הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 05.2013)

תאריך: 20 במאי 2015

שם תכשיר באנגלית ומספר הרישום: Afinitor 2.5mg, 5mg, 10mg [33388, 32045-6]

שם בעל הרישום: נוברטיס פארמה סרויסס איי ג'י

טופס זה מיועד לפירוט ההחמרות בלבד!

טקסט שחור – טקסט מאושר
טקסט עם קו תחתי – הוספת טקסט לעלון המאושר
~~טקסט עם קו חוצה~~ – מחיקת טקסט מהעלון המאושר
טקסט המסומן בצהוב – החמרה

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
~~***Dosing in TSC with***~~ ***SEGA associated with TSC*** Careful titration may be required to obtain the optimal therapeutic effect. Doses that will be tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus and may contribute to this variance (see section 4.5). ….. Everolimus whole blood trough concentrations should be assessed at least 1 week after commencing treatment for patients <3 years of age and approximately 2 weeks after commencing treatment for patients ≥3 years of age. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml….. ~~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.~~	***Dosing in TSC with SEGA TSC*** 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.	***4.2 Posology and method of administration***

Table 2 Afinitor dose adjustment ~~and management~~ recommendations ~~for adverse drug reactions~~ **ראו נספח 2** ***Therapeutic drug monitoring for patients treated for TSC*** *.....For patients <3 years of age, trough concentrations should be monitored at least 1 week after start of treatment or after any change in dose or pharmaceutical form (see section 5.2).* *Therapeutic drug monitoring of everolimus blood concentrations, using a validated assay, is an option to be considered for patients treated for renal angiomyolipoma associated with TSC (see section 5.1) after initiation of or change in co-administration of CYP3A4 inducers or inhibitors (see sections 4.4 and 4.5) or after any change in hepatic status (Child-Pugh) (see "Hepatic impairment" below and section 5.2).* ***~~4.3 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~~	**Table 1 Afinitor dose adjustment and management recommendations for adverse drug reactions** **ראו נספח 1** ***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.	

~~trough concentration within the target range to obtain optimal efficacy, subject to tolerability.~~		
Haemorrhage Serious cases of haemorrhage, some with a fatal outcome, have been reported in patients treated with everolimus in the oncology setting. No serious cases of renal haemorrhage were reported in the TSC setting. Caution is advised in patients taking Afinitor, particularly during concomitant use with active substances known to affect platelet function or that can increase the risk of haemorrhage as well as in patients with a history of bleeding disorders. Healthcare professionals and patients should be vigilant for signs and symptoms of bleeding throughout the treatment period, especially if risk factors for haemorrhage are combined. **Interactions:** Concomitant treatment with ***potent*** CYP3A4 inhibitors result in dramatically increased blood concentrations of everolimus (see section 4.5).		**4.4 Special warnings and precautions for use**
Table 2 Effects of other active substances on everolimus **ראו נספח 4** (בטקסט החדש חלק זה מופיע בפורמט טבלה) **Women of childbearing potential/ Contraception in males and females** Women of childbearing potential ~~should be advised to~~ must use a highly effective method of contraception… **Pregnancy** ~~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.~~	**8. Interactions** **ראו נספח 3** **Women of childbearing potential** Women of childbearing potential should be advised to use a highly effective method of contraception… **Pregnancy** 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.	**4.5 Interaction with other medicinal products and other forms of interaction** **4.6 Fertility, Pregnancy and Lactation**

Afinitor is not recommended during pregnancy and in women of childbearing potential not using contraception.		
~~No studies on the effects on the ability to drive and use machines have been performed.~~ Afinitor may have a minor or moderate influence on the ability to drive and use machines.	No studies on the effects on the ability to drive and use machines have been performed.	**4.7 Effects on ability to drive and use machines**

Table ~~7-1~~3 Adverse ~~drug~~ reactions reported in ~~from~~ oncology clinical studies~~trials~~ **ראו נספח 6** The most frequent adverse reactions….. ~~acne,~~ menstruation irregular, acne, sinusitis, otitis media and pneumonia. **Table 3-1 Adverse reactions reported in TSC studies** **ראו נספח 8** **Description of selected adverse reactions** In clinical studies for TSC indications, everolimus has been associated with haemorrhage events. On rare occasions, fatal outcomes were observed in the oncology setting (see section 4.4). No serious cases of renal haemorrhage were reported in the TSC setting. In clinical studies for oncology indications and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhoea (secondary amenorrhoea and other menstrual irregularities). ….. Additional adverse reactions of relevance observed in oncology clinical studies and post-marketing spontaneous reports, were cardiac failure, pulmonary embolism, deep vein thrombosis, impaired wound healing and hyperglycaemia ….. Elderly patients In the oncology safety pooling …The most common adverse reactions leading to discontinuation were pneumonitis (including interstitial lung disease), fatigue, dyspnoea, and stomatitis.	**Table 0-1 Adverse drug reactions from oncology trials** **ראו נספח 5** The most frequent adverse reactions….. acne, menstruation irregular, sinusitis and pneumonia. **Table 3 Adverse reactions reported in TSC studies** **ראו נספח 7**	4.8 Undesirable effects

It is essential to assess everolimus blood levels in cases of suspected overdose. General supportive measures should be initiated in all cases of overdose.		4.9 Overdose

נספח 1 – Table 1 מהעלון לרופא - טקסט נוכחי (על מנת להקל על קריאת הנתונים בטבלה, מוצג הטקסט הנקי כפי שמאושר היום, לפני העדכונים).

Table 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

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
		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.
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.

נספח 2 – Table 1 מהעלון לרופא - טקסט חדש (על מנת להקל על קריאת הנתונים בטבלה, מוצג הטקסט הנקי לאחר העדכונים, כאשר ההחמרות מסומנות בצהוב כנדרש).

Table 2 Afinitor dose adjustment recommendations

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment
Non-infectious pneumonitis		
	Grade 2	Consider interruption of therapy, until symptoms improve to Grade≤ 1. Re-initiate Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients). Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt Afinitor until symptoms resolve to Grade ≤1. Consider re-initiating Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients). If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Afinitor treatment. .
Stomatitis		
	Grade 2	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients).
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients).
	Grade 4	Discontinue Afinitor treatment.
Other non-hematologic toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at same dose. If toxicity recurs at Grade 2, interrupt Afinitor until

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment
		recovery to Grade ≤1. Re-initiate Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients).
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients). If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Afinitor treatment.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate Afinitor (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients).
	Grade 4	Discontinue Afinitor treatment.
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at same dose
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients).
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment(5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients)..
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/l) and no fever.

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment
	Grade 4	Re-initiate treatment (5 mg daily for oncology patients and approximately 50% lower than the daily dose previously administered for TSC patients). Discontinue Afinitor treatment.

נספח 3 – מהעלון לרופא – טקסט נוכחי כפי שמאושר היום, לפני העדכונים (בנספח 4 מופיע הטקסט החדש בפורמט טבלה)

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).

נספח 4 – Table 2 מהעלון לרופא – טקסט חדש (על מנת להקל על קריאת הנתונים בטבלה, מוצג הטקסט הנקי לאחר העדכונים, כאשר ההחמרות מסומנות בצהוב כנדרש).

Effects of other active substances on everolimus Table 2

Active substance by interaction	**Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Potent* CYP3A4/PgP inhibitors**		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C_{max} ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Afinitor and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
***Moderate* CYP3A4/PgP inhibitors**		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C_{max} ↑2.0-fold (range 0.9-3.5)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. *Oncology patient and patients with renal angiomyolipoma associated with TSC:* If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close
Imatinib	AUC ↑ 3.7-fold C_{max} ↑ 2.2-fold	
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C_{max} ↑2.3-fold (range1.3-3.8)	
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C_{max} ↑1.8-fold (range 1.3-2.6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Dronedarone	Not studied. Increased exposure expected.	

Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration. (see also Therapeutic drug monitoring in section 4.2). *For patients with SEGA associated with TSC:* If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the daily dose by approximately 50%. Further dose reduction may be required to manage adverse reactions (see sections 4.2 and 4.4). Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration. The everolimus trough concentration should be assessed approximately 2 weeks after any change in dose (see sections 4.2 and 4.4)
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
***Potent and moderate* CYP3A4 inducers**		
Rifampicin	AUC ↓63% (range 0-80%) C_{max} ↓58% (range 10-70%)	Avoid the use of concomitant potent CYP3A4 inducers. *For oncology patients and patients with renal angiomyolipoma associated with TSC:* If patients require co-administration of a potent CYP3A4 inducer, a Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied
Dexamethasone	Not studied. Decreased exposure expected.	
Antiepileptic agents (e.g. carbamazepine, phenobarbital, phenytoin)	Not studied. Decreased exposure expected.	

		on Day 4 and 8 following start of the inducer. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration (see also Therapeutic drug monitoring in section 4.2). *For patients with SEGA associated with TSC:* Patients receiving concomitant potent CYP3A4 inducers may require an increased Afinitor dose to achieve the same exposure as patients not taking potent inducers. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml. If concentrations are below 5 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 potent inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration. The everolimus trough concentrations should be assessed approximately 2 weeks after any change in dose (see sections 4.2 and 4.4)
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's Wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

נספח 5 – Table 7-1 מהעלון לרופא – טקסט נוכחי (על מנת להקל על קריאת הנתונים בטבלה, מוצג הטקסט הנקי כפי שמאושר היום, לפני העדכונים).

Table 0-1 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
Hepatobiliary disorders	

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
Uncommon	Amenorrhea
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*

נספח 6 – Table 3 מהעלון לרופא – טקסט חדש (על מנת להקל על קריאת הנתונים בטבלה, מוצג הטקסט הנקי לאחר העדכונים, כאשר ההחמרות מסומנות בצהוב כנדרש).

Table 3 Adverse reactions reported in oncology clinical studies

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,diabetesmellitus, hyperlipidemia, hypokalemia, dehydration, hypocalcaemia
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Eye disorders	
Common	eyelid oedema
uncommon	Conjunctivitis
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Hemorrhage[b] ,hypertension.
Uncommon	Flushing, 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, mucosal inflammation, oral pain, dyspepsia, dysphagia
Hepatobiliary disorders	
common	Aspartate aminotransferase increased, alanine aminotransferase increased
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, mild alopecia, acne, erythema, onychoclasis, palmar-plantar erythrodysaesthesia syndrome, , skin exfoliation, skin lesion
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria*, blood creatinine increased* renal failure*
Uncommon	Increased daytime urination, acute renal failure
Reproductive system and breast disorders	
Common	Menstruation irregular[e]
Uncommon	Amenorrhea[e]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, peripheral edema
Common	Pyrexia,
Uncommon	Non-cardiac chest pain
Rare	Impaired wound healing
Investigations	
Very common	Weight decreased

See also subsection "Description of selected adverse reactions" *

[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 pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and hepatitis B* **(***see also section 4.4***)]**

[b] *Includes different bleeding events not listed individually*

[c] *Includes (common) pneumonitis, interstitial lung disease, lung infiltration; and (rare): pulmonary alveolar hemorrhage, pulmonary toxicity and alveolitis*

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

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

נספח 7 – Table 3-1 מהעלון לרופא – טקסט נוכחי (על מנת להקל על קריאת הנתונים בטבלה, מוצג הטקסט הנקי כפי שמאושר היום, לפני העדכונים).

Table 3 Adverse reactions reported in TSC studies

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	bronchitis viral
Blood and lymphatic system disorders	
Common	Neutropenia, anemia, leukopenia, lymphopenia, thrombocytopenia,
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Hyperlipidemia, decreased appetite, hypertriglyceridemia,hypophosphatemia,
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
Common	Diarrhea, nausea, vomiting, abdominal pain, oral pain, flatulence, constipation, gastritis
Skin and subcutaneous tissue disorders	
Very Common	Acne
Common	Rash, acneiform dermatitis, dry skin
Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	
Uncommon	Rhabdomyolysis

Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very Common	Amenorrhea, menstruation irregular
Common	Vaginal hemorrhage, menorrhagia, ovarian cyst, menstruation delayed
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 Includes (very common: stomatitis, mouth ulceration; aphthous stomatitis uncommon gingival pain, glossitis, lip ulceration.*

[c]*Includes common): rash, rash erythematous (uncommon): erythema, rash macular, rash maculo-papular, rash generalized.*

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

Table 3-1 Adverse reactions reported in TSC studies

Infections and infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, sinusitis, pneumonia[a], otitis media
Common	, Urinary tract infection, pharyngitis, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis, herpes zoster
Uncommon	bronchitis viral
Blood and lymphatic system disorders	
Common	Neutropenia, anemia, leukopenia, lymphopenia, thrombocytopenia,
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Hyperlipidemia, decreased appetite, hypertriglyceridemia, hypophosphatemia, hyperglycemia
Psychiatric disorders	
Common	Irritability, aggression
Uncommon	Insomnia
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[b]
Common	Diarrhoea, nausea, vomiting, abdominal pain, oral pain, flatulence, constipation, gastritis
Skin and subcutaneous tissue disorders	
Very Common	Acne
Common	Rash[c], acneiform dermatitis, dry skin, pruritus, alopecia
Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	
Uncommon	Rhabdomyolysis

Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very Common	Amenorrhea[d], menstruation irregular[d]
Common	Vaginal hemorrhage, menorrhagia, ovarian cyst, menstruation delayed[d]
General disorders and administration site conditions	
Common	Fatigue, pyrexia,
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased, weight decreased
Uncommon	Blood follicle stimulating hormone increased

[a]*Includes* pneumocystis jirovecii (carinii) pneumonia (PJP, PCP)

[b] *Includes (very common) stomatitis, mouth ulceration; aphthous stomatitis and (uncommon) gingival pain, glossitis, lip ulceration.*

[c]*Includes (common) rash, rash erythematous erythema* (*uncommon*) *rash macular, rash maculo-papular, rash generalized.*

[d]*frequency is based upon number of women from 10 to 55 years of age in the pooled data*

הודעה על החמרה (מידע בטיחות) בעלון לצרכן
(מעודכן 05.2013)

תאריך: 20 במאי 2015

שם תכשיר באנגלית ומספר הרישום: Afinitor 2.5mg, 5mg, 10mg [33388, 32045-6]

שם בעל הרישום: נוברטיס פארמה סרויסס איי ג'י

טופס זה מיועד לפירוט ההחמרות בלבד!

טקסט שחור – טקסט מאושר
טקסט עם קו תחתי – הוספת טקסט לעלון המאושר
~~טקסט עם קו חוצה~~ – מחיקת טקסט מהעלון המאושר
טקסט המסומן בצהוב – החמרה

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
! נטילת תרופות אחרות		• ..... • תרופה לויסות דופק לב: דרונדארון. • ..... • תרופה אשר מעכבת גדילת תאים לא תקינים: אימטיניב.
4. תופעות לוואי	**תופעות לוואי רציניות שנצפו במהלך הטיפול בחולים עם גידול בכליה הנקרא אנגיומיוליפומה הקשור בטרשת קרשית ובחולים עם גידול מוחי מסוג אסטרוציטומה סאבאפנדימאלית של תאים ענקיים הקשור בטרשת קרשית:** ..... **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 אחרות שנצפו במהלך הטיפול בסרטן שד מתקדם עם קולטן הורמונאלי חיובי, סרטן כליות מתקדם או גידולים נוירואנדוקרינים מתקדמים שמקורם בלבלב:**	**תופעות לוואי רציניות שנצפו במהלך הטיפול בחולים עם גידול בכליה הנקרא אנגיומיוליפומה הקשור בטרשת קרשית ובחולים עם גידול מוחי מסוג אסטרוציטומה סאבאפנדימאלית של תאים ענקיים הקשור בטרשת קרשית:** ..... **תופעות לוואי שכיחות (common) תופעות שמופיעות ב- ~~1 - 10~~ אצל עד משתמש 1 מתוך 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) • פריחה של שלפוחיות קטנות מלאות נוזל המופיעות על עור אדמומי, סימנים של זיהום ויראלי בעל פוטנציאל להיות חמור (הרפס זוסטר [שלבקת חוגרת]) ..... **אם תרגיש באחת מתופעות לוואי אלו, פנה מייד לרופא שלך כי יתכן שתוצאותיהן מסכנות חיים.** ..... **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 (common) תופעות שמופיעות באצל 1 - 10 עד משתמש 1 מתוך 10 משתמשים. מתוך 100	**תופעות לוואי שכיחות (common) תופעות שמופיעות ב~~א~~אצל ~~1 -~~ 10 עד משתמש 1 משתמשים. ~~מתוך 100~~:**
	.....	..... קילוף עור.....
	תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות ב 1 - 10 משתמשים מתוך 1,000	**תופעות לוואי שאינן שכיחות (uncommon) תופעות שמופיעות אצל ~~ב 1 -~~ 10 עד משתמש 1 מתוך 100 משתמשים ~~מתוך 1,000~~** .....;גלי חום; עין ורודה או אדומה (דלקת הלחמית).
	.....	.....
	תופעות לוואי נוספות שנצפו במהלך הטיפול בטרשת קרשית (tuberous sclerosis complex).	**תופעות לוואי נוספות שנצפו במהלך הטיפול הקשור בטרשת קרשית (tuberous sclerosis complex):.**
	תופעות לוואי שכיחות מאוד (very common)תופעות שמופיעות ביותר ממשתמש אחד מעשרה	**תופעות לוואי שכיחות מאוד (very common)תופעות שמופיעות ביותר ממשתמש אחד מעשרה** .....זיהום באוזן התיכונה; .....
	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); רמה גבוהה של שומנים בדם, (יתר שומן בדם, עליה בטריגליצרידים); רמה נמוכה של זרחן בדם (היפופוספטמיה); דימום או חבלה ספונטניים, סימנים של רמה נמוכה של טסיות (תרומבוציטופניה); 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 בבטן התחתונה ובאזור האגן שעשוי להיות חד, עם שיבושים במחזור הווסת (ציסטה בשחלה); כמות עודפת של גזים במעיים (נפיחנות); 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 יכולת לישון (נדודי שינה); חוסר	**תופעות לוואי שכיחות (common) תופעות שמופיעות ~~ב~~אצל ~~1 -~~ 10 עד משתמש 1 משתמשים. ~~מתוך 100~~** זיהום בדרכי השתן; חניכיים נפוחות ומדממות, סימנים לזיהום בחניכיים (gingivitis); ~~זיהום באוזן התיכונה;~~ דלקת בעור (צלוליטיס); גרון כואב (דלקת לוע); רמה גבוהה של שומנים בדם, (יתר שומן בדם, עליה בטריגליצרידים); רמה נמוכה של זרחן בדם (היפופוספטמיה); רמה גבוהה של סוכר ~~בדם (היפרגליקמיה); רמה נמוכה של נתרן בדם (היפונתרמיה)~~ 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; דימום או חבלה ספונטניים, סימנים של רמה נמוכה של טסיות (תרומבוציטופניה); שיעול; כאב בפה; דימום מהאף; דלקת בדופן הקיבה (gastritis); שלשול; ~~כאב בפה; הקאה;~~ 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 (נפיחנות); עצירות; כאב בטן, בחילה, הקאה, שלשול, נפיחות של הבטן, סימנים לדלקת של הקרום הרירי המרפד את הקיבה (דלקת קיבה, דלקת קיבה ומעי ויראלית); יובש בעור, עקצוץ; 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;

	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.**	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): ירידה במשקל. אם אחת מהתופעות המצוינות מעלה משפיעות עליך באופן חמור, **פנה לרופא המטפל שלך.** ..... התפרצות מחדש של דלקת כבד B (הפטיטיס B) אובחנה במספר חולים אשר נוטלים אפיניטור. דווח לרופא שלך אם אתה חש בתסמינים של דלקת כבד B במהלך הטיפול באפיניטור. התסמינים הראשוניים כוללים חום, תפרחת עור, כאבים ודלקת במפרקים. תסמינים אחרים יכולים לכלול עייפות, איבוד תיאבון, בחילה, צהבת (הצהבה של העור) וכאבי בבטן ימנית עליונה. צואה בהירה או שתן כהה, הם יכולים להיות סימנים לצהבת.