C2324), a randomized, double-blind, multicenter phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pancreatic neuroendocrine tumors (pNET), demonstrated a statistically significant clinical benefit of Afinitor over placebo by a 2.4-fold prolongation in median progression-free-survival PFS (see Table 7).

The primary endpoint for the trial was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumors, version 1.0) as per investigator radiology review.

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

In total, 410 patients were randomized 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). Median duration of blinded study treatment was 37.8 weeks for patients receiving Afinitor and 16.1 weeks for those receiving placebo.

Table 7 RADIANT-3 – Progression Free Survival results

Analysis	N	Afinitor N=207	Placebo N=203	Hazard Ratio (95%CI)	p-value[b]
	410	Median progression-free survival (months) (95% CI)			
Investigator radiological review		11.04 (8.41 to 13.86)	4.60 (3.06 to 5.39)	0.35 (0.27 to 0.45)	<0.0001
Independent radiological review [a]		11.40 (10.84 to 14.75)	5.39 (4.34 to 5.55)	0.34 (0.26 to 0.44)	<0.0001

[a] Includes adjudication for discrepant assessments between investigator radiological review and central radiological review

[b]One-sided p-value from a stratified log-rank test

Eighteen-months PFS rates were 34.2% for Afinitor therapy compared to 8.9% for placebo.

The objective response rate per investigator assessment was 4.8% for the everolimus arm vs. 2.0% for the placebo arm. Tumor reduction was also evident in 64.4% of patients in the everolimus arm versus 20.6% for placebo.

At the time of the final overall survival (OS) analysis, the median duration of OS was 44 months for the everolimus arm versus 37.7 months for the placebo arm, respectively [HR=0.94 (95% CI 0.73 to 1.20)] ; p=0.300. Following disease progression, crossover to open-label Afinitor occurred in 172 of 203 patients (84.7%) randomized to placebo and may have confounded the detection of any treatment-related difference in overall survival.

RADIANT-4 (Study CRAD001T2302), a randomized, double-blind, multicenter phase III study of Afinitor plus best supportive care (BSC) versus placebo plus best supportive care was conducted in patients with advanced non-functional neuroendocrine tumors (NET) of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome.

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

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Disease Control Rate (DCR = proportion of patients with a best overall response of complete response, partial response or stable disease), Safety, change in Quality of Life (QoL) via FACT-G and time to WHO PS deterioration.

A total of 302 patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) (n = 205) or placebo (n = 97). The median age of patients was 63 years (range 22 to 86) and 76% were Caucasian. The median duration of blinded treatment was 40.4 weeks for patients receiving Afinitor and 19.6 weeks for those receiving placebo. Patients in the placebo arm did not cross-over to everolimus at the time of progression.

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

The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 2.8-fold prolongation in median PFS (see Table 8).

The analysis of PFS based on local investigator assessment was supportive and showed a 2.6-fold prolongation in median progression-free-survival (see Table 8).

Table 8 RADIANT-4 – Progression Free Survival results

Analysis	N	Afinitor N=205	Placebo N=97	Hazard Ratio (95%CI)	p-value[a]
	302	Median progression-free survival (months) (95% CI)			
Independent radiological review		11.01 (9.2 to 13.3)	3.91 (3.6 to 7.4)	0.48 (0.35 to 0.67)	<0.001
Investigator radiological review		14.39 (11.24 to 17.97)	5.45 (3.71 to 7.39)	0.40 (0.29 to 0.55)	<0.001

[a] *One-sided p-value from a stratified log-rank test*

The overall PFS benefit favored Afinitor across predefined demographic and prognostic stratification subgroups (e.g., prior SSA treatment, tumor origin grouping and WHO performance status) and with a hazard ratio range of 0.43 to 0.63). A post-hoc subgroup analysis of PFS showed a positive PFS benefit for sites of tumor origin by gastrointestinal [HR=0.60 (95% CI:0.39 to 0.91)], lung [HR=0.50 (95% CI:0.28 to 0.88)] and carcinoma of unknown primary/other origin [HR=0.50 (95% CI:0.22 to 1.16)].

