CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203985Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
AFINITOR DISPERZ (everolimus tablets for oral suspension)
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	08/2012
Dosage and Administration (2)	08/2012
Warnings and Precautions (5)	08/2012

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor indicated for the treatment of:

- postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole. (1.1)
- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced or metastatic. The safety and effectiveness of AFINITOR in the treatment of patients with carcinoid tumors have not been established. (1.2)
- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.3)
- adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in the 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. (1.4)

AFINITOR and AFINITOR DISPERZ are kinase inhibitors indicated for the treatment of:

- pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. The effectiveness is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC has not been demonstrated. (1.5)

----------DOSAGE AND ADMINISTRATION----------

Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

- 10 mg once daily with or without food. (2.1)
- For patients with hepatic impairment, reduce the AFINITOR dose. (2.2)
- If moderate inhibitors of CYP3A4 and/or P-glycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

SEGA with TSC:

- 4.5 mg/m^2 once daily; adjust dose to attain trough concentrations of 5-15 ng/mL. (2.3)
- Assess trough concentrations approximately 2 weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4 and/or PgP inducers or inhibitors, a change in hepatic function, or a change in dosage form between AFINITOR Tablets and AFINITOR DISPERZ. (2.3, 2.4)
- For patients with severe hepatic impairment reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ. (2.3, 2.5)
- If concomitant use of moderate inhibitors of CYP3A4 and/or PgP is required, reduce the dose of AFINITOR Tablets or AFINITOR DISPERZ by 50%. (2.3, 2.5)
- If concomitant use of strong inducers of CYP3A4 is required, double the dose of AFINITOR Tablets or AFINITOR DISPERZ. (2.3, 2.5)

----------DOSAGE FORMS AND STRENGTHS----------

AFINITOR Tablets: 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets with no score (3.1)
AFINITOR DISPERZ (everolimus tablets for oral suspension): 2 mg, 3 mg, and 5 mg tablets for oral suspension with no score (3.2)

----------CONTRAINDICATIONS----------

Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes and topical treatments. (5.3)
- Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed. (5.4)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.6)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.9)
- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.10, 8.1)

----------ADVERSE REACTIONS----------

Advanced HR+ BC, advanced PNET, advanced RCC: Most common adverse reactions (incidence ≥30%) include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache and decreased appetite. (6.1, 6.2, 6.3)
Renal angiomyolipoma with TSC: Most common adverse reaction (incidence ≥ 30%) is stomatitis. (6.4)
SEGA with TSC: Most common adverse reactions (incidence ≥ 30%) are stomatitis and respiratory tract infection. (6.5)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 2.5, 5.7, 7.1)
- Moderate CYP3A4 and/or PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.3, 2.5, 5.7, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2.2, 2.3, 2.5, 5.7, 7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: For advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC patients with hepatic impairment, reduce AFINITOR dose. For SEGA patients with severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ. (2.2, 2.3, 2.5, 5.8, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)

AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

1.2 Advanced Neuroendocrine Tumors of Pancreatic Origin (PNET)

AFINITOR® is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) 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.

1.3 Advanced Renal Cell Carcinoma (RCC)

AFINITOR® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

1.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)

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 the 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.

1.5 Subependymal Giant Cell Astrocytoma (SEGA) with Tuberous Sclerosis Complex (TSC)

AFINITOR® Tablets and AFINITOR® DISPERZ are indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

The effectiveness of AFINITOR Tablets and AFINITOR DISPERZ is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC have not been demonstrated *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

AFINITOR is available in two dosage forms: tablets (AFINITOR Tablets) and tablets for oral suspension (AFINITOR DISPERZ). AFINITOR DISPERZ is recommended only for the treatment of patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC) in conjunction with therapeutic drug monitoring *[see Clinical Pharmacology (12.3)]*.

2.1 Recommended Dose in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC, and Renal Angiomyolipoma with TSC

The recommended dose of AFINITOR Tablets is 10 mg, to be taken once daily at the same time every day. Administer either consistently with food or consistently without food *[see Clinical Pharmacology (12.3)]*. AFINITOR Tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

Continue treatment until disease progression or unacceptable toxicity occurs.

2.2 Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC, and Renal Angiomyolipoma with TSC

Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered *[see Warnings and Precautions (5)]*.

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

Table 1: AFINITOR Dose Adjustment and Management Recommendation for Adverse Reactions

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] 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[c]	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 wks.
	Grade 3 Symptomatic, interfering with ADL[c]; 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 a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Symptomatic and unable to adequately aliment 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).[d]
	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 a 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.

