מרץ 2015

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: Afinitor 2.5, 5, 10 mg, tablets
אפיניטור 2.5, 5, 10 מ"ג, טבליות

אנו שמחים לבשרכם על עדכונים בהתוויות התכשירים שבנדון.
העדכונים מודגשים בכחול.

א. עבור החוזקים הרשומים 2.5, 5 ו-10 מ"ג נוספה התוויה ונעשו שינויים עריכתיים בנוסחי ההתוויות הרשומות כפי שמפורט להלן:

Afinitor 2.5, 5 & 10 mg are indicated for the:

- For the treatment of patients with SEGA associated with tuberous sclerosis Complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.The effectiveness of Afinitor is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.
- Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. The safety and effectiveness of AFINITOR® in the treatment of patients with carcinoid tumors have not been established.
- For the treatment of hormone receptor – positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence ~~of~~ or progression follwing a non – steroidal aromatase inhibitor.
- Afinitor ® is indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of Afinitor in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

ב. עבור החוזק הרשום 2.5 מ"ג נוספה ההתוויה הבאה שלפני-כן היתה רשומה עבור החוזקים 5 ו- 10 מ"ג בלבד:

- Treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

המרכיב הפעיל: Everolimus 2.5mg (Afinitor 2.5 mg); Everolimus 5mg (Afinitor 5mg); Everolimus 10mg (Afinitor 10mg)

המרכיבים הבלתי פעילים :

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

בהתאם לכך בדצמבר 2014 אושרו עדכונים בעלונים לצרכן ולרופא של התכשירים שבנדון.

לתשומת לבכם, בנוסף לשינויים הרלוונטים להתוויות, העדכונים בעלונים כוללים עדכוני פורמט, שינויים רבים הנוגעים למידע הבטיחות של התכשירים ועדכון בתנאי האחסון של התכשירים כפי שמפורט להלן :

~~Store below 30~~Do not store above 25ºC.

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

העלונים העדכניים לרופא ולצרכן מצורפים בהמשך למכתב זה.

העלונים לצרכן ולרופא נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,

מגר׳ נעמה אור

״פורמט עלון זה נקבע ע״י משרד הבריאות ותוכנו נבדק ואושר על ידו בדצמבר 2014״

AFINITOR® (everolimus)

2.5 mg, 5 mg and 10 mg tablets

Prescribing information

1 Name of the medicinal product

Afinitor® 2.5 mg

Afinitor® 5 mg

Afinitor® 10 mg

2 Description and Composition

Pharmaceutical form

Tablet

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.

Active substance

2.5 mg tablets

- Each tablet contains 2.5 mg everolimus.

5 mg tablets

- Each tablet contains 5 mg everolimus.

10 mg tablets

- Each tablet contains 10 mg everolimus.

Excipients

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

3 Indications

Afinitor 2.5, 5 & 10mg are indicated for the:

1. Treatment of patients with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.
2. Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. The safety and effectiveness of AFINITOR® in the treatment of patients with carcinoid tumors have not been established.
3. Treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.
4. Treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.
5. Treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

4 Dosage and administration

4.1 Dosage

Treatment with Afinitor should be initiated and supervised 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.

4.1.1 General target population

4.1.1.1 Dosing in hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of 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 4.3 Method of Administration).

4.1.1.2 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:

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

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. Different strengths of Afinitor Tablets can be combined to attain the desired dose.

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA (see section 4.2 Therapeutic drug monitoring for patients treated for TSC with SEGA). Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL.

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 12 Clinical pharmacology).

Once a stable 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.

4.1.2 Dose Modifications

4.1.2.1 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 6 Warnings and precautions).

Table 4-1 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 4-1 Afinitor dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, not interfering with ADL[3]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade≤ 1. Re-initiate Afinitor at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Symptomatic, interfering with ADL[3] O_2 indicated	Interrupt Afinitor until symptoms resolve to Grade ≤1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating Afinitor at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening, ventilatory support indicated	Discontinue Afinitor, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate Afinitor at 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).[4]
	Grade 3 Symptomatic and unable to adequately eat or hydrate orally	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]
	Grade 4 Symptoms associated with life-threatening Consequences	Discontinue Afinitor and treat with appropriate medical therapy.

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
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 Afinitor at the same dose. If toxicity recurs at Grade 2, interrupt Afinitor until recovery to Grade ≤1. Re-initiate Afinitor at lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating Afinitor at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Afinitor 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 Afinitor at lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.

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

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

[3] Activities of daily living (ADL)

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

4.1.2.2. CYP3A4/PgP inhibitors

Avoid the use of strong CYP3A4/PgP inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) (see section 6 Warnings and precautions and section 8 Interactions).

Moderate CYP3A4 or PgP inhibitors:

Use caution when administered 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%. For dose reductions below the lowest available strength, alternate day dosing should be considered. (see sections 6 Warnings and precautions and 8 Interactions).

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma and TSC with renal**

angiomyolipoma: If the moderate CYP3A4/PgP inhibitor is discontinued, consider a washout period of approximately 2 to 3 days should be allowed before the Afinitor dose is increased. The Afinitor dose should be returned to the dose used prior to initiation of the moderate CYP3A4 -/- PgP inhibitor -(see sections 6 Warning and precautions and 8 Interactions).

• **TSC with SEGA:** Everolimus trough concentrations should be assessed approximately 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 4.2 Therapeutic drug monitoring for patients treated for TSC with SEGA, 6 Warnings and precautions and 8 Interactions).

4.1.2.3 Strong CYP3A4/PgP inducers

Avoid the use of concomitant strong CYP3A4/ PgP inducers.

Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of pancreatic origin ,advanced renal cell carcinoma and TSC with renal angiomyolipoma: If patients require co-administration of a strong CYP3A4/ PgP 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 3 to 5 days, before the AFINITOR dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer (see sections 6 Warnings and Precautions and 8 Interactions).
TSC with SEGA: Patients receiving concomitant strong CYP3A4 inducers (e.g., the enzyme inducing antiepileptic drugs carbamazepine, phenobarbital, and phenytoin) may require an increased Afinitor dose to attain trough concentrations of 3 to 15 ng/mL. If concentrations are below 3 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, checking the trough level and assessing tolerability before increasing the dose. If the strong inducer is discontinued, the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later (see sections 4.2 Therapeutic drug monitoring for patients treated for TSC with SEGA, 6 Warnings and Precautions and 8 Interactions).

4.1.3 Special populations:

4.1.3.1 Pediatric population

- Afinitor is not recommended for use in pediatric cancer patients.
- The safety and efficacy of Afinitor in pediatric patients with renal angiomyolipoma associated with TSC in the absence of SEGA have not been established. No data are available.
- The safety and efficacy of Afinitor in children below the age of 1 year with TSC who have SEGA have not been established. No data are available.
- 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 TSC who have SEGA and hepatic impairment.

4.1.3.2 Geriatrics (≥ 65 years)

No dosage adjustment is required (see section 12 Clinical pharmacology).

4.1.3.3 Renal impairment

No dosage adjustment is required (see section 12 Clinical pharmacology).

4.1.3.4 Hepatic impairment

Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of 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 recommended starting dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B) – 25% of the recommended starting dose calculated based on BSA (rounded to the nearest strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic (Child-Pugh) status. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL (see section 4.2 Therapeutic drug monitoring for patients treated for TSC with SEGA). Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment. (see section 12 Clinical pharmacology).

Patients <18 years of age

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

4.2. Therapeutic drug monitoring for patients treated for TSC with SEGA

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 2 weeks after the initial dose, after any change in dose, after an initiation or change in co-administration of CYP3A4/PgP inducers and/or inhibitors (see sections 6 Warnings and Precautions and 8 Interactions), or after any change in hepatic (Child-Pugh) status (see sections 4 Dosage and administration and 12 Clinical Pharmacology). Dosing should be titrated with the objective of attaining everolimus trough concentrations of 3 to 15 ng/mL, subject to tolerability (see section 12 Clinical pharmacology). The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

4.3 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 12 Clinical pharmacology).

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 12 Clinical pharmacology).

5. Contraindications

Afinitor is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients (see section 6 Warnings and precautions).

6. Warnings and precautions

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see section 7 Adverse drug reactions). Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or 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 4 Dosage and administration, Table 4-1).

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 reinitiated at a daily dose approximately 50% lower than the dose previously administered depending on 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 4 Dosage and administration, Table 4-1).

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 7 Adverse drug reactions). Localised and systemic infections, including pneumonia, mycobacterial infections, 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 occurred in patients taking Afinitor. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

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

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

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 5 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).

Oral ulceration

Mouth ulcers, stomatitis, and oral mucositis have been seen in patients treated with Afinitor (see section 7 Adverse drug reactions). In such cases topical treatments are recommended, but alcohol- hydrogen peroxide-, iodine-, or thyme-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 8 Interactions).

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor. 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 7 Adverse drug reactions.

Impaired Wound Healing

Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the peri-surgical period.

Geriatric Patients

In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study, the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients $\geq$ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients $\geq$ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended

Laboratory tests and monitoring

Renal function

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking Afinitor(see section 7 Adverse drug reactions). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter.

Blood glucose

Hyperglycaemia, has been reported in patients taking Afinitor (see section 7 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 glycaemic 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 haemoglobin, lymphocytes, platelets and neutrophils have been reported in patients treated with Afinitor (see section 7 Adverse drug reactions). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

Drug-drug interactions

Co-administration with strong CYP3A4/ PgP inhibitors should be avoided (see section 8 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 4 Dosage and administration and 8 Interactions).

Co-administration with strong CYP3A4/PgP inducers should be avoided (see section 8 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 Section 4 Dosage and administration and section 8 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 8 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 section 12 Clinical pharmacology).

Afinitor is not recommended in patients with severe hepatic impairment (Child-Pugh C) for the treatment of hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, or TSC who have renal angiomyolipoma unless the potential benefit outweighs the risk (see sections 4 Dosage and administration and 12 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) or in patients ≥ 18 years of age with severe hepatic impairment (Child-Pugh C) (see sections 4 Dosage and administration and 12 Clinical pharmacology).

Vaccinations

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

Lactose

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

Wound healing complications

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

7 Adverse drug reactions

Oncology - Summary of safety profile

Adverse drug reaction (ADR) information is based on pooled safety data in patients receiving Afinitor (N=2470) 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, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, hyperglycemia, weight decreased, pruritus, asthenia, peripheral edema, asthenia, hypercholesterolemia, epistaxis, and headache.

The most common grade 3/ 4 ADRs (incidence ≥100/1 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and pneumonia.

Tabulated summary of adverse drug reactions from clinical trials in oncology

Table 7-1 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 adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥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 7-1 Adverse drug reactions from oncology trials

Infections and infestations	
Very common	Infections[a]
Blood and lymphatic system disorders	
Very common	Anemia,
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, hyperglycemia, hypercholesterolemia
Common	Hypertriglyceridemia, hypophosphatemia, diabetes mellitus, hyperlipidemia, hypokalemia, dehydration, hypocalcaemia
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia

Eye disorders	
Common	Conjunctivitis, eyelid oedema
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Hemorrhage[b,] hypertension.
Uncommon	Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis[c], epistaxis
Common	Cough, dyspnea
Uncommon	Hemoptysis, pulmonary embolism
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis[d], diarrhea, 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 syndromee , skin exfoliation, acneiform dermatitis, onychoclasis, alopecia, skin lesion
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	Amenorrhea[f]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, peripheral edema
Common	Pyrexia, mucosal inflammation
Uncommon	Non-cardiac chest pain
Rare	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 and uncommon:*	

herpes zoster, sepsis and isolated cases of opportunistic infections (e.g. aspergillosis, candidiasis and hepatitis B)
[b]*Includes different bleeding events not listed individually*
[c]*Includes common: pneumonitis, interstitial lung disease, lung infiltration; and rare: alveolitis, pulmonary alveolar hemorrhage, and pulmonary toxicity*
[d]*Includes very common: stomatitis; common: aphthous stomatitis, mouth and tongue ulceration; uncommon: glossitis, glossodynia*
[e]*reported as palmar-plantar erythrodysesthesia 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):

- Hematology: hemoglobin decreased, lymphocytes decreased, white blood cells decreased. platelets 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 and potassium decreased.

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

- Hematology: lymphocytes decreased, hemoglobin 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 (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=251) in two 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 7-2 and section 3 Indications:

Table 7-2 Afinitor TSC studies in the pooled safety data

Indication	Study Name	Active Treatment Arm	Comparator or Control Arm
TSC - Renal Angiomyolipoma	EXIST-2 (M2302)	everolimus, N=79	placebo, N=39
TSC - SEGA	EXIST-1 (M2301))	everolimus, N=78	placebo, N=39
TSC – SEGA[1]	CRAD001C2485	everolimus, N=28	n/a

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

The most frequent ADRs (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety database are (in decreasing order): stomatitis, amenorrhea, upper respiratory tract infections, hypercholesterolemia, nasopharyngitis, acne, menstruation irregular, sinusitis, and pneumonia.

The most frequent grade 3/4 adverse reactions (incidence ≥1/100 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, amenorrhea, pneumonia, neutropenia, pyrexia and gastroenteritis viral.