The overall response rate as per independent assessment was 2% in the everolimus arm vs. 1% in the placebo arm. Disease control rate (CR or PR or SD) for everolimus was 82.4% vs. 64.9% in the placebo arm. Tumor reduction was also evident indicating that 63.6% of patients in the everolimus arm experienced tumor shrinkage versus 25.9% for placebo.

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

Clinically or statistically significant differences were not observed between the two treatment arms in terms of time to deterioration of WHO PS (HR: 1.02; 95% CI: 0.65, 1.61) and time to deterioration of FACT-G total score (HR: 0.74; 95% CI: 0.50, 1.10).

RADIANT-2 (Study CRAD001C2325), a randomized, double-blind, multicenter phase III study of Afinitor plus depot octreotide (Sandostatin LAR®) versus placebo plus depot octreotide in patients with advanced neuroendocrine tumors (carcinoid tumor) primarily of gastrointestinal or lung origin showed evidence of clinical benefit of Afinitor over placebo by a 5.1-month

prolongation in median PFS (see Table 9). Although statistical significance was not reached for the primary analysis (boundary for statistical significance was p=0.0246), analyses which adjusted for informative censoring and imbalances in the two treatment arms showed a treatment effect in favor of everolimus.

RADIANT-2 enrolled patients with advanced neuroendocrine tumors (carcinoid tumor) primarily of gastrointestinal or lung origin whose disease had progressed within the prior 12 months and had a history of secretory symptoms. 80.1% of the patients in the Afinitor group received somatostatin analog therapy prior to study entry compared to 77.9% in the placebo group.

The primary endpoint is PFS evaluated by RECIST as per independent radiological review.

Secondary endpoints include safety, objective response, response duration, and overall survival.

In total, 429 patients were randomized 1:1 to receive either Afinitor 10 mg/day (n=216) or placebo (n=213), in addition to depot octreotide (Sandostatin LAR®, administered intramuscularly) 30 mg every 28 days. Median duration of blinded study treatment was 37.0 weeks for patients receiving Afinitor and 36.6 weeks for those receiving placebo. Notable imbalances were evident for several important baseline prognostic factors, mainly in favor of the placebo group.

Table 9 RADIANT-2 – Progression Free Survival results

Analysis	N	Afinitor[a] N=216	Placebo[a] N=213	Hazard Ratio (95%CI)	p-value[c]
	429	Median progression-free survival (months) (95% CI)			
Independent radiological review[b]		16.43 (13.67 to 21.19)	11.33 (8.44 to 14.59)	0.77 (0.59 to 1.00)	0.026
Investigator radiological review		11.99 (10.61 to 16.13)	8.61 (8.08 to 11.14)	0.78 (0.62 to 0.98)	0.018

[a] Plus depot octreotide (Sandostatin LAR®)

[b] Includes adjudication for discrepant assessments between investigator radiological review and central radiological review

[c] One-sided p-value from a stratified log-rank test

Additional analyses for independent radiological review which adjusted for informative censoring and imbalances in the two treatment arms showed a treatment effect in favor of everolimus. Results of an additional adjusted multivariate analysis which corrected for imbalances between treatment arms yielded a HR of 0.73 (95% CI 0.56 to 0.97). The estimated HR (95% CI) from the IPCW analysis was 0.60 (0.44 to 0.84) in favor of Afinitor.

Eighteen-months PFS rates were 47.2% for everolimus therapy plus depot octreotide (Sandostatin LAR®) compared with 37.4% for placebo plus depot octreotide (Sandostatin LAR®).

The objective response rate per independent radiological review was 2.3% for the everolimus plus depot octreotide (Sandostatin LAR®) arm vs. 1.9% for the placebo plus depot octreotide (Sandostatin LAR®) arm. Tumor reduction was also evident in 75.0% of patients in the everolimus plus depot octreotide (Sandostatin LAR®) arm versus 44.8% in the placebo plus depot octreotide (Sandostatin LAR®) arm.

The final analysis of overall survival did not show a statistically significant difference in OS (HR =1.16; (95% CI: 0.91 to 1.49)). There were 133 (61.6%) deaths in the everolimus plus depot octreotide arm and 120 (56.3%) in the placebo plus depot octreotide arm. Crossover of >58% of patients from placebo to open-label Afinitor following disease progression, imbalance between treatment arms in subsequent use of octreotide and imbalance of key prognostic factors at baseline likely confounded the detection of any treatment-related difference in OS. When adjusted for important prognostic factors, the OS hazard ratio inclined towards unity (HR 1.06; 95% CI: 0.82, 1.36).

Advanced renal cell carcinoma

RECORD-1 (CRAD001C2240), a phase III, international, multicenter, randomized, double-blind study comparing Afinitor 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-alpha was also permitted.

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumors) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumor response rate, overall survival, disease-related symptoms, and quality of life. 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 randomized 2:1 to receive Afinitor (n=277) or placebo (n=139). Demographics were well balanced (pooled median age 61 years [range 27 to 85], 77% male, 88% Caucasian, 74% one prior VEGFR-TKI therapy). Median duration of blinded study treatment was 141 days for patients receiving Afinitor and 60 days for those receiving placebo.

Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 10).

Table 10 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 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 [a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6 to 5.8)	1.9 (1.8 to 2.2)	0.32 (0.25 to 0.41)	<0.001 [a]
MSKCC prognostic score					
Favourable risk	120	5.8 (4.0 to 7.4)	1.9 (1.9 to 2.8)	0.31 (0.19 to 0.50)	<0.001 [b]

Population	N	Afinitor N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value
Intermediate risk	235	4.5 (3.8 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.001 [b]
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.007 [b]
Prior VEGFR-TKI therapy					
Sunitinib only	184	3.9 (3.6 to 5.6)	1.8 (1.8 to 1.9)	0.34 (0.23 to 0.51)	<0.001 [b]
Sorafenib only	124	5.9 (4.9 to 11.4)	2.8 (1.9 to 3.6)	0.25 (0.16 to 0.42)	<0.001 [b]
Sunitinib and sorafenib	108	4.0 (3.6 to 5.4)	1.8 (1.8 to 2.0)	0.32 (0.19 to 0.54)	<0.001 [b]

[a] Log-rank test stratified by prognostic score
[b] Unstratified one-sided log-rank test

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

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

Final overall survival results yielded a trend in favor of Afinitor; the difference between treatment arms was not statistically significant (HR 0.90; 95% CI: 0.71 to 1.14; p=0.183). Crossover to open-label Afinitor following disease progression occurred in 111 of 139 patients (79.9%) allocated to placebo and may have confounded the detection of any treatment-related difference in overall survival. A strong trend is evident supporting better quality of life among patients receiving Afinitor as measured by disease-related symptoms (HR 0.75; 95% CI: 0.53 to 1.06; p=0.053).

Tuberous sclerosis complex (TSC) with renal angiomyolipoma

EXIST-2 (Study CRAD001M2302), a randomized, double-blind, multicenter phase-III study of Afinitor versus placebo was conducted in patients with TSC who have angiomyolipoma (n=113) or sporadic LAM who have angiomyolipoma (n=5). Patients were randomized in a 2:1 ratio to receive either Afinitor Tablets or matching placebo. Presence of at least one angiomyolipoma ≥ 3 cm in longest diameter using CT/MRI (based on local radiology assessment) was required for entry.

The primary efficacy endpoint was angiomyolipoma response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

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

A total of 118 patients were randomized, 79 to Afinitor 10 mg daily and 39 to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease

characteristics and history of prior anti-angiomyolipoma therapies. Median age was 31 years (range: 18 to 61; 46.6% were <30 years at enrolment), 33.9% were male, and 89.0% were Caucasian. Of the enrolled patients, 83.1% had angiomyolipomas ≥ 4 cm (with 28.8% with angiomyolipomas ≥ 8 cm), 78.0% had bilateral angiomyolipomas, and 39.0% had undergone prior renal embolization/nephrectomy; 96.6% had skin lesions at baseline and 44.1% had target SEGAs (at least one SEGA ≥ 1 cm in longest diameter).

The median duration of blinded study treatment was 48.1 weeks (range 2 to 115) for patients receiving Afinitor and 45.0 weeks (range 9 to 115) for those receiving placebo.

Results showed that Afinitor was superior to placebo for the primary endpoint of best overall angiomyolipoma response (p<0.0001) (see Table 11).

Patients initially treated with placebo were allowed to cross over to everolimus at the time of angiomyolipoma progression and upon recognition that treatment with everolimus was superior to treatment with placebo. At the time of the final analysis (4 years following the last patient randomization), the median duration of exposure to everolimus was 204.1 weeks (range 2 to 278).

Among patients treated with everolimus during the study, no cases of angiomyolipoma-related nephrectomy and only one case of renal embolization were reported.

Table 11 EXIST-2 - Angiomyolipoma response

	Primary Analysis[3]			Final analysis[4]
	Afinitor N=79	**Placebo N=39**	**p-value**	**Afinitor N=112**
Angiomyolipoma response rate[1,2] - %	**41.8**	**0**	**<0.0001**	**58.0**
95% CI	(30.8, 53.4)	(0.0, 9.0)		(48.3, 67.3)
Best overall angiomyolipoma response - %				
Response	41.8	0		58.0
Stable disease	40.5	79.5		30.4
Progression	1.3	5.1		0.9
Not evaluable	16.5	15.4		10.7

[1] Per independent central radiology review

[2] Angiomyolipoma responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of angiomyolipoma volume relative to baseline, plus absence of new angiomyolipoma ≥ 1.0 cm in longest diameter, plus no increases in renal volume > 20% from nadir, plus absence of Grade ≥ 2 angiomyolipoma-related bleeding.

[3]Primary analysis for double blind period

[4]Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.1 weeks

Reduction in angiomyolipoma volume was evident in 95.5% of patients in the Afinitor arm versus 59.4% in the placebo arm at primary analysis.

In the final analysis, reduction in angiomyolipoma volume improved with longer term treatment with Afinitor. At weeks 12, 96 and 192, ≥30% reductions in volume were observed in 75.0% (78/104), 80.6% (79/98) and 85.2% (52/61) of the treated patients, respectively. Similarly, at

the same timepoints, ≥50% reductions in volume were observed in 44.2% (46/104), 63.3% (62/98) and 68.9% (42/61) of the treated patients, respectively.

Afinitor was associated with a clinically relevant and statistically significant prolongation in time to angiomyolipoma progression (HR 0.08; 95% CI: 0.02, 0.37; p<0.0001) at the primary analysis. Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the Afinitor arm. Progressions were observed in 3.8% (3/79) of patients in the Afinitor arm compared with 20.5% (8/39) in the placebo arm. Estimated progression-free rates at 6 months were 98.4% for the Afinitor arm and 83.4% for the placebo arm. At the final analysis, median time to angiomyolipoma progression was not reached. Angiomyolipoma progressions were observed in 14.3% of the patients (16/112). The estimated angiomyolipoma progression-free rates at 24 months and 48 months were 91.6% (95% CI: 84.0%, 95.7%) and 83.1% (95% CI: 73.4%, 89.5%) respectively.

At the primary analysis, Afinitor demonstrated clinically meaningful and statistically significant improvements in skin lesion response (p=0.0002), with response rates of 26.0% (20/77) (95% CI: 16.6, 37.2) for the Afinitor arm and 0% (0/37) (95% CI: 0.0, 9.5) for the placebo arm. At the final analysis, the skin lesion response rate had increased to 68.2% (73/107) (95% CI: 58.5%, 76.9%), with one patient reporting a confirmed complete clinical skin lesion response and no patients experiencing progressive disease as their best response.

In an exploratory analysis of patients with TSC with angiomyolipoma who also had SEGA, the SEGA response rate (proportion of patients with ≥50% reduction from baseline in target lesion volumes in the absence of progression) was 10.3% (4/39) in the everolimus arm at the primary analysis (versus no responses reported in the 13 patients randomized to placebo with a SEGA lesion at baseline) and increased to 48.0% (24/50) at the final analysis.

In EXIST-2, 12 of 16 evaluable patients evaluated for angiomyolipoma volume for up to 1 year after discontinuation of everolimus, experienced an increase in tumor volume compared to their most recent tumor volume assessment performed before treatment discontinuation; though the angiomyolipoma volume did not exceed that measured at baseline. Two of 16 evaluable patients developed protocol-defined angiomyolipoma progression by virtue of angiomyolipoma-related bleeding (n=1) and increase in kidney volume (n=1). These findings suggest that persistence of clinically significant angiomyolipoma volume reduction requires ongoing treatment in most patients.

TSC with SEGA

Phase III trial in patients with TSC who have SEGA

EXIST-1 (Study CRAD001M2301), a randomized, double-blind, multicenter phase-III study of Afinitor versus placebo was conducted in patients with TSC who have SEGA, irrespective of age. Patients were randomized in a 2:1 ratio to receive either Afinitor or matching placebo. Presence of at least one SEGA lesion ≥ 1.0 cm in longest diameter using MRI (based on local radiology assessment) was required for entry. In addition, serial radiological evidence of SEGA growth, presence of a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus was required for entry.

The primary efficacy endpoint was SEGA response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Key secondary endpoints in hierarchal order of testing included the absolute change in frequency of total seizure events per 24-hour EEG from baseline to Week 24, time to SEGA progression, and skin lesion response rate. Angiomyolipoma response rate was evaluated as an exploratory analysis.

A total of 117 patients were randomized, 78 to Afinitor and 39 to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies. Median age was 9.5 years (range: 0.8 to 26.6; 69.2% were 3 to < 18 years at enrolment; 17.1% were < 3 years at enrolment), 57.3% were male, and 93.2% were Caucasian. The median duration of blinded study treatment was 52.2 weeks (range 24 to 89) for patients receiving Afinitor and 46.6 weeks (range 14 to 88) for those receiving placebo.

Results showed that Afinitor was superior to placebo for the primary endpoint of best overall SEGA response ($p<0.0001$).(see Table 12).

At the time of final analysis, the median duration of exposure to everolimus among all such patients was 204.9 weeks (range 8.1 to 253.7). The best overall SEGA response rate had increased to 57.7% (95% CI: 47.9, 67.0) at the final analysis.

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

Table 12 EXIST-1 – SEGA response

	Primary analysis[3]			Final analysis[4]
	Afinitor N=78	**Placebo N=39**	**p-value**	**Afinitor N=111**
SEGA response rate[1,2] - (%)	34.6	0	<0.0001	57.7
95% CI	24.2, 46.2	0.0, 9.0		47.9, 67.0
Best overall SEGA response - (%)				
Response	34.6	0		57.7
Stable disease	62.8	92.3		39.6
Progression	0	7.7		0
Not evaluable	2.6	0		2.7

[1] Per independent central radiology review

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

[3]Primary analysis for double blind period

[4]Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.9 weeks

Consistent treatment effects were observed across all subgroups (e.g., EIAED use vs. EIAED non-use, sex, age (<3, 3 to <18, and ≥18 years), evaluated at the primary efficacy analysis, ranging from 23% to 52% responders in the Afinitor arm versus 0% responders in the placebo arm.

During the double-blind period, reduction of SEGA volume was evident within the initial 12 weeks of treatment with Afinitor: 29.7% (22/74) of patients had ≥50% reductions in volume and 73.0% (54/74) of patients had ≥ 30% reductions in volume. Sustained reductions were evident at Week 24, 41.9% (31/74) of patients had ≥50% reductions and 78.4% (58/74) of patients had ≥ 30% reductions in SEGA volume.

In the everolimus treated population (N=111) of the study, including patients who crossed over from the placebo group, tumor response, starting as early as after 12 weeks on everolimus, was sustained at later time points. The proportion of patients achieving at least 50% reductions in SEGA volume was 45.9% (45/98) and 62.1% (41/66) at Weeks 96 and 192 after start of everolimus treatment. Similarly, the proportion of patients achieving at least 30% reductions in SEGA volume was 71.4% (70/98) and 77.3% (51/66) at Weeks 96 and 192 after start of everolimus treatment.

Analysis of the first key secondary endpoint, change in seizure frequency, was inconclusive.

Median time to SEGA progression based on central radiology review was not reached in either treatment arm. Progressions were only observed in the placebo arm (15.4%; unadjusted p=0.0002). Estimated progression-free rates at 6 months were 100% for the Afinitor arm and 85.7% for the placebo arm. The long-term follow up of patients randomized to everolimus and

patients randomized to placebo who thereafter crossed over to everolimus demonstrated durable responses.

Additional clinical benefits of Afinitor were observed such as reductions in severity of skin lesions and size of renal angiomyolipoma.

At the time of the primary analysis, Afinitor demonstrated clinically meaningful improvements in skin lesion response (unadjusted p=0.0004), with response rates of 41.7% (95% CI: 30.2, 53.9) for the Afinitor arm and 10.5% (95% CI: 2.9, 24.8) for the placebo arm. At the final analysis, the skin lesion response rate increased to 58.1% (95% CI: 48.1, 67.7).

At the time of the primary analysis, angiomyolipoma responses were only observed in the everolimus arm (n/N:16/30; 53.3%; 95% CI: 34.3, 71.7). At the time of final analysis, among the 41 TSC-SEGA patients with an angiomyolipoma lesion(s) present at start of treatment with everolimus, 30 patients (73.2%; 95% CI: 57.1, 85.8) achieved, as their best overall response, at least a 50% reduction in sum of angiomyolipoma volumes. Among the 37 patients with evaluable angiomyolipoma tumor assessments, 35 patients (94.6%) experienced a reduction in the sum of target angiomyolipoma volumes relative to baseline as their best percentage change. Over the entire duration of the study, no new angiomyolipoma lesions were observed, nor were instances of grade 2 or worse bleeding episodes reported.

NON-CLINICAL SAFETY DATA

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

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

In juvenile rat toxicity studies at doses as low as 0.15 mg/kg/day, systemic toxicity included decreased body weight gain and food consumption, and delayed attainment of some developmental landmarks at all doses, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding, where young animals appeared to be more susceptible, it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse effects of everolimus as compared to adult animals at doses of 0.5 to 5 mg/kg per day. No relevant toxicity was evident in juvenile monkeys at doses up to 0.5 mg/kg/day for 4-weeks.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not

indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure from a 10 mg daily dose.

Reproductive toxicity

For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

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

Afinitor should not be used after the date marked "EXP" on the pack.

Afinitor must be kept out of the sight and reach of children.

INSTRUCTIONS FOR USE AND HANDLING

The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of Afinitor Tablets or Afinitor Dispersible Tablets. Wash hands thoroughly before and after preparation of either suspension.

Preparing AFINITOR oral suspension using Dispersible Tablets

Important Information

- **Take AFINITOR Dispersible Tablets as a suspension only**. AFINITOR Dispersible Tablets are prepared as a suspension of un-dissolved medicine that is mixed with water, and then it is taken by mouth. Do not chew, crush, or swallow AFINITOR Dispersible Tablets whole.
- Caregivers are advised to avoid contact with suspensions of AFINITOR Dispersible Tablets.
- Keep AFINITOR Dispersible Tablets and the prepared suspension out of the reach of children.
- Only use water (tap water or non-sparkling bottled water) with AFINITOR Dispersible Tablets to prepare the suspension. Do not prepare the suspension with juice or any other liquids.
- The suspension must be given right away. If you do not give the dose within 60 minutes after it has been prepared, throw away the dose and prepare a new dose of AFINITOR Dispersible Tablets.

- Before starting to prepare the suspension, collect all of the supplies that you will need to prepare and take the suspension. Do not use any of these supplies for purposes other than preparing and taking the AFINITOR Dispersible Tablets suspension.

Supplies needed to prepare the suspension in an oral syringe:

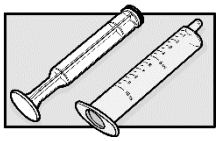
- Blister card with AFINITOR Dispersible Tablets
- Scissors to open the blister card
- 2 clean drinking glasses
- Approximately 30 mL of water
- 10 mL oral syringe (for one time use)

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

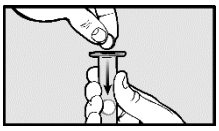
- Blister card with AFINITOR Dispersible Tablets
- Scissors to open the blister card
- 30 mL dose cup for measuring water (you can ask your pharmacist for this)
- 1 clean drinking glass (maximum size 100 mL)
- Water to prepare the suspension
- Spoon for stirring

Preparing a dose of AFINITOR suspension using an oral syringe

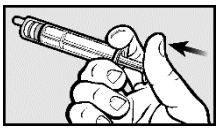
1. Wash and dry your hands before preparing the medication.



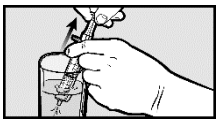
2. Take a 10 mL oral syringe and pull back on the plunger. Remove the plunger from the barrel of the syringe.



3. Use scissors to open the blister card along the dotted line. Remove the prescribed number of dispersible tablets from the blister card. Place the dispersible tablets (maximum of five 2-mg tablets, three 3-mg tablets, or two 5-mg tablets) into the oral syringe immediately.

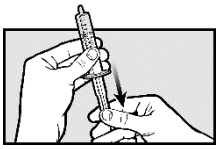


4. Re-insert the plunger into the barrel of the oral syringe and push the plunger in until it comes into contact with the dispersible tablets.

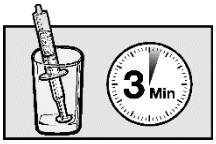


5. Fill a drinking glass with water and pull up about 5 mL of water into the oral syringe by slowly pulling back on the plunger.

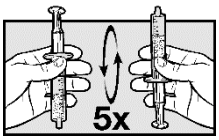
Note: The amount of water in the syringe does not need to be accurate. All dispersible tablets should be covered by water. In case dispersible tablets remain in the dry upper part of the syringe, make them move into the water by gentle tapping.



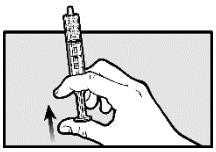
6. Hold the oral syringe with the tip pointing up. Pull back on the plunger to draw back about 4 mL of air.



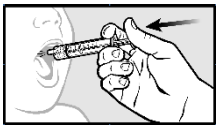
7. Place the filled oral syringe in the clean, empty glass with the tip pointing up. Allow the dispersible tablets **3 minutes** to break apart. Make sure to proceed further only when the 3 minutes are over and when the dispersible tablets have completely broken apart.



8. Slowly turn the oral syringe up and down five times just before giving the dose. Do not shake the oral syringe.

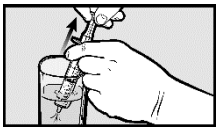


9. Hold the oral syringe in an upright position (with the tip up). Carefully remove most of the air by pushing up gently on the plunger.

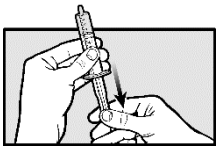


10. Give the full contents of the oral syringe slowly and gently into the mouth right away, within 60 minutes of preparing it.

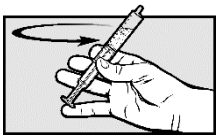
11. Carefully remove the oral syringe from patient's mouth.



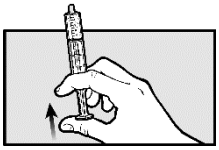
12. Insert the tip of the oral syringe into the drinking glass that is filled with water, and pull up about 5 mL of water by slowly pulling back on the plunger.



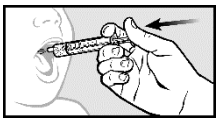
13. Hold the oral syringe with the tip pointing up and use the plunger to draw back about 4 mL of air.



14. With the tip of the oral syringe still pointing up, swirl the contents be gently rotating the syringe in a circular motion to suspend any remaining particles of the medication.



15. While holding the oral syringe in an upright position (with the tip up), carefully remove most of the air by pushing up gently on the plunger.



16. Give the full contents of the oral syringe slowly and gently into the mouth of the patient by pushing on the plunger.

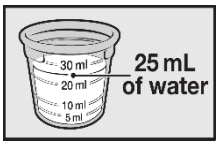
17. Carefully remove the oral syringe from patient's mouth. **If the total prescribed dose is more than 10 mg, repeat steps 2 to 17 to finish giving the dose.**

18. Throw away the oral syringe in your household trash.

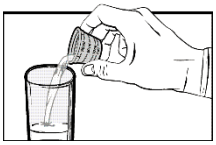
19. Wash your hands.

Preparing a dose of AFINITOR suspension using a small drinking glass

1. Wash and dry your hands before preparing the medication.

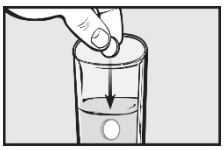


2. Add about 25 mL of water to the 30 mL dose cup. The amount of water added does not need to be exact.

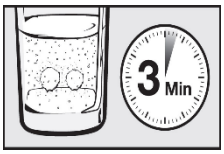


3. Pour the water from the dose cup into a small drinking glass (maximum size 100 mL).

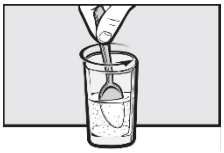
4. Use scissors to open the blister card along the dotted line and remove the prescribed number of dispersible tablets from the blister card.



5. Add the prescribed number of dispersible tablets into the water (maximum of five 2-mg tablets, three 3-mg tablets, or two 5-mg tablets).

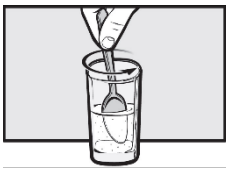


6. Wait 3 minutes to allow the dispersible tablets to break apart.

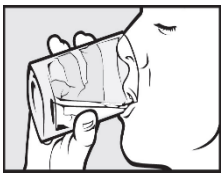


7. Gently stir the contents of the glass with a spoon.

8. Drink the full amount of the suspension right away, within 60 minutes of preparing it.

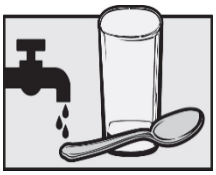


9. Refill the glass with the same amount of water (about 25 mL). Stir the contents with the same spoon.



10. Drink the full amount right away so that you take any remaining medicine.

    If the total prescribed dose is more than 10 mg, repeat steps 2 to 10 to finish taking the dose.



11. Wash the glass and the spoon thoroughly with water. Wipe the glass and spoon with a clean paper towel and store them in a dry and clean place until your next dose.

12. Wash your hands.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: Jul 2021

Novartis Pharma AG, Basel, Switzerland