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
		Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption.
		Re-initiate Afinitor at a lower dose.
		Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue AFINITOR and treat with appropriate medical therapy.

[a] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.
[b] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.
[c] Activities of daily living (ADL)
[d] Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.7)]*. Dose adjustments are recommended:

- Mild hepatic impairment (Child-Pugh class A) – The recommended dose is 7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated.
- Moderate hepatic impairment (Child-Pugh class 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 class C) – If the desired benefit outweighs the risk, a dose of 2.5 mg daily may be used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

CYP3A4 and/or P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

Use caution when co-administered with moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4 and/or PgP inhibitor, reduce the AFINITOR dose to 2.5 mg daily. The reduced dose of AFINITOR is predicted to adjust the area under the curve (AUC) to the range observed without inhibitors. An AFINITOR dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the AFINITOR dose is increased. If the moderate inhibitor is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the moderate CYP3A4 and/or PgP inhibitor.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment.

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). If patients require co-administration of a strong CYP3A4 inducer, consider increasing the AFINITOR dose from 10 mg daily up to 20 mg daily, using 5 mg increments. This dose of AFINITOR is predicted, based on pharmacokinetic data, 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, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Warnings and Precautions (5.7) and Drug Interactions (7.2)]*.

St. John's Wort (*Hypericum perforatum*) may decrease everolimus exposure unpredictably and should be avoided.

2.3 Recommended Dose in SEGA with TSC

The recommended starting dose is 4.5 mg/m^2, once daily. The recommended starting dose for patients with severe hepatic impairment (Child-Pugh class C) or requiring moderate CYP3A4 and/or PgP inhibitors is 2.5 mg/m^2, once daily *[see Dosage and Administration (2.5)]*. The recommended starting dose for patients requiring a concomitant strong CYP3A4 inducer is 9 mg/m^2, once daily *[see Dosage and Administration (2.5)]*. Round dose to the nearest strength of either AFINITOR Tablets or AFINITOR DISPERZ.

Use therapeutic drug monitoring to guide subsequent dosing *[see Dosage and Administration (2.4)]*. Adjust dose at two week intervals as needed to achieve and maintain trough concentrations of 5 to 15 ng/mL *[see Dosage and Administration (2.4, 2.5)]*.

Continue treatment until disease progression or unacceptable toxicity occurs. The optimal duration of therapy is unknown.

2.4 Therapeutic Drug Monitoring in SEGA with TSC

Monitor everolimus whole blood trough levels routinely in all patients. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Assess trough concentrations approximately two weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4 and/or PgP inducers or inhibitors, a change in hepatic function, or a change in dosage form between AFINITOR Tablets and AFINITOR DISPERZ. 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.

Titrate the dose to attain trough concentrations of 5 to 15 ng/mL.

- For trough concentrations less than 5 ng/mL, increase the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- For trough concentrations greater than 15 ng/mL, reduce the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- If dose reduction is required for patients receiving the lowest available strength, administer every other day.

2.5 Dose Modifications in SEGA with TSC

Adverse Reactions

Reduce dose or withhold AFINITOR Tablets or AFINITOR DISPERZ for severe or intolerable adverse reactions *[see Warnings and Precautions (5)]*. Reduce the dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. If dose reduction is required for patients receiving the lowest available strength, administer every other day *[see Table 1 in Dosage and Administration (2.2)]*.

Hepatic Impairment

- Reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% in patients with SEGA who have severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.3)]*. Adjustment to the starting dose for patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment may not be needed. Subsequent dosing should be based on therapeutic drug monitoring.

- Assess everolimus trough concentrations approximately two weeks after commencing treatment, a change in dose, or any change in hepatic function *[see Dosage and Administration (2.3, 2.4)]*.

CYP3A4 and/or P-glycoprotein (PgP) Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving AFINITOR Tablets or AFINITOR DISPERZ *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

For patients who require treatment with moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem):

- Reduce the AFINITOR Tablets or AFINITOR DISPERZ dose by approximately 50%. Administer every other day if dose reduction is required for patients receiving the lowest available strength *[see Dosage and Administration (2.3)]*.
- Assess everolimus trough concentrations approximately two weeks after dose reduction *[see Dosage and Administration (2.3, 2.4)]*.
- Resume the dose that was used prior to initiating the CYP3A4 and/or PgP inhibitor 2 to 3 days after discontinuation of a moderate inhibitor. Assess the everolimus trough concentration approximately two weeks later *[see Dosage and Administration (2.3, 2.4)]*.

Do not ingest foods or nutritional supplements (e.g., grapefruit, grapefruit juice) that are known to inhibit cytochrome P450 or PgP activity.

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available *[see Warnings and Precautions (5.7) and Drug Interactions (7.2)]*. For patients who require treatment with a strong CYP3A4 inducer:

- Double the dose of AFINITOR Tablets or AFINITOR DISPERZ *[see Dosage and Administration (2.3)]*.
- Assess the everolimus trough concentration two weeks after doubling the dose and adjust the dose if necessary to maintain a trough concentration of 5 to 15 ng/mL *[see Dosage and Administration (2.3, 2.4)]*.
- Return the AFINITOR Tablets or AFINITOR DISPERZ dose to that used prior to initiating the strong CYP3A4 inducer if the strong inducer is discontinued, and assess the everolimus trough concentrations approximately two weeks later *[see Dosage and Administration (2.3, 2.4)]*.

Do not ingest foods or nutritional supplements (e.g., St. John's Wort (*Hypericum perforatum*)) that are known to induce cytochrome P450 activity.

2.6 Administration of AFINITOR Tablets in SEGA with TSC

Do not combine the two dosage forms (AFINITOR Tablets and AFINITOR DISPERZ) to achieve the desired dose. Use one dosage form or the other.

Administer AFINITOR Tablets orally once daily at the same time every day. Administer either consistently with food or consistently without food *[see Clinical Pharmacology (12.3)]*.

AFINITOR Tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

2.7 Administration and Preparation of AFINITOR DISPERZ in SEGA with TSC

Do not combine the two dosage forms (AFINITOR Tablets and AFINITOR DISPERZ) to achieve the desired dose. Use one dosage form or the other.

Administer AFINITOR DISPERZ (everolimus tablets for oral suspension) as a suspension only.

Administer AFINITOR DISPERZ orally once daily at the same time every day. Administer either consistently with food or consistently without food *[see Clinical Pharmacology (12.3)]*.

Administer suspension immediately after preparation. Discard suspension if not administered within 60 minutes after preparation.

Prepare suspension in water only.

Using an oral syringe:

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

Using a small drinking glass:

- Place the prescribed dose of AFINITOR DISPERZ into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg of AFINITOR DISPERZ per glass. If higher doses are required, prepare an additional glass. Do not break or crush tablets.
- Allow 3 minutes for suspension to occur.
- Stir the contents gently with a spoon, immediately prior to drinking.
- After administration of the prepared suspension, add 25 mL of water and stir with the same spoon to re-suspend remaining particles. Administer the entire contents of the glass.

3 DOSAGE FORMS AND STRENGTHS

3.1 AFINITOR (everolimus) Tablets

2.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “LCL” on one side and “NVR” on the other.

5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other.

7.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “7P5” on one side and “NVR” on the other.

10 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other.

3.2 AFINITOR DISPERZ (everolimus tablets for oral suspension)

2 mg tablet for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and no score, engraved with “D2” on one side and “NVR” on the other.

3 mg tablet for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and no score, engraved with “D3” on one side and “NVR” on the other.

5 mg tablet for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and no score, engraved with “D5” on one side and “NVR” on the other.

4 CONTRAINDICATIONS

AFINITOR is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. 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 and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis 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 causes have been excluded by means of appropriate investigations. Advise patients 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. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting 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 *[see Table 1 in Dosage and Administration (2.2)]*.

For cases of grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For cases of grade 3 non-infectious pneumonitis interrupt AFINITOR until resolution to less than or equal to grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances *[see Table 1 in Dosage and Administration (2.2)]*. If toxicity recurs at grade 3, consider discontinuation of AFINITOR. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, 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 respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an 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.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44-86% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4-9% of patients *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. In such cases, topical treatments are recommended, but alcohol-, 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 Drug Interactions (7.1)]*.

5.4 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR *[see Laboratory Tests and Monitoring (5.6)]*.

5.5 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 ≥ 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 ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended *[see Dosage and Administration (2.2), Use in Specific Populations (8.5)]*.

5.6 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. 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 and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.7 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4 inhibitors should be avoided *[see Dosage and Administration (2.2, 2.5) and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 and/or PgP inhibitor *[see Dosage and Administration (2.2, 2.5) and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer *[see Dosage and Administration (2.2, 2.5) and Drug Interactions (7.2)]*.

5.8 Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

5.9 Vaccinations

During AFINITOR treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations according to American Council on Immunization Practices (ACIP) guidelines prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

5.10 Embryo-fetal Toxicity

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to use a highly effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label *[see Warnings and Precautions (5)]*:

- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.
- Oral ulcers *[see Warnings and Precautions (5.3)]*.
- Renal failure *[see Warnings and Precautions (5.4)]*.

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

6.1 Clinical Study Experience in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer

The efficacy and safety of AFINITOR (10 mg/day) plus exemestane (25 mg/day) (n=485) versus placebo plus exemestane (25 mg/day) (n=239) was evaluated in a randomized, controlled trial in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (range 28-93), and 75% were Caucasian. Safety results are based on a median follow-up of approximately 13 months.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common grade 3/4 adverse reactions (incidence ≥ 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hyperglycemia, increased AST, anemia, leukopenia, thrombocytopenia, lymphopenia, increased ALT, and hypertriglyceridemia. The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, decreased potassium, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred more frequently in patients who received AFINITOR plus exemestane (2%) compared to patients on the placebo plus exemestane arm (0.4%). The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the AFINITOR plus exemestane and placebo plus exemestane treatment groups, respectively. Dose adjustments (interruptions or reductions) were more frequent among patients in the AFINITOR plus exemestane arm than in the placebo plus exemestane arm (63% versus 14%).

Table 2 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 2: Adverse Reactions Reported ≥ 10% of Patients with Advanced HR+ BC*

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**41**	**9**	**90**	**22**	**5**
Gastrointestinal disorders						
Stomatitis[b]	67	8	0	11	0.8	0
Diarrhea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0
Constipation	14	0.4	0	13	0.4	0
Dry mouth	11	0	0	7	0	0
General disorders and administration site conditions						
Fatigue	36	4	0.4	27	1	0
Edema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
Infections and infestations						
Infections[c]	50	4	1	25	2	0
Investigations						
Weight decreased	25	1	0	6	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycemia	14	5	0.4	2	0.4	0
Musculoskeletal and connective tissue disorders						
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0
Pain in extremity	9	0.4	0	11	2	0
Nervous system disorders						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
Psychiatric disorders						
Insomnia	13	0.2	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	24	0.6	0	12	0	0
Dyspnea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis[d]	19	4	0.2	0.4	0	0
Skin and subcutaneous tissue disorders						
Rash	39	1	0	6	0	0

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
Vascular disorders						
Hot flush	6	0	0	14	0	0
Median duration of treatment[e]	**23.9 weeks**			**13.4 weeks**		

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*160 patients (33.2%) were exposed to AFINITOR therapy for a period of ≥ 32 weeks)

[a] Exemestane (25 mg/day)

[b] Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

[c] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), and also including candidiasis (<1%), and sepsis (<1%), and hepatitis C (<1%).

[d] Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

[e] Exposure to AFINITOR or placebo

Key observed laboratory abnormalities are presented in Table 3.

Table 3: Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced HR+ BC

Laboratory parameter	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[b]						
Hemoglobin decreased	68	6	0.6	40	0.8	0.4
WBC decreased	58	1	0	28	5	0.8
Platelets decreased	54	3	0.2	5	0	0.4
Lymphocytes decreased	54	11	0.6	37	5	0.8
Neutrophils decreased	31	2	0	11	0.8	0.8
Clinical chemistry						
Glucose increased	69	9	0.4	44	0.8	0.4
Cholesterol increased	70	0.6	0.2	38	0.8	0.8
Aspartate transaminase (AST) increased	69	4	0.2	45	3	0.4
Alanine transaminase (ALT) increased	51	4	0.2	29	5	0
Triglycerides increased	50	0.8	0	26	0	0
Albumin decreased	33	0.8	0	16	0.8	0
Potassium decreased	29	4	0.2	7	1	0
Creatinine increased	24	2	0.2	13	0	0

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[a] Exemestane (25 mg/day)
[b] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.

6.2 Clinical Study Experience in Advanced Pancreatic Neuroendocrine Tumors

In a randomized, controlled trial of AFINITOR (n=204) versus placebo (n=203) in patients with advanced PNET the median age of patients was 58 years (range 20-87), 79% were Caucasian, and 55% were male. Patients on the placebo arm could cross over to open-label AFINITOR upon disease progression.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common grade 3-4 adverse reactions (incidence ≥ 5%) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were decreased hemoglobin, hyperglycemia, alkaline phosphatase increased, hypercholesterolemia, bicarbonate decreased, and increased aspartate transaminase (AST). The most common grade 3-4 laboratory abnormalities (incidence ≥ 3%) were hyperglycemia, lymphopenia