Tabulated summary of adverse reactions from clinical trials in TSC

Table 7-3 shows the incidence of ADRs based on pooled data in patients receiving everolimus in the TSC studies (including both the double-blind and open-label study and extension periods). 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 7-3 Adverse drug reactions from clinical trials in TSC

Infections and infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, sinusitis, pneumonia
Common	Otitis media, urinary tract infection, pharyngitis, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis.
Uncommon	Herpes zoster, bronchitis viral
Blood and lymphatic system disorders	
Common	Neutropenia, anemia, leukopenia, lymphopenia, thrombocytopenia,
Immune system disorders	
Uncommon	Hypersensitivity
Musculoskeletal and connective tissue disorders	
Uncommon	Rhabdomyolysis
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Hyperlipidemia, decreased appetite, hypophosphatemia, hypertriglyceridemia

Psychiatric disorders	
Common	Insomnia
Uncommon	Aggression
Nervous system disorders	
Common	Headache, dysgeusia
Vascular disorders	
Common	Hypertension, lymphedema
Respiratory, thoracic and mediastinal disorders	
Common	Cough, epistaxis
Uncommon	Pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis[a]
Common	Diarrhea, nausea, vomiting, abdominal pain, oral pain, flatulence, constipation, gastritis
Skin and subcutaneous tissue disorders	
Very Common	Acne
Common	Rash[b], dermatitis acneiform, dry skin
Uncommon	Angioedema
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very Common	Amenorrhea[c], menstruation irregular[c]
Common	Vaginal hemorrhage, menorrhagia, ovarian cyst, menstruation delayed[c]
General disorders and administration site conditions	
Common	Fatigue, pyrexia, irritability
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased
Uncommon	Blood follicle stimulating hormone increased

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

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

[c]*frequency is based upon number of women 10 to 55 yrs of age 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):

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

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

- Hematology: neutrophils decreased, partial thromboplastin time increased (common) and lymphocytes decreased , hemoglobin decreased (all uncommon).
- Clinical chemistry: phosphate decreased, alkaline phosphatase increased, AST increased, (common); cholesterol increased, triglycerides increased, ALT increased, potassium decreased, and glucose (fasting) increased (uncommon).

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 6 Warnings and precautions).

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

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 6 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 6 Warnings and precautions).

Special populations

Pediatrics

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

The safety of AFINITOR in pediatric patients with SEGA was demonstrated in two clinical trials.

In EXIST-1, the overall nature, type, and frequency of ADRs across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious ADRs in patients < 3 years of age. A total of 2 of 13 patients (15.4%) < 3 years of age had at least one serious ADR due to infection, compared to 0 of 7 patients (0%) treated with placebo. No patient in any age group discontinued Afinitor due to infection.

In Study CRAD001C2485, the frequency of ADRs across the age groups was generally similar. The long term effects of Afinitor on growth and pubertal development are unknown.

Everolimus clearance normalized to body surface area was higher in pediatric patients than in adults with SEGA (see section 12 Clinical Pharmacology). The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 3 to 15 ng/mL are the same for adult and pediatric patients with SEGA (see section 4 Dosage and administration).

Geriatrics

In the pooled safety database, 35% of the Afinitor-treated patients were ≥65 years of age.

The number patients with an ADR leading to discontinuation of Afinitor was higher in patients ≥65 years of age (19% vs. 13%). The most common ADRs (≥1/100) leading to discontinuation were pneumonitis (including interstitial lung disease), stomatitis, fatigue and dyspnea.

8. Interactions

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump 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, voriconazole, ritonavir, clarithromycin and telithromycin) should be avoided.

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

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

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

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

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 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 4 Dosage and administration and 6 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)*, corticosteroids (e.g. dexamethasone, prednisone, prednisolone), anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin,) and anti HIV agents (e.g. efavirenz, nevirapine).

Agents whose plasma concentration may be altered by everolimus:

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

In vitro, everolimus competitively inhibited the metabolism of the CYP3A4 substrate ciclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus C_{max} with an oral dose of 10 mg daily or 70 mg weekly is more than 12- to 36-fold below the Ki-values of the *in vitro* inhibition. An effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates was therefore cosidered 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 administrations. (see section 6 Warnings and precautions).

Coadministration 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 C_{min} and C_{2h} 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 6 Warnings and precautions). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

9. Women of child-bearing potential, pregnancy and breast-feeding and fertility

Women of child-bearing potential

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

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed.

Based on non-clinical findings, male and female fertility may be compromised by treatment with Afinitor (see section 14 Non-clinical safety data).

Pregnancy

There are no adequate data from the use of Afinitor in pregnant women. Studies in animals have shown reproductive toxicity effects including embryo-toxicity and feto-toxicity (see section 14 Non-clinical safety data). The potential risk for humans is unknown. Afinitor should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. Male patients taking Afinitor should not be prohibited from attempting to father children.

Breast-feeding

It is not known whether everolimus is excreted in breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking Afinitor should therefore not breast-feed.

10. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Afinitor.

11. 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.

12. Clinical pharmacology

Pharmacotherapeutic group, ATC code

Protein kinase inhibitors, L01XE10.

Mechanism of action (MOA)

Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signalling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream on the PI3K/AKT pathway, which is dysregulated in the majority of human cancers.

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 Akt, HER2, or 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.

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 activation function domain 1 of the estrogen receptor, which is responsible for ligand-independent receptor activation. In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

Pharmacodynamics (PD)

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor, specifically targeting the mTOR-raptor signal transduction complex (mTORC1). mTOR is a key serine-threonine kinase in the PI3K /AKT signaling cascade, a pathway known to be dysregulated in the majority of human cancers. Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signaling capacity. 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-BP). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits 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). 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.

In a mouse neuronal model of TSC in which TSC1is ablated in most neurons during cortical development, everolimus improved median survival from 33 days to more than 100 days, and behavior, phenotype, and weight gain all also markedly improved. There was brain penetration, with accumulation over time with repetitive treatment, and effective reduction of levels of phospho-S6, a downstream marker of mTORC1. Neurofilament abnormalities, myelination, and cell enlargement were all improved by the treatment, although dysplastic neuronal features persisted, and there were only modest changes in dendritic spine density and length. Mice treated with everolimus for 23 days only (postnatal days 7 to 30) displayed a persistent improvement in phenotype, with median survival of 78 days. In summary, everolimus is a highly active in this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 and Akt signaling and, consequently, cell size and myelination.

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%. Light fat meals reduced AUC by 32% and C_{max} by 42%.

Food, however, had no apparent effect on the post absorption phase concentration-time profile 24 h post-dose.

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.

Patients with 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 6 Warnings and precautions and 4 Dosage and administration).

Patients with renal impairment

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

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

Pediatric patients

- There is no indication for use of Afinitor in the pediatric cancer population (see section 4 Dosage and administration) or in paediatric patients with TSC who have renal angiomyolipoma in the absence of SEGA.
- 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.

Elderly patients

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

Ethnicity

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

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

Exposure-response relationships

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

13. 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. Patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) or matching placebo in addition to open-label exemestane (25 mg daily). Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

The primary endpoint for the 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 randomised 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 245-fold prolongation in median PFS (median: 7.82months versus 3.19 months), resulting in a 55% risk reduction of progression or death (PFS HR 0.45; 95% CI: 0.38, 0.54; one-sided log-rank test p-value <0.0001 per local investigator assessment (see Table 13-1 and Figure 13-1)].

The analysis of PFS based on independent central radiological assessment was supportive and showed a 2.7 -fold prolongation in median progression-free-survival (11.01months versus 4.14 months), resulting in a 62% risk reduction of progression or death (PFS HR 0.38; 95% CI: 0.31, 0.48; one-sided log-rank test p-value<0.0001 (see Table 13-1 and Figure 13-2).

Objective response as per investigator assessment based on RECIST was observed in 12.6% of patients (95% CI:9.8,15.9) in the everolimus + exemestane arm vs. 1.7 % (95% CI: 0.5 - 4.2) in the placebo + exemestane arm (p<0.0001 for comparison between arms). Clinical benefit rate for everolimus + exemestane was 51.3% vs. 26.4 % in the control arm; p<0.0001(see Table 13-1).

Table 13-1 BOLERO-2 – efficacy results

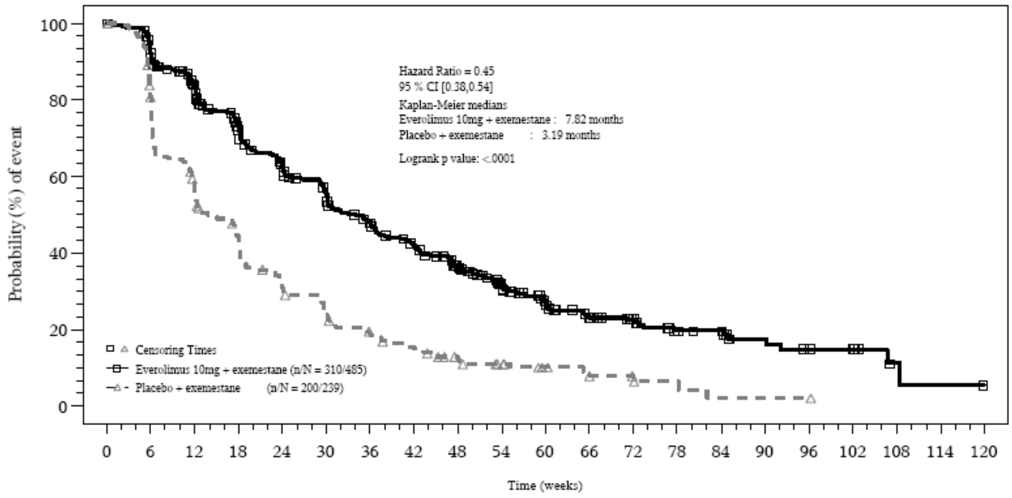
Analysis	Afinitor[a] N = 485	Placebo[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.82 (6.93 to 8.48)	3.19 (2.76 to 4.14)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.01 (9.66 to 15.01)	4.14 (2.89 to 5.55)	0.38 (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 13-3).

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

Figure 13-1 BOLERO-2 - Kaplan-Meier progression-free survival curves (investigator radiological review)

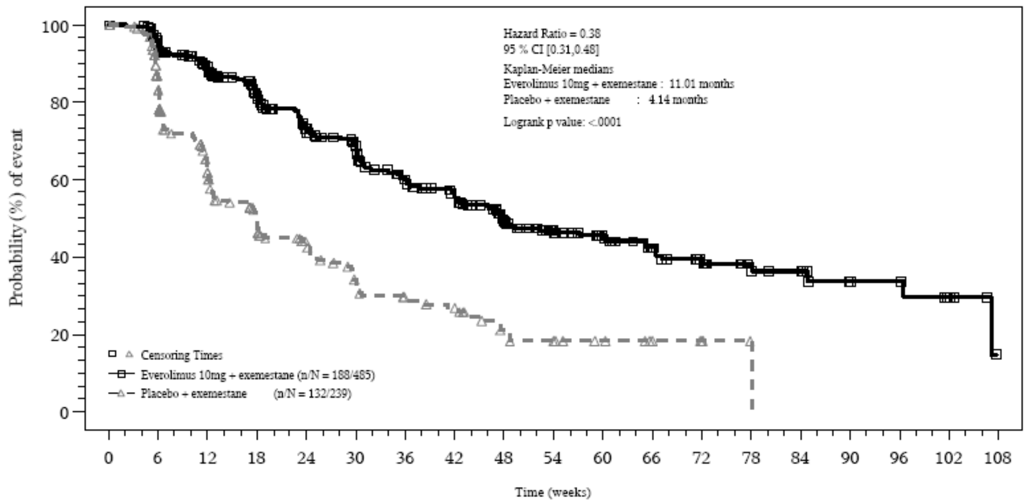


Number of Patients still at Risk

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

- One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.

Figure 13-2 BOLERO-2 - Kaplan-Meier progression-free survival curves (independent radiological review)

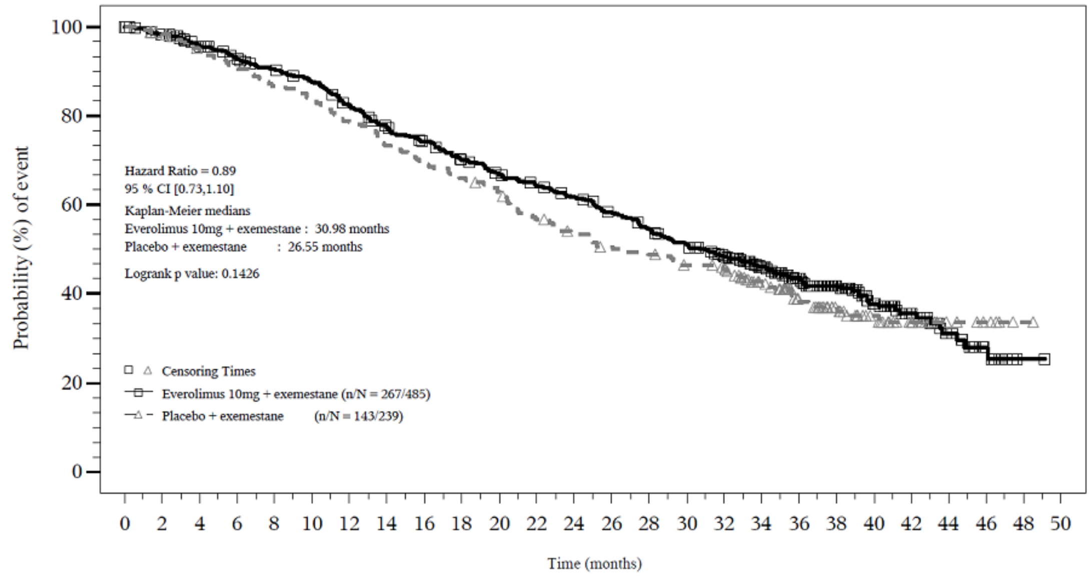


Number of Patients still at Risk

Time(weeks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108
Everolimus	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
Placebo	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

- One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.

Figure 13-3 BOLERO-2 – Kaplan-Meier plot of overall survival (Full Analysis Set)



Number of Patients still at Risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Everolimus	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
Placebo	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS

The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analyzed subgroups, a positive treatment effect was seen with everolimus + exemestane with an estimated hazard ratio vs. placebo + exemestane ranging from 0.25 to 0.62 (see Table 13-2. Subgroup analyses demonstrated a homogeneous and consistent treatment effect irrespective of sensitivity to prior hormonal therapy and presence of visceral metastasis, and across major demographic and prognostic subgroups.

Table 13-2 Analysis of PFS as per investigator by subgroup - Full Analysis Set

	n	Everolimus + exemestane	Placebo + exemestane	HR[1]	95% CI
		Median PFS (months)			
Sensitivity to prior hormonal therapy					
No	114	6.83	2.83	0.55	0.35, 0.84
Yes	610	8.05	3.94	0.43	0.35, 0.53
Presence of visceral metastasis					
No	318	9.86	4.21	0.41	0.31, 0.55
Yes	406	6.83	2.76	0.47	0.37, 0.60

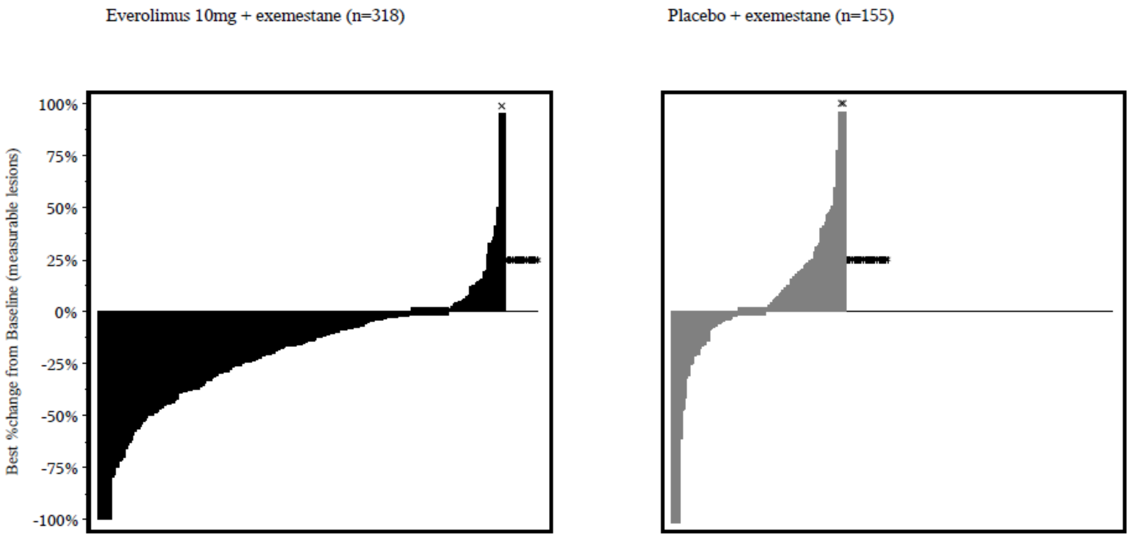
	n	Everolimus + exemestane	Placebo + exemestane	HR[1]	95% CI
		Median PFS (months)			
Age group					
< 65 years	449	8.31	2.92	0.38	0.30, 0.47
≥ 65 years	275	6.83	4.01	0.59	0.43, 0.80
Region					
Asia	137	8.48	4.14	0.60	0.40, 0.92
Europe	275	7.16	2.83	0.45	0.34, 0.61
North America	274	8.41	2.96	0.38	0.28, 0.51
Other	38	4.53	1.48	0.40	0.19, 0.87
Japanese					
Japanese	106	8.54	4.17	0.58	0.36, 0.94
Non-Japanese	618	7.16	2.83	0.42	0.35, 0.51
Prior chemotherapy					
No	231	6.97	3.45	0.53	0.39, 0.73
Yes	493	8.18	3.19	0.41	0.33, 0.52

	n	Everolimus + exemestane	Placebo + exemestane	HR[1]	95% CI
		Median PFS (months)			
Bone only lesions at baseline					
No	573	6.90	2.83	0.48	0.39, 0.58
Yes	151	12.88	5.29	0.33	0.21, 0.53
Baseline ECOG performance status					
0	435	8.25	4.11	0.48	0.38, 0.60
1 or 2	274	6.93	2.76	0.39	0.29, 0.52
PgR status					
Negative	184	6.93	2.83	0.51	0.36, 0.73
Positive	523	8.08	3.32	0.41	0.33, 0.51
Race					
Asian	143	8.48	4.14	0.62	0.41, 0.94
Caucasian	547	7.36	2.96	0.42	0.34, 0.51
Other	34	6.93	1.41	0.25	0.10, 0.66
Prior use of hormonal therapy other than NSAI					
No	326	7.00	4.11	0.52	0.40, 0.68
Yes	398	8.11	2.76	0.39	0.31, 0.50
Number of organs involved					
1	219	11.50	4.37	0.40	0.28, 0.57
2	232	6.70	3.45	0.52	0.39, 0.71
≥ 3	271	6.93	2.56	0.41	0.30, 0.54
Number of prior therapies					
1	118	8.05	4.37	0.60	0.39, 0.92
2	217	6.93	2.96	0.45	0.32, 0.63
≥ 3	389	8.18	2.96	0.41	0.32, 0.52

[1] *Hazard ratio obtained using unstratified Cox model*

Tumor reduction was also evident from the corresponding waterfall plot. Results indicate that 70.8% of patients in the everolimus + exemestane arm experienced tumor shrinkage versus 29.7% for placebo + exemestane (Figure 13-4 Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per investigator).

Figure 13-4 Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per investigator



	Everolimus	Placebo
Decrease in best percentage change from baseline	70.75% (225)	29.68% (46)
Zero change in best percentage change from baseline	8.49% (27)	12.90% (20)
Increase in best percentage change from baseline	12.58% (40)	36.77% (57)
* % change in target lesion available but contradicted by Overall lesion response = PD	8.18% (26)	20.65% (32)

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 (11.04 months versus 4.6 months), resulting in a 65% risk reduction in PFS (HR 0.35; 95%CI: 0.27, 0.45; p<0.0001) (see Table 13-3 and Figure 13-5).

RADIANT-3 enrolled patients with advanced pNET whose disease had progressed within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes/no) and by WHO performance status (0 *vs*. 1 and 2). Treatment with somatostatin analogs was allowed as part of BSC.

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. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label Afinitor.

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 10mg/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.

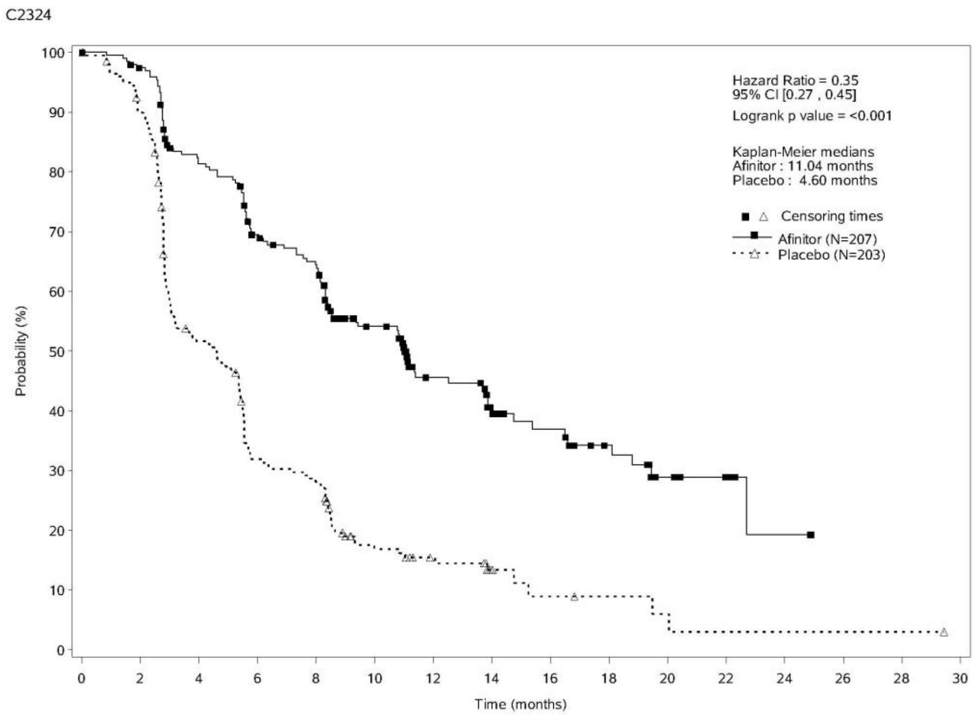
Table 13-3 RADIANT-3 – Progression Free Survival results

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

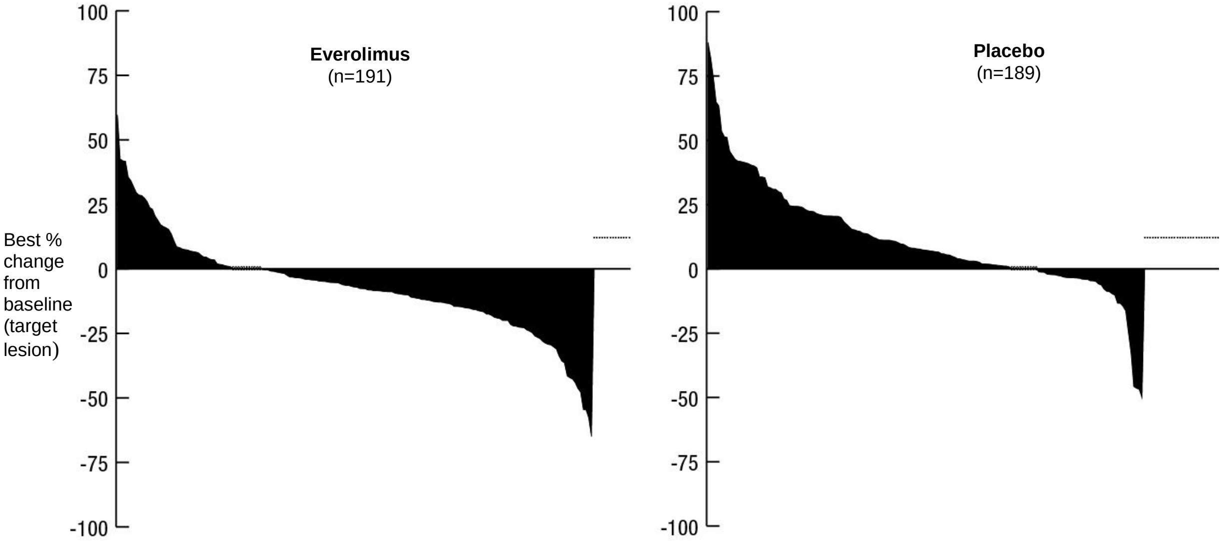
Figure 13-5 RADIANT-3 – Kaplan-Meier progression-free survival curves (investigator radiological review)



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 from the corresponding waterfall plot. Results indicate that 64.4% of patients in the everolimus arm experienced tumor shrinkage versus 20.6% for placebo (Figure 13-6).

Figure 13-6 Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per investigator assessment



	Everolimus n (%)	Placebo n (%)
Decrease in best percentage change from baseline	123 (64.4%)	39 (20.6%)
Zero change in best percentage change from baseline	11 (5.8%)	10 (5.3%)
Increase in best percentage change from baseline	43 (22.5%)	112 (59.3%)
% change in target lesion available but contradicted by overall lesion response = PD*	14 (7.3%)	28 (14.8%)

*Patients for whom the best % change in target lesions was either unavailable or was contradicted by overall lesion response of "unknown" were excluded from this analysis. Percentages use remaining number of evaluable patients (n) as denominator.

The overall survival results are not yet mature and no statistically significant difference in OS was noted (HR=0.99 (95% CI 0.68 to 1.43) in an updated analysis). Crossover of >72% of patients from placebo to open-label Afinitor following disease progression likely confounded the detection of any treatment-related difference in OS.

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 (16.43 months versus 11.33 months; HR 0.77; 95%CI: 0.59 to 1.00; one sided p=0.026), resulting in a 23% risk reduction in primary PFS (see Table 13-4 and Figure 13-7). 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. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label Afinitor.

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

In total, 429 patients were randomized 1:1 to receive either Afinitor 10mg/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 13-4 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

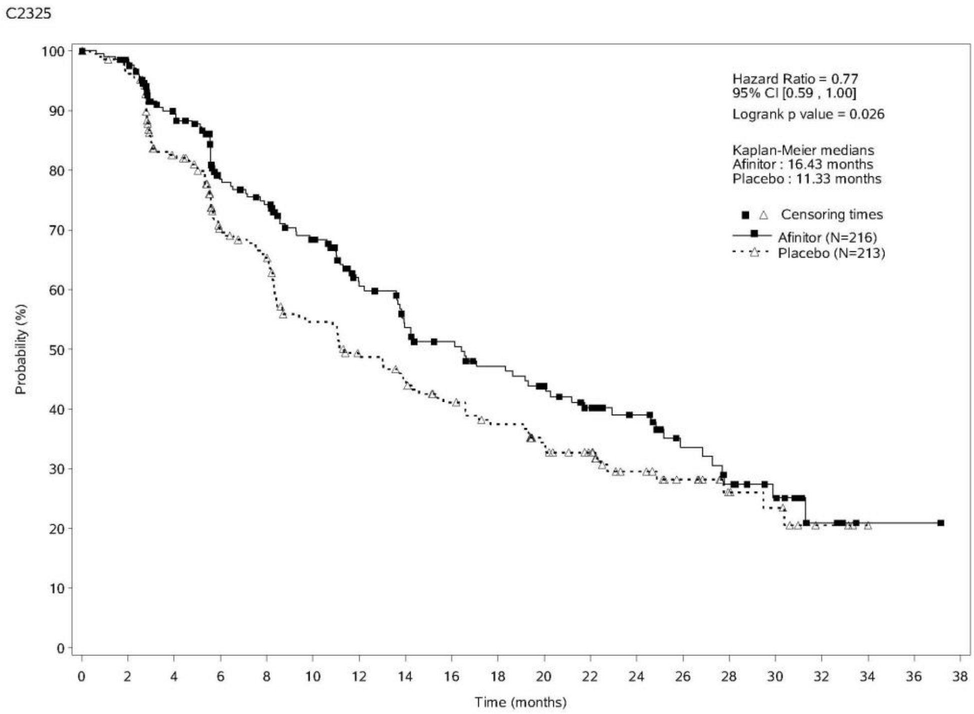
[a] Plus depot octreotide (Sandostatin LAR®)

[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). A Cox model with Inverse Probability of Censoring Weights (IPCW) was used to address and correct for informative censoring and imbalances in baseline characteristics between the two study arms. The estimated HR (95% CI) from the IPCW analysis was 0.60 (0.44 to 0.84) in favor of Afinitor.

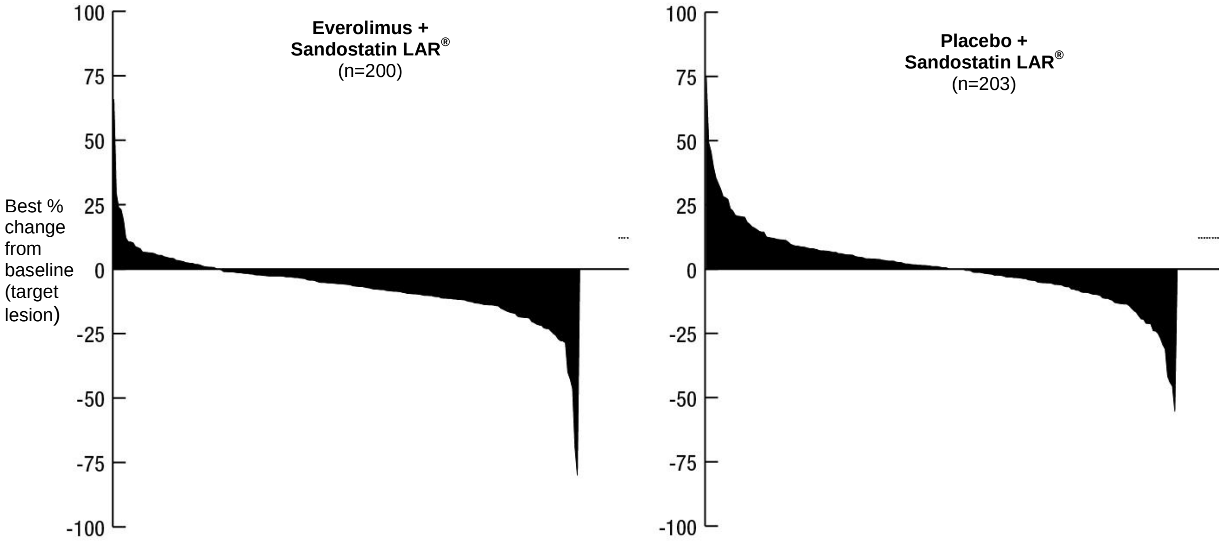
Figure 13-7 RADIANT-2 – Kaplan-Meier progression-free survival curves (independent radiological review)



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 from the corresponding waterfall plot. Results indicate that 75.0% of patients in the everolimus plus depot octreotide (Sandostatin LAR®) arm experienced tumor shrinkage versus 44.8% in the placebo plus depot octreotide (Sandostatin LAR®) arm (Figure 13-8).

Figure 13-8 Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per independent radiology review



	Everolimus + Sandostatin LAR® n (%)	Placebo + Sandostatin LAR® n (%)
Decrease in best percentage change from baseline	150 (75.0%)	91 (44.8%)
Increase in best percentage change from baseline	43 (21.5%)	94 (46.3%)
Zero change in best percentage change from baseline	3 (1.5%)	10 (4.9%)
% change in target lesion available but contradicted by overall lesion response = PD*	4 (2.0%)	8 (3.9%)

*Patients for whom the best % change in target lesions was either unavailable or was contradicted by overall lesion response of "unknown" were excluded from the analysis. Percentages use remaining number of evaluable patients (n) as denominator.

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. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- *vs* intermediate- *vs* poor-risk groups) and prior anticancer therapy (1 *vs* 2 prior VEGFR-TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid 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. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label Afinitor 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were 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 13-5 and Figure 13-9).

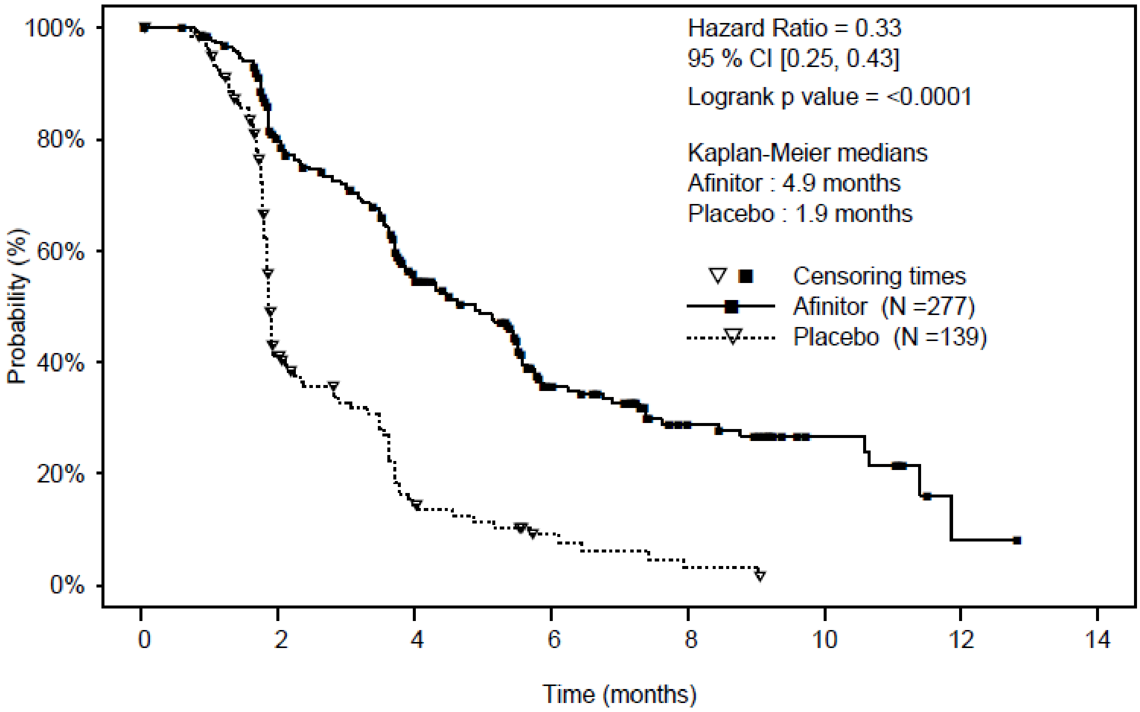
Table 13-5 RECORD-1 - Progression Free Survival results

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]
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	2.8	0.25	<0.001 [b]

Population	N	Afinitor N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value
		(4.9 to 11.4)	(1.9 to 3.6)	(0.16 to 0.42)	
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

Figure 13-9 RECORD-1 - Kaplan-Meier progression-free survival curves



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 randomised, 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); the difference observed was both clinically relevant and statistically significant. Response rates were 41.8% (95% CI: 30.8, 53.4) for the Afinitor arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (see Table 13-6). No patient receiving Afinitor required surgery or embolization, while one patient on placebo required bilateral renal embolization.

Long term follow-up

Cumulative long term experience with a median duration of exposure of 125.7 weeks (range 2 to 201) demonstrated the angiomyolipoma response rate had increased to 53.6% (95% CI: 43.9, 63.0).

Table 13-6 EXIST-2 - Angiomyolipoma response

	Primary Analysis[3]			Long term efficacy follow-up[4]
	Afinitor N=79	**Placebo N=39**	**p-value**	**Afinitor N=112**
Primary analysis[3]				
Angiomyolipoma response rate[1,2] - %	**41.8**	**0**	**<0.0001**	**53.6**
95% CI	(30.8, 53.4)	(0.0, 9.0)		(43.9, 63.0)
Best overall angiomyolipoma response - %				
Response	41.8	0		53.6
Stable disease	40.5	79.5		33.9
Progression	1.3	5.1		0.9
Not evaluable	16.5	15.4		11.6

[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

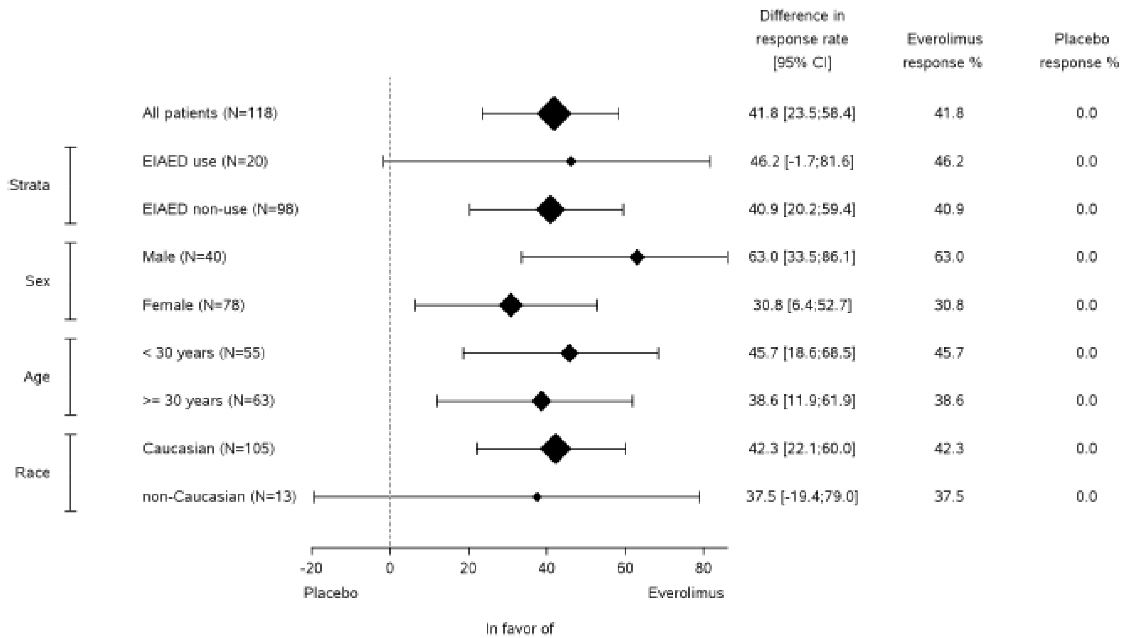
[4]Long term efficacy analysis includes patients who crossed over from the placebo group; median duration of exposure of 125.7 wks

Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, age, and race)(see Table 13-7, Figure 13-10).

Table 13-7 EXIST-2 - Angiomyolipoma response by subgroup

Subgroup	Afinitor		Placebo		Difference in response rates (95% CI)
	N	Responders %	N	Responders %	
All patients	**79**	**41.8**	**39**	**0**	**41.8 (23.5, 58.4)**
Modified strata					
EIAED use	13	46.2	7	0	46.2 (-1.7, 81.6)
No EIAED use	66	40.9	32	0	40.9 (20.2, 59.4)
Sex					
Male	27	63.0	13	0	63.0 (33.5, 86.1)
Female	52	30.8	26	0	30.8 (6.4, 52.7)
Age					
<30 years	35	45.7	20	0	45.7 (18.7, 68.5)
≥30 years	44	38.6	19	0	38.6 (11.9, 61.9)
Race					
Caucasian	71	42.3	34	0	42.3 (22.1, 60.0)
Non-Caucasian	8	37.5	5	0	37.5 (-19.4, 79.0)

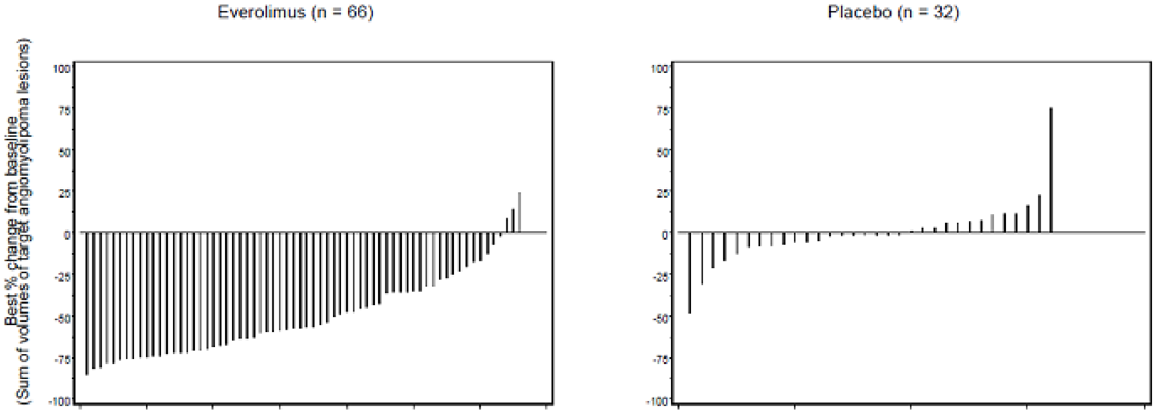
Figure 13-10 EXIST-2 – Forest plot of angiomyolipoma response by subgroup



The waterfall plots provide a graphical representation of the reduction in angiomyolipoma volume (

Figure 13-11); 95.5% of patients in the Afinitor arm experienced angiomyolipoma shrinkage versus 59.4% in the placebo arm.

Figure 13-11 EXIST-2 - Angiomyolipoma shrinkage: best percentage change from baseline[1,2]



[1] *Per independent central radiology review*

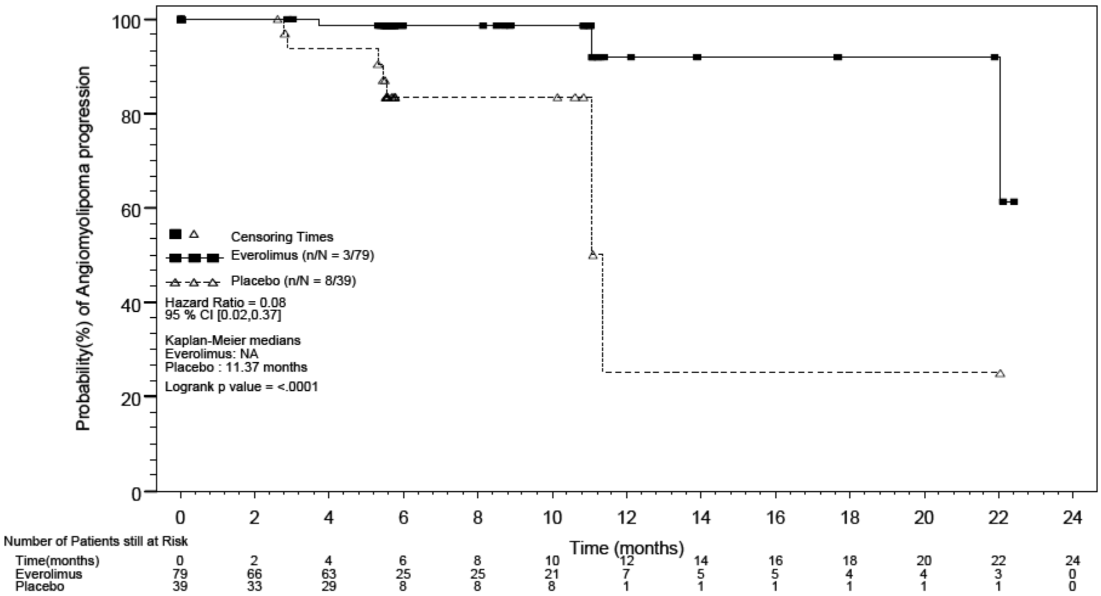
[2] *Patients for whom the best % change in sum of volumes of target angiomyolipoma lesions was not available and patients with overall angiomyolipoma response = Not evaluable were excluded from the graph.*

Angiomyolipoma shrinkage was evident within the initial 12 weeks of treatment with Afinitor: 75.7% of patients had ≥ 30% reductions and 41.9% had ≥ 50% reductions at the time of the first radiological evaluation (Week 12). Sustained reductions were evident at subsequent time points; at Week 24, 80.3% of patients had ≥ 30% reductions and 54.9% had ≥ 50% reductions.

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) (

Figure 13-12). 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% of patients in the Afinitor arm compared with 20.5% 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.

Figure 13-12 Kaplan-Meier plot of time to angiomyolipoma progression[1,2]



[1] p-value is obtained from the one-sided stratified log-rank test.
[2] Hazard ratio <1 implies reduced risk of angiomyolipoma progression in the Everolimus group.

[1] Per independent central radiology review

[2] Angiomyolipoma progression was defined as: ≥ 25% increase in the sum of angiomyolipoma volume relative to baseline, or appearance of new angiomyolipoma ≥ 1.0 cm in longest diameter, or an increase in renal volume > 20% from nadir, or Grade ≥ 2 angiomyolipoma-related bleeding.

Afinitor also demonstrated clinically meaningful and statistically significant improvements in skin lesion response (p=0.0002), with response rates of 26.0% (95% CI: 16.6, 37.2) for the Afinitor arm and 0% (95% CI: 0.0, 9.5) for the placebo arm (see Table 13-8).

Table 13-8 EXIST-2 - Best overall skin lesion response

	Afinitor N=77	Placebo N=37	p-value[1]
Skin lesion response rate [1,2,3,4] - %	**26.0**	**0**	**0.0002**

95% CI	(16.6, 37.2)	(0.0, 9.5)
Best overall skin lesion response – %		
Complete clinical response	0	0
Partial response	26.0	0
Stable disease	71.4	97.3
Progressive disease	0	0
Not evaluable	2.6	2.7

[1] Complete clinical response or partial response
[2] Per investigator
[3] Skin lesion response was determined for the 114 patients with ≥ 1 skin lesion at baseline.
[4] Skin lesion response was defined as ≥ 50% improvement in appearance of skin lesions by Physician's Global Assessment of Clinical Condition.

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.

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. Of the enrolled patients, 79.5% had bilateral SEGAs, 42.7% had ≥ 2 target SEGA lesions, 25.6% had inferior growth, 9.4% had evidence of deep parenchymal invasion, 6.8% had radiographic evidence of hydrocephalus, and 6.8% had undergone prior SEGA-related surgery; 94.0% had skin lesions at baseline and 37.6% had target renal angiomyolipomas (at least one angiomyolipoma ≥ 1 cm in longest diameter). 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). Response rates were 34.6% (95% CI: 24.2, 46.2) for the Afinitor arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (see Table 13-9). In addition, all 8 patients on the Afinitor arm who had radiographic evidence of hydrocephalus at baseline had a decrease in ventricular volume and no patient required surgical intervention during the course of this study.

Long term follow-up

Cumulative long term experience with a median duration of exposure of 127.4 weeks (range 8.1 to 176.1) demonstrated the SEGA response rate had increased to 48.6% (95% CI: 39.0, 58.3).

Table 13-9 EXIST-1 – SEGA response

	Primary analysis[3]			Long term efficacy follow-up[4]
	AFINITOR N=78	Placebo N=39	p-value	Afinitor N=111
Primary analysis				
SEGA response rate1,2 - (%)	34.6	0	<0.0001	48.6
95% CI	24.2, 46.2	0.0, 9.0		39.0, 58.3
Best overall SEGA response - (%)				
Response	34.6	0		48.6
Stable disease	62.8	92.3		48.6
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]*Long term efficacy analysis includes patients who crossed over from the placebo group; median duration of exposure of 127.4 wks*

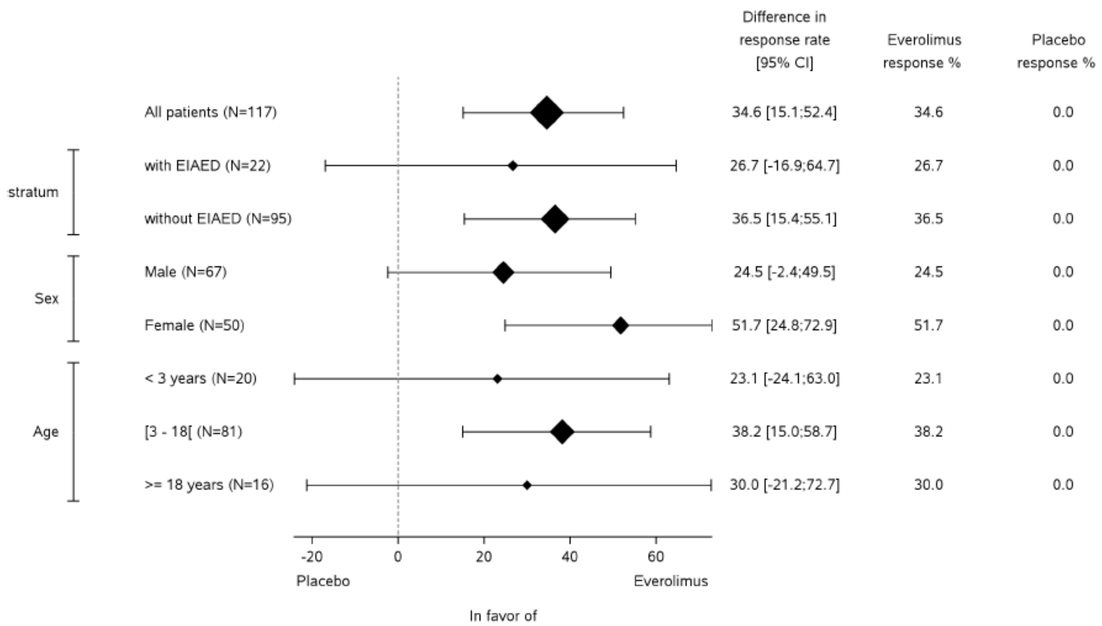
Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, and age) (see Table 13-10, Figure 13-13)

Table 13-10 EXIST-1 - SEGA response by subgroup

Subgroup	Afinitor N	Afinitor Responders %	Placebo N	Placebo Responders %	Difference in response rates (95% CI)
All patients	78	34.6	39	0	34.6 (15.1, 52.4)
Modified strata					
EIAED use	15	26.7	7	0	26.7 (-16.9, 64.7)
No EIAED use	63	36.5	32	0	36.5 (15.4, 55.1)
Sex					
Male	49	24.5	18	0	24.5 (-2.4, 49.5)
Female	29	51.7	21	0	51.7 (24.8, 72.9)
Age					
<3 years	13	23.1	7	0	23.1 (-24.1, 63.0)

3-<18 years	55	38.2	26	0	38.2 (15.0, 58.7)
≥18 years	10	30.0	6	0	30.0 (-21.2, 72.7)

Figure 13-13 EXIST-1 - Forest plot of SEGA response by subgroup



For the primary analysis of the double blind period, SEGA shrinkage was evident within the initial 12 weeks of treatment with Afinitor: 73.0% of patients had ≥ 30% reductions and 29.7% had ≥ 50% reductions at the time of the first radiological evaluation (Week 12). Sustained reductions were evident at subsequent time points; at Week 24, 78.4% of patients had ≥ 30% reductions and 41.9% had ≥ 50% reductions.

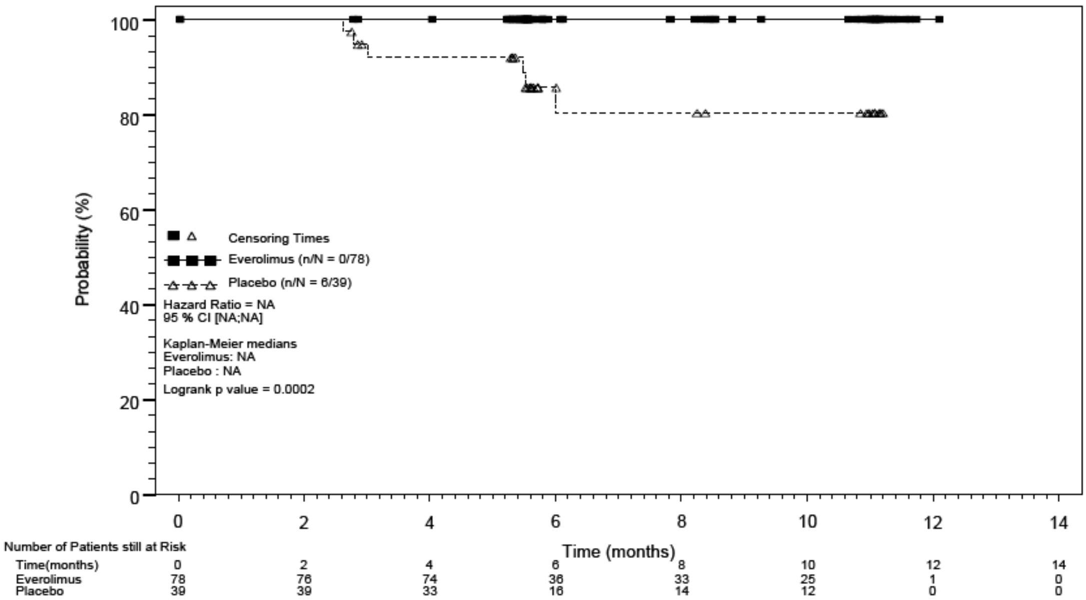
In the expanded population of the extension phase of the study following cross-over of placebo patients, a high proportion of patients reported SEGA volume reductions of ≥ 30% (67.9%, 74.3%, and 75.0% of patients, respectively) and ≥ 50% (27.4%, 37.1%, and 46.2% of patients, respectively) at Weeks 12, 24, and 48. Favorable results persisted at Week 96 and Week 144: 72.4% and 75.9% of patients achieved a reduction of ≥ 30% and 47.4 and 37.9% of patients achieved a reduction of ≥ 50% at Week 96 and Week 144, respectively. The reduction from baseline in sum of volumes apparent at Week 12 persisted over time.

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) (

Figure 13-14). Estimated progression-free rates at 6 months were 100% for the Afinitor arm and 85.7% for the placebo arm.

Figure 13-14 EXIST-1 - Kaplan-Meier plot of time to SEGA progression



[1] Per independent central radiology review

[2] SEGA progression was defined as: ≥ 25% increase in the sum of SEGA volume relative to baseline, or unequivocal worsening of non-target SEGA lesions, or appearance of new SEGA ≥ 1.0 cm in longest diameter, or new or worsening hydrocephalus

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 (see Table 13-11).

Table 13-11 EXIST-1 - best overall skin lesion response

	Afinitor N=72	Placebo N=38	p-value
Skin lesion response rate[1,2,3,4] - %	41.7	10.5	0.0004
95% CI	(30.2, 53.9)	(2.9, 24.8)	
Best overall skin lesion response - %			
Complete clinical response	0	0	
Partial response	41.7	10.5	
Stable disease	58.3	86.8	
Progression	0	0	
Not evaluable	0	2.6	

	Afinitor N=72	Placebo N=38	p-value

[1] Complete clinical response or partial response

[2] Per investigator

[3] Skin lesion response was determined for the 110 patients with ≥ 1 skin lesion at baseline.

[4] Skin lesion response was defined as ≥ 50% improvement in appearance of skin lesions by Physician's Global Assessment of Clinical Condition.

Phase II trial in patients with TSC who have SEGA

Study CRAD001C2485, a prospective, open-label, phase II study was conducted to evaluate the safety and efficacy of Afinitor in patients with SEGA. Serial radiological evidence of SEGA growth was required for entry.

Change in SEGA volume during the core 6-month treatment phase, as assessed via an independent central radiology review, was the primary efficacy endpoint. After the core treatment phase, patients could enter into the extension treatment phase where SEGA volume was assessed every 6 months.

In total, 28 patients received treatment with Afinitor; median age was 11 years (range 3 to 34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA including 12 patients with SEGA in the contralateral ventricle. Median duration of exposure was 57.6 months (range: 4.7 – 70.5 months)Afinitor was associated with a clinically relevant and statistically significant reduction in primary SEGA volume at 6 months relative to baseline ($p<0.001$). Tumor shrinkage was most rapid during the initial 3 months of treatment with evidence of a sustained response at subsequent timepoints (see Table 13-12). No patient developed new lesions, worsening hydrocephalus, increased intracranial pressure, and none required surgical resection or other therapy for SEGA.

Table 13-12 C2485- Response of primary SEGA lesion to Afinitor therapy

SEGA volume (cm^3)	Independent central review							
	Baseline N=28	Month 3 N=26	Month 6 N=27	Month 12 N=26	Month 24 N=24	Month 36 N=23	Month 48 N=24	Month 60 N=9
Primary tumor volume								
Mean (standard deviation)	2.45 (2.813)	1.47 (1.646)	1.33 (1.497)	1.26 (1.526)	1.19 (1.042)	1.26 (1.298)	1.16 (0.961)	1.13 (0.873)
Median	1.74	0.84	0.93	0.84	0.94	1.12	1.02	1.17
Range	0.49 - 14.23	0.25 - 8.32	0.31 - 7.98	0.29 - 8.18	0.20 - 4.63	0.22 – 6.52	0.18 - 4.19	0.21 - 2.91
Reduction from baseline								
Mean (standard deviation)		1.08 (1.338)	1.19 (1.433)	1.07 (1.276)	1.25 (1.994)	1.41 (1.814)	1.43 (2.267)	1.78 (1.689)
Median		0.63	0.83	0.85	0.71	0.71	0.83	1.64
Range		-0.12 – 5.91	0.06 – 6.25	0.02 – 6.05	-0.55 – 9.60	0.15 – 7.71–	0.00 - 10.96	-0.02 - 4.54
Percentage reduction from baseline, n (%)								
≥ 50%		10 (38.5)	9 (33.3)	9 (34.6)	12 (50.0)	10 (43.5)	14 (58.3)	5 (55.6)
≥ 30%		17 (65.4)	21 (77.8)	20 (76.9)	19 (79.2)	18 (78.3)	19 (79.2)	7 (77.8)
> 0%		25 (96.2)	27 (100.0)	26 (100.0)	23 (95.8)	23 (100.0)	23 (95.8)	8 (88.9)
No change		0	0	0	0	0	1 (4.2)	0
% Increase		1 (3.8)	0	0	1 (4.2)	0	0	1 (11.1)

The primary analysis was supported by the:

- Change in primary SEGA volume as per local investigator assessment ($p<0.001$), with 75% and 39% of patients experiencing reductions of ≥30% and ≥50%, respectively.
- Change in total SEGA volume as per independent central review ($p<0.001$) or local investigator assessment ($p<0.001$).

One patient met the prespecified criteria for treatment success (>75% reduction in SEGA volume) and was temporarily taken off trial therapy; however, SEGA re-growth was evident at the next assessment at 4.5 months and treatment was restarted.

Long-term follow-up to a median duration of 57.6 months (range: 4.7 – 70.5 months)demonstrated sustained efficacy.

14. Non-clinical safety data

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

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

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

In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the $AUC_{0\text{-}24h}$ 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 foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions.

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.

15. Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 25ºC.

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

Keep out of the reach and sight of children.

Instructions for use and handling

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

Manufacturer:

Novartis Pharma Stein AG, Switzerland

For Novartis Pharma AG, Basel, Switzerland

License Holder:

Novartis Pharma Services AG

36 Shacham St., Petach-Tikva.

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו- 1986

התרופה משווקת על פי מרשם רופא בלבד.

אפיניטור טבליות 2.5 מ"ג, 5 מ"ג, 10 מ"ג

כל טבליה מכילה:

אפיניטור 2.5 מ"ג:	אוורולימוס 2.5 מ"ג	Everolimus 2.5 mg
אפיניטור 5 מ"ג:	אוורולימוס 5 מ"ג	Everolimus 5 mg
אפיניטור 10 מ"ג:	אוורולימוס 10 מ"ג	Everolimus 10 mg

חומרים בלתי פעילים ואלרגניים: ראה סעיף 6 "מידע נוסף".

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. שמור עלון זה. יתכן ויהיה לך צורך לקרוא אותו שוב. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול במחלתך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם דומה.

1. למה מיועדת התרופה?

אפיניטור טבליות 2.5, 5 ו- 10 מ"ג:

- טיפול בחולים עם גידול מוחי מסוג אסטרוציטומה סאבאפנדימאלית של תאים ענקיים [Subependymal Giant Cell Astrocytoma (SEGA)] הקשור בטרשת קרשית (tuberous sclerosis complex).
- טיפול בחולים מבוגרים עם גידול בכליה הנקרא אנגיומיוליפומה [angiomyolipoma (AML)] כאשר הגידול הכלייתי אינו מצריך ניתוח מיידי. סוג זה של גידולים קשור במצב גנטי המכונה טרשת קרשית (tuberous sclerosis complex).
- טיפול בחולים עם גידולים נוירואנדוקרינים מתקדמים שמקורם בלבלב שאינם ניתנים להסרה באמצעות ניתוח, שהתקדמו מקומית או מחלה גרורתית. הבטיחות והיעילות של אפיניטור בטיפול בחולים עם גידולים קרצינואידים עדיין לא מבוססים.
- טיפול בסרטן שד מתקדם עם קולטן הורמונאלי חיובי ו HER2 שלילי, בשילוב עם אקסמסטן, בנשים בגיל הבלות, ללא מחלה גרורתית מפושטת באיברים פנימיים המלווה בתסמינים, לאחר חזרה של המחלה או התקדמות של המחלה בעקבות טיפול של מעכבי ארומאטאז שאינם סטרואידלים.
- לטיפול בסרטן כליות מתקדם (advanced Renal Cell Carcinoma [RCC]) לאחר כישלון בטיפול בתרופות מסוימות.

קבוצה תרפויטית: Anticancer medicine

אפיניטור זו תרופה אנטי-סרטנית שיכולה לחסום תאים מסוימים בגוף מלגדול. היא מכילה את החומר הפעיל הנקרא אוורולימוס.

במידה ויש לך שאלות כלשהן על אפיניטור או מדוע תרופה זו נרשמה עבורך, פנה לרופא שלך.

2. לפני שימוש בתרופה

X **אין להשתמש בתרופה אם:**

- אם הינך אלרגי (בעל רגישות יתר) ל- everolimus, לתרופות דומות כגון sirolimus (rapamycin) , temsirolimus או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה, המפורטים בסעיף 6 "מידע נוסף" בעלון זה.

במקרה זה, **יש ליידע את הרופא מבלי ליטול אפיניטור.**
במידה והינך חושב שהינך אלרגי, יש להתייעץ עם הרופא.

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

יש לעקוב אחר כל הוראות הרופא בזהירות. הן עלולות להיות שונות מהמידע הכללי המופיע בעלון זה.

אפיניטור יירשם לך רק על-ידי רופא עם ניסיון בשימוש בטיפולים נוגדי סרטן או בטיפול בחולים עם טרשת קרשית.

! לפני הטיפול באפיניטור, ספר לרופא אם אחד מהמצבים להלן חל עליך:

- אם יש לך בעיות כלשהן עם הכבד שלך או היו לך מחלות כלשהן אשר יתכן והשפיעו על הכבד שלך. יתכן ויהיה צורך לשנות את המינון של אפיניטור שהינך נוטל או להפסיק את הטיפול באופן זמני או קבוע.
- אם יש לך סוכרת (רמות גבוהות של סוכר בדם). הטיפול באפיניטור עלול לגרום לעלייה של רמות הסוכר בדם ולהחמיר סוכרת. הדבר עלול לגרום לצורך בטיפול תרופתי. יש לספר לרופא אם אתה מרגיש צמא מוגבר או עלייה בתכיפות במתן שתן.
- אם יש לך זיהומים כלשהם. יש צורך לטפל בזיהום שלך לפני התחלת הטיפול באפיניטור. כמו כן יש ליידע את הרופא לפני נטילת התרופה אם הינך מצוי בסיכון לזיהומים - זאת היות ואפיניטור מחליש את המערכת החיסונית .
- אם הינך סובל או סבלת בעבר מבעיות בכליות.
- אם היתה לך בעבר דלקת כבד B [הפטיטיס B], מאחר ועשויה להיות הפעלה מחדש במהלך הטיפול עם אפיניטור (ראה סעיף 4: "תופעות לוואי").
- אם אתה נוטל תרופות אחרות (ראה בסעיף זה את תת הסעיף: "נטילת תרופות אחרות").
- אם הינך בהריון, חושבת שאת יכולה להיות בהריון, או אם את חושבת שיש סיכוי שתהיי בהריון בזמן הטיפול באפיניטור (ראי בסעיף זה את תת הסעיף "הריון והנקה").
- אם הינך מניקה (ראי בסעיף זה את תת הסעיף "הריון והנקה").
- חיסון: אם עליך ליטול חיסון כלשהו בזמן השימוש בתרופה – היוועץ ברופא (ראה בסעיף זה את תת הסעיף "חיסונים").
- אם יש לך רמות גבוהות של כולסטרול או שומני דם אחרים.
- אם עברת לאחרונה ניתוח, או אם עדיין יש לך פצעים מניתוח: אפיניטור עלול להעלות את הסיכון להתעוררות בעיה בריפוי פצעים.

! מה עליך לדעת במהלך הטיפול באפיניטור:

- **בעיות בריאה או בנשימה:** מטופלים יכולים לפתח בעיות בנשימה או בריאה, כגון תהליך דלקתי ברקמת הריאה (pneumonitis), תסחיף ריאתי או תסמונת מצוקה נשימתית חדה. **פנה לרופא מיד** במידה ואתה חש בסימפטומי ריאה/נשימה חדשים או בסימפטומים קיימים מוחמרים כגון: שיעול, כאב בחזה או קוצר נשימה, היות ויתכן כי לבעיות חמורות בריאה או בנשימה יהיו השלכות מסכנות חיים. יתכן והרופא שלך יצטרך להורות לך להפסיק את הטיפול באפיניטור לזמן מה או באופן קבוע, ולהוסיף תרופה על מנת לעזור עם תופעת לוואי זו. יתכן והרופא שלך יתחיל מחדש את הטיפול באפיניטור במינון נמוך יותר.

- **זיהום:** אפיניטור עשוי לגרום לך להיות יותר חשוף לזיהום (כגון דלקת ריאות [pneumonia], זיהום בדרכי השתן, זיהום פטרייתי או זיהום ויראלי כגון הפעלה מחדש של דלקת כבד B [הפטיטיס B]). זיהומים מסוימים עלולים להיות חמורים ועם השלכות מסכנות חיים. **פנה לרופא מיד** במידה ויש לך סימפטומים של זיהום. יתכן והרופא שלך יצטרך להורות לך להפסיק את הטיפול באפיניטור לזמן מה או באופן קבוע, ולהוסיף תרופה על מנת לעזור עם תופעת לוואי זו.
- **תגובות אלרגיות:** אם במהלך הטיפול באפיניטור הינך מפתח סימפטומים כגון נפיחות של דרכי הנשימה או הלשון ו/או קשיי נשימה, אלו עשויים להיות סימנים של תגובה אלרגית חמורה. במקרה כזה יש לפנות מיידית לרופא.
- **כיבים בפה:** מטופלים יכולים לפתח כיבים ופצעים בפה. **פנה לרופא** במידה ויש לך כאב או אי נוחות בפה או שיש לך פצעים פתוחים בפה. יתכן והרופא שלך יצטרך להורות לך להפסיק את הטיפול באפיניטור לזמן מה או באופן קבוע. יתכן ותצטרך טיפול עם ג'ל או שטיפת פה. שטיפות פה מסוימות וג'לים מסוימים יכולים להחמיר את מצב הכיבים, לכן אין לנסות שום דבר ללא בדיקה עם הרופא שלך. יתכן והרופא שלך יתחיל מחדש את הטיפול באפיניטור באותו המינון או במינון נמוך יותר.
- **הפרעות בכליות:** במספר חולים אשר נטלו אפיניטור נצפתה אי ספיקת כליות. אי ספיקת כליות עלולה להיות חמורה ועם השלכות מסכנות חיים. הרופא שלך יעקוב אחר תפקוד הכליות שלך במהלך הטיפול עם אפיניטור.
- **חיסון:** אם עליך לקבל חיסון במהלך הטיפול עם אפיניטור, פנה קודם לרופא שלך לקבלת ייעוץ. עבור ילדים חולים עם SEGA שאינם דורשים טיפול מיידי, השלם את סדרת החיסונים החיים המומלצת בגיל הילדות לפני תחילת הטיפול, בהתאם להנחיות הטיפול המקומיות.
  אין לקבל חיסון חי ואין לשהות בקרבת אנשים אשר חוסנו לאחרונה בתרכיב חיסון מסוג זה.

! נטילת תרופות אחרות

אפיניטור עלול להתנגש עם תרופות אחרות. יתכן ויהיה צורך לשנות את המינון של אפיניטור.
אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח:

- תרופות מסוימות המשמשות לטיפול בזיהומים. אלו כוללות תרופות לטיפול במחלות פטרייתיות (תרופות אנטי-פטרייתיות כגון: קטוקונאזול, איטראקונאזול , ווריקונאזול ופלוקונאזול) או תרופות לטיפול בסוגים של זיהומים בקטריאליים (אנטיביוטיקות כגון: קלריתרומיצין, טליתרומיצין או אריתרומיצין).
- תרופות מסוימות המשמשות לטיפול בשחפת, כגון: ריפאמפיצין או ריפאבוטין.
- St. John's Wort - מוצר צמחי המשמש לטיפול בדיכאון ומצבים אחרים (ידוע גם בשם *Hypericum Perforatum*).
- קורטיקוסטרואידים מסוימים כגון: דקסאמתאזון, פרדניזון או פרדניזולון.
- תרופות אשר מפסיקות פרכוסים או התקפי אפילפסיה (תרופות אנטיאפילפטיות כגון: פניטואין, קארבאמזפין או פנובארביטל).
- תרופות מסוימות המשמשות לטיפול באיידס (HIV) כגון: ריטונאויר, אמפרנאויר, פוסאמפרנאויר, אפאוירנז או נביראפין, סאקוינאויר, אינדינאויר, אטאזנאויר, נלפינאויר.
- תרופות מסוימות המשמשות לטיפול בבעיות לב או לחץ דם גבוה (כגון: וראפאמיל או דילטיאזם).
- תרופות המדכאות את פעילות מערכת החיסון כגון: ציקלוספורין, תרופה המשמשת למניעת דחיית שתל על-ידי הגוף.
- מעכבי האנזים angiotensin converting enzyme (ACE), תרופות המשמשות לטיפול בלחץ דם גבוה או בעיות לב וכלי דם אחרות.
- אפרפיטנט, תרופה המשמשת למניעת בחילה והקאה.
- מידאזולם, תרופה המשמשת לטיפול בהתקפים חריפים, או משמשת להרגעה לפני או במהלך ניתוח או הליך רפואי.
- נפאזודון, תרופה המשמשת לטיפול בדיכאון.

יש להימנע מתרופות אלו במהלך הטיפול שלך באפיניטור. אם הינך נוטל אחת מתרופות אלו, יתכן והרופא ירשום לך תרופה אחרת על מנת למנוע הופעת תופעות לוואי נוספות הנובעות משילוב של תרופות מסוימות

עם אפיניטור. מטופלים עם SEGA אשר נוטלים תרופות נגד פרכוסים, שינוי במינון של התרופה נגד פרכוסים (העלאה או הורדה) עלול להצריך שינוי במינון אפיניטור.

במהלך הטיפול באפיניטור אין להתחיל טיפול בתרופה חדשה ללא בדיקה מוקדמת עם הרופא שרשם לך אפיניטור. זה כולל תרופות מרשם, תרופות ללא מרשם, תרופות צמחיות או אלטרנטיביות.

! שימוש בתרופה ומזון
יש ליטול אפיניטור בכל יום באותו הזמן, בעקביות עם מזון או בעקביות ללא מזון.

אין לשתות מיץ אשכוליות או לאכול אשכוליות, קרמבולה (star fruit) או תפוזי סביליה. זה עלול להעלות את רמת אפיניטור בדם, יתכן אף לרמה מזיקה.

! אנשים מבוגרים יותר (גיל 65 ומעלה)
במידה ואתה בן 65 שנים ומעלה, אתה יכול ליטול אפיניטור באותו מינון כמו מבוגרים צעירים יותר.

! ילדים ומתבגרים (מתחת לגיל 18)

- טיפול בסרטן שד מתקדם עם קולטן הורמונאלי חיובי, סרטן כליות מתקדם או בגידולים נוירואנדוקריניים מתקדמים שמקורם בלבלב:
אין להשתמש באפיניטור בילדים ומתבגרים.
- טיפול בטרשת קרשית (tuberous sclerosis complex) עם אנגיומיוליפומה כלייתית:
התרופה אינה מיועדת לשימוש בילדים ומתבגרים עם טרשת קרשית שיש להם אנגיומיוליפומה כלייתית.
- טיפול בטרשת קרשית (tuberous sclerosis complex) עם SEGA:
ניתן להשתמש באפיניטור בילדים ומתבגרים בעלי תפקודי כבד תקינים.

! הריון והנקה
אפיניטור יכול לפגוע בעובר ולכן אינו מומלץ במהלך ההריון. יש לספר לרופא אם את בהריון או חושבת שהינך יכולה להיות בהריון.
אפיניטור עלול לפגוע בתינוק. אין להניק במהלך הטיפול באפיניטור. אמרי לרופא במידה והינך מניקה.
אם הינך בהריון או מניקה יש להיוועץ ברופא או ברוקח לפני השימוש בתרופות כלשהן.

! נשים בגיל הפוריות
נשים בגיל הפוריות צריכות להשתמש באמצעי מניעה יעילים ביותר (כגון קונדומים או גלולות) במהלך הטיפול באפיניטור ולמשך 8 שבועות לאחר הפסקת הטיפול.
במידה והינך חושבת שנכנסת להריון, פני לרופא לייעוץ לפני נטילה נוספת של אפיניטור.

! פוריות
יתכן ויש לאפיניטור השפעה על פוריות הגבר והאישה. היעדרות של מחזור הווסת בנשים שקודם לכן קיבלו ווסת (secondary amenorrhea) נצפתה בנשים מסוימות אשר נטלו אפיניטור. אם הנכם מעוניינים בהריון - היוועצו ברופא.

! נהיגה ושימוש במכונות
אין לנהוג או להפעיל מכונות מסוכנות בזמן השימוש בתרופה אם הינך חש בעייפות, היות ועייפות יתרה הינה תופעת לוואי שכיחה של אפיניטור. באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקרבת
הכביש וכדומה.

! מידע חשוב על חלק מהמרכיבים של התרופה
אפיניטור מכיל לקטוז. אם נאמר לך על-ידי רופא שהינך רגיש לסוכרים מסוימים, היוועץ ברופא לפני נטילת אפיניטור.

3. כיצד תשתמש בתרופה?

תמיד יש להשתמש לפי הוראות הרופא.

עליך לבדוק עם הרופא או הרוקח אם אינך בטוח.

המינון ואופן הטיפול יקבעו על-ידי הרופא בלבד. אל תיטול יותר ממה שהרופא אמר לך. אין לשנות את המינון מבלי לשוחח עם הרופא.

במידה והינך סובל מתופעות לוואי מסוימות מנטילת אפיניטור יתכן והרופא שלך יצטרך להפחית את מינון האפיניטור שאתה צריך ליטול; או להורות לך להפסיק את הטיפול באפיניטור לזמן מה או באופן קבוע.

אין לעבור על המנה המומלצת.

מתי ליטול אפיניטור
יש ליטול אפיניטור פעם ביום בכל יום בערך באותו הזמן. חשוב ליטול אפיניטור בערך באותו הזמן בכל יום, על מנת שתהיה כמות קבועה של תרופה בזרם הדם.

כיצד ליטול אפיניטור
יש ליטול טבליות אפיניטור דרך הפה.
אין ללעוס, לחצות או לכתוש את הטבליות! יש לבלוע את הטבליות בשלמותן עם כוס מים.

במידה ואתה נוטל טבליות אפיניטור לטיפול בטרשת קרשית (tuberous sclerosis complex) עם SEGA ואם אינך מסוגל לבלוע את הטבליות, אתה יכול לערבב אותן בתוך כוס של מים:
- יש לשים את הטבליה(ות) הנדרשת(ות) בתוך כוס המכילה בקירוב 30 מ"ל (2 כפות) של מים.
- יש לערבב בעדינות את התוכן עד אשר הטבליה(ות) עובר(ות) פירוק (בקירוב כ-7 דקות) ולשתות באופן מיידי.
- יש לשטוף את הכוס עם כמות מים זהה (בקירוב 30 מ"ל), ולשתות את כל התוכן על מנת לוודא שאתה מקבל את המנה המלאה של אפיניטור.

הנחיות לשימוש וטיפול באפיניטור טבליות
מטפלים מומלצים להימנע ממגע עם תרחיף של אפיניטור. יש לשטוף ידיים ביסודיות לפני ואחרי ההכנה של התרחיף.

משך הטיפול באפיניטור
יש להמשיך ליטול טבליות אפיניטור כל עוד הרופא הורה לך.

בדיקות ומעקב
בתקופת הטיפול בתרופה זו עליך לעבור בדיקות דם שגרתיות, אשר ינטרו את כמות תאי הדם (תאי דם לבנים, תאי דם אדומים וטסיות) בגופך על מנת לראות אם לאפיניטור יש השפעה שאינה רצויה על תאים אלו. יבוצעו גם בדיקות דם כדי לנטר את תפקוד הכליות שלך (רמות של קראטינין, חנקן אוריאה בדם או חלבון בשתן), תפקוד הכבד (רמה של טרנסאמינאזות) ורמות הסוכר והשומנים בדם שלך, היות וגם הללו עשויים להיות מושפעים מאפיניטור.
במידה והינך נוטל אפיניטור לטיפול בטרשת קרשית עם SEGA, בדיקות דם שגרתיות נדרשות על מנת למדוד כמה אפיניטור יש בדמך כי זה יעזור לרופא שלך להחליט כמה אפיניטור אתה צריך ליטול.

אם נטלת בטעות מינון גבוה יותר
אם נטלת מנת יתר או אם בטעות בלע ילד או אדם אחר מן התרופה, פנה מיד לרופא או לחדר מיון של בית חולים, והבא אריזת התרופה איתך. יתכן ויהיה צורך בטיפול רפואי דחוף.

אם שכחת ליטול את התרופה
אם שכחת ליטול תרופה זו בזמן הדרוש, ניתן ליטול עד 6 שעות מהזמן הרגיל אשר אתה נוטל את התכשיר.

אם נזכרת לאחר יותר מ-6 שעות מהזמן הרגיל שבו אתה נוטל אפיניטור, יש לדלג על המנה של אותו היום. ביום הבא, קח את המנה הבאה בזמן הרגיל והיוועץ ברופא. אין ליטול מנה כפולה כדי לפצות על מנה שנשכחה.

יש להתמיד בטיפול כפי שהומלץ על-ידי הרופא.

גם אם חל שיפור במצב בריאותך, אין להפסיק הטיפול בתרופה ללא התייעצות עם הרופא.

אין ליטול תרופות בחושך! בדוק התווית והמנה <u>בכל פעם</u> שהינך נוטל תרופה. הרכב משקפיים אם הינך זקוק להם.

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

4. <u>תופעות לוואי</u>

כמו בכל תרופה, השימוש באפיניטור עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן. אפיניטור יכול גם להשפיע על תוצאות בדיקות דם מסוימות.

הפסק ליטול אפיניטור ופנה לעזרה רפואית באופן מיידי, אם אתה או ילדך חווה אחד מהסימנים הבאים של תגובה אלרגית:

- קשיים בנשימה או בבליעה
- נפיחות של הפנים, שפתיים, לשון או גרון
- גירוד חמור בעור, עם פריחה אדומה או נפיחויות בולטות

תופעות לוואי מסוימות עשויות להיות רציניות:

יש לפנות מיד לרופא אם אתה חווה אחת מתופעות לוואי אלו, היות ויכולות להיות לכך השלכות מסכנות חיים.

<u>תופעות לוואי רציניות שנצפו במהלך הטיפול בסרטן שד מתקדם עם קולטן הורמונאלי חיובי ,סרטן כליות מתקדם ובגידולים נוירואנדוקריניים מתקדמים שמקורם בלבלב.</u>

תופעות לוואי שכיחות מאוד (very common) תופעות שמופיעות ביותר ממשתמש אחד מעשרה

- עלייה בטמפרטורת הגוף או צמרמורות, סימנים של זיהומים
- חום, שיעול, קשיי נשימה, צפצופים, סימנים של דלקת בריאה (תהליך דלקתי ברקמת הריאה [pneumonitis])

תופעות לוואי שכיחות (common) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 100

- צמא מופרז, מתן שתן בתדירות גבוהה, תיאבון מוגבר עם ירידה במשקל, עייפות (סוכרת)
- דימום, לדוגמא בדופן המעיים
- ירידה חמורה במתן השתן, סימנים של כשל כלייתי (אי ספיקת כליות)

תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 1,000

- קוצר נשימה, קשיים בנשימה בזמן שכיבה, נפיחות בכפות הרגליים או הרגליים, סימנים של אי ספיקת לב
- פריחה, גירוד, סרפדת, קשיים בנשימה או בבליעה, סחרחורת, סימנים של תגובה אלרגית חמורה (רגישות יתר)
- נפיחות ו/או כאב באחת הרגליים, בדרך כלל בשוק. אדמומיות או עור חמים באזור המושפע, סימנים של חסימת כלי דם (וריד/עורק) ברגליים עקב קריש דם.
- התקפה פתאומית של קוצר נשימה, כאב בחזה או שיעול דמי, סימנים פוטנציאלים של תסחיף ריאתי (מצב המתרחש כאשר עורק אחד או יותר בריאות שלך נחסם)
- ירידה חמורה במתן השתן, נפיחות ברגליים, הרגשת בלבול וכאב בגב, סימנים של כשל כלייתי פתאומי (אי ספיקת כליות חדה)
- חום, פריחה, כאבים במפרקים ודלקת, עייפות, אובדן תיאבון, בחילה, צהבת (הצהבה של העור), כאב בבטן ימנית עליונה, צואה בהירה או שתן כהה (יכולים גם כן להיות סימנים להפעלה מחודשת של דלקת הכבד מסוג B [הפטיטיס B])

תופעות לוואי נדירות (rare) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 10,000

- קוצר נשימה או נשימה מהירה (סימנים של תסמונת מצוקה נשימתית חדה)
- נפיחות של דרכי-הנשימה או הלשון, עם או ללא הפרעה בנשימה (אנגיואדמה)

תופעות לוואי רציניות שנצפו <u>במהלך הטיפול בחולים עם גידול בכליה הנקרא אנגיומיוליפומה הקשור בטרשת קרשית ובחולים עם גידול מוחי מסוג אסטרוציטומה סאבאפנדימאלית של תאים ענקיים הקשור בטרשת קרשית.</u>

תופעות לוואי שכיחות מאוד (very common) תופעות שמופיעות ביותר ממשתמש אחד מעשרה

- חום, שיעול, קשיי נשימה, צפצופים, סימנים של דלקת בריאה (דלקת ריאות [pneumonia])

תופעות לוואי שכיחות (common) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 100

- נפיחות, תחושת כובד או הידוק, כאב, תנועתיות מוגבלת של חלקי הגוף, סימן אפשרי להצטברות נוזלים חריגה ברקמה רכה עקב חסימה במערכת-הלימפה (lymphedema)

תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 1,000

- פריחה של שלפוחיות קטנות מלאות נוזל המופיעות על עור אדמומי, סימנים של זיהום ויראלי בעל פוטנציאל להיות חמור (הרפס זוסטר [שלבקת חוגרת])
- פריחה, גירוד,סרפדת, קשיים בנשימה או בבליעה, סחרחורת, סימנים של תגובה אלרגית חמורה (רגישות יתר)
- נפיחות של דרכי-הנשימה או הלשון, עם או ללא הפרעה בנשימה (אנגיואדמה)
- חום, שיעול, קשיי נשימה, צפצופים, סימנים של דלקת בריאה (תהליך דלקתי ברקמת הריאה [pneumonitis])

תופעות לוואי נוספות:

אם תופעות לוואי אלו מחמירות, אנא פנה לרופא שלך, רוקח או איש צוות רפואי. רוב תופעות הלוואי הן קלות עד בינוניות ובדרך כלל יעלמו לאחר מספר ימים של הפסקת טיפול.

תופעות לוואי אחרות שנצפו במהלך הטיפול בסרטן שד מתקדם עם קולטן הורמונאלי חיובי, סרטן כליות מתקדם או גידולים נוירואנדוקרינים מתקדמים שמקורם בלבלב.

תופעות לוואי שכיחות מאוד (very common) תופעות שמופיעות ביותר ממשתמש אחד מעשרה

רמות גבוהות של סוכר בדם (היפרגליקמיה) ; אובדן תיאבון; הפרעה בטעם; כאב ראש; דימום מהאף; כיבים בפה; אי נוחות בבטן כולל בחילה, שלשול; פריחה בעור; גרד (pruritus) ; הרגשת חולשה או עייפות; עייפות, קוצר נשימה, סחרחורת, חיוורון, סימנים של רמה נמוכה בתאי דם אדומים (אנמיה) ; נפיחות בזרועות, ידיים, כפות הרגליים, קרסוליים או אזור אחר בגוף (סימנים של בצקת); איבוד משקל; רמה גבוהה של שומנים בדם (יתר כולסטרול בדם) ; שינויים בתוצאות בדיקות דם כגון : ירידה ברמת ההמוגלובין.
אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.**

תופעות לוואי שכיחות (common) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 100

דימום או חבלה ספונטניים, סימנים של רמה נמוכה של טסיות (תרומבוציטופניה); צמא, ירידה במתן השתן, שתן כהה, עור סמוק ויבש, אי שקט (סימנים של התייבשות); בעיות בשינה (נדודי שינה); כאב ראש, סחרחורת, סימנים של לחץ דם גבוה (יתר לחץ דם); חום, כאב גרון או כיבים בפה עקב זיהומים, סימנים של רמה נמוכה של תאי דם לבנים (לויקופניה, לימפופניה, נויטרופניה); שיעול; קוצר נשימה (דיספניאה) ; חום; זיהום בדופן הפנימית של הפה, קיבה, מעיים; יובש בפה; צרבת (קשיי עיכול); הקאות; קושי בבליעה(דיספגיה); כאב בטן; אקנה; פריחה וכאב של כפות הידיים או כפות הרגליים (hand foot syndrome); האדמה של העור (אדמנת); כאב במפרקים; כאב בפה; הפרעות במחזור הווסת כגון מחזורי

ווסת לא סדירים; רמה גבוהה של שומנים בדם (יתר שומן בדם, עלייה בטריגליצרידים); רמה נמוכה של אשלגן בדם (היפוקלמיה); רמה נמוכה של זרחן בדם (היפופוספטמיה); רמה נמוכה של סידן בדם (היפוקלצמיה), יובש בעור; הפרעות בציפורניים; נשירת שיער; חבורות בעור; בדיקות דם של הכבד שאינן תקינות (עלייה באלאנין ובאספרטט אמינוטרנספראז); בדיקות דם של הכליה שאינן תקינות (עלייה בקריאטינין); חלבון בשתן; הפרשות מהעיניים המלוות בגרד, אודם ונפיחות; נפיחות של העפעפיים; השרה של שכבות עור ותאים, מצב דלקתי של העור המאופיין באודם, גרד, ציסטות המדליפות נוזלים שלאחר מכן עוטות קליפה, מתקלפות או נעשות קשיחות (dermatitis acneiform); ציפורניים פריכות, שבירה של ציפורני הידיים והרגליים.
אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.**

תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 1,000
חולשה, דימום או חבלה ספונטניים וזיהומים שכיחים עם סימנים כגון חום, צמרמורות, גרון כואב או כיבים בפה, סימנים של רמה נמוכה של תאי דם (פנציטופניה); אובדן חוש הטעם (ageusia); שיעול דמי (יריקת דם); העדר מחזור (אל-וסת); מתן שתן בתדירות גבוהה יותר במהלך היום; כאבים בחזה.
אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.**

תופעות לוואי נדירות (rare) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 10,000
עייפות, קוצר נשימה, סחרחורת, חיוורון, סימנים של רמה נמוכה של תאי דם אדומים (סוג של אנמיה הנקראת pure red cell aplasia); החלמה לא תקינה של פצעים.
אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.**

תופעות לוואי נוספות שנצפו במהלך הטיפול בטרשת קרשית (tuberous sclerosis complex).

תופעות לוואי שכיחות מאוד (very common) תופעות שמופיעות ביותר ממשתמש אחד מעשרה
דלקת של דרכי הנשימה העליונות, כאב גרון ונזלת (nasopharyngitis), כאב ראש, לחץ בעיניים, באף או באזור הלחיים, סימנים של דלקת בסינוסים והמעברים של האף (סינוסיטיס); רמה גבוהה של שומנים בדם (יתר כולסטרול בדם); כיבים בפה; אקנה (חטטת); הפרעות במחזור הווסת כגון היעדר של מחזור הווסת (אל-וסת), מחזורי ווסת לא סדירים.
אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.**

תופעות לוואי שכיחות (common) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 100
זיהום בדרכי השתן; חניכיים נפוחות ומדממות, סימנים לזיהום בחניכיים (gingivitis); זיהום באוזן התיכונה; דלקת בעור (צלוליטיס); גרון כואב (דלקת לוע); דימום או חבלה ספונטניים, סימנים של רמה נמוכה של טסיות (תרומבוציטופניה); רמה נמוכה של זרחן בדם (היפופוספטמיה); רמה גבוהה של שומנים בדם (יתר שומן בדם, עלייה בטריגליצרידים); ירידה בתיאבון; עייפות, קוצר נשימה, סחרחורת, חיוורון, סימנים של רמה נמוכה של תאי דם אדומים (אנמיה); חום, כאב גרון או כיבים בפה עקב זיהומים, סימנים של רמה נמוכה של תאי דם לבנים (לויקופניה, לימפופניה, נויטרופניה); כאב ראש, סחרחורת, סימנים של לחץ דם גבוה (יתר לחץ דם); כאב ראש; הפרעה בטעם; שיעול; דימום מהאף; שלשול; כאב בפה; אי נוחות בבטן כמו בחילה; הקאה; כאב בטן; כאב חמור בבטן התחתונה ובאזור האגן שעשוי להיות חד, עם שיבושים במחזור הווסת (ציסטה בשחלה); כמות עודפת של גזים במעיים (נפיחות); עצירות; כאב בטן, בחילה, הקאה, שלשול, נפיחות של הבטן, סימנים לדלקת של הקרום הרירי המרפד את הקיבה (דלקת קיבה, דלקת קיבה ומעי ויראלית); פריחה בעור; מצב דלקתי של העור המאופיין באודם, גרד, ציסטות המדליפות נוזלים שלאחר מכן עוטות קליפה, מתקלפות או נעשות קשיחות (dermatitis acneiform); יובש בעור; חלבון בשתן; הרגשת עייפות; חוסר יכולת לישון (נדודי שינה); הפרעות במחזור הווסת כגון עיכוב במחזור הווסת, דימום יתר בווסת (menorrhagia) או דימום וגינלי; חוסר שקט; חום; רמה גבוהה של אנזים בדם הנקרא לקטאט דהידרוגינאז, הנותן מידע על בריאותם של איברים מסוימים; רמה גבוהה יותר של ההורמון בדם המעורר ביוץ (עלייה בהורמון הצהבה LH).
אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.**

תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 1,000
שיעול עם ליחה, כאב בחזה, חום, סימנים של דלקת בדרכי הנשימה (דלקת סימפונות ויראלית/ברונכיטיס ויראלי); תוקפנות; רמה גבוהה יותר של הורמון הרבייה הנשי בדם (עלייה בהורמון מגרה זקיק, FSH), עוויתות שרירים, חום, שתן אדום-חום, סימנים של הפרעת שרירים (rhabdomyolysis).

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא הוזכרה בעלון, עליך להתייעץ עם הרופא.

תופעות לוואי ותגובות בין-תרופתיות בילדים:
על ההורים לדווח לרופא המטפל על כל תופעת לוואי וכן על כל תרופה נוספת הניתנת לילד/ ה !

5. איך לאחסן את התרופה?

- מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וראייתם של ילדים ו/או תינוקות ועל-ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
- אין לאחסן מעל ל- 25°C.
- יש לאחסן באריזה המקורית כדי להגן מאור ולחות. אין להשתמש אם אתה מבחין כי האריזה פגומה.
- פתח את אריזת הבליסטר מיד לפני נטילת טבליות אפיניטור.

6. מידע נוסף

- **נוסף על החומר הפעיל התרופה מכילה גם:**

Lactose anhydrous, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and butylated hydroxytoluene.

כל טבליה של אפיניטור 2.5 מ״ג מכילה 71.875 מ״ג lactose anhydrous ו-2.450 מ״ג lactose monohydrate.

כל טבליה של אפיניטור 5 מ״ג מכילה 143.75 מ״ג lactose anhydrous ו- 4.90 מ״ג lactose monohydrate.

כל טבליה של אפיניטור 10 מ״ג מכילה 287.50 מ״ג lactose anhydrous ו-9.80 מ״ג lactose monohydrate.

- **כיצד נראית התרופה ומה תוכן האריזה**
הטבליות הן בצבע לבן עד מעט צהבהב, מאורכות, עם קצוות משופעים וללא חריץ חיתוך.
2.5 מ״ג: הטבליות חרותות עם הדפס "LCL" בצד אחד ו- "NVR" בצד השני.
5 מ״ג: הטבליות חרותות עם הדפס "5" בצד אחד ו- "NVR" בצד השני.
10 מ״ג: הטבליות חרותות עם הדפס "UHE" בצד אחד ו- "NVR" בצד השני.
כל אריזה מכילה 30 טבליות.

- **בעל הרישום וכתובתו:** נוברטיס פארמה סרויסס איי ג׳י, רח׳ שחם 36, פתח-תקווה.

- **שם היצרן וכתובתו:** נוברטיס פארמה שטיין איי ג׳י, שוויץ עבור נוברטיס פארמה איי ג׳י, בזל, שוויץ.

- עלון זה נבדק ואושר ע״י משרד הבריאות בתאריך: דצמבר 2014.

- מס' רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות:

אפיניטור 2.5 מ"ג: 146 82 33388
אפיניטור 5 מ"ג: 142 86 32045
אפיניטור 10 מ"ג: 142 87 32046

- לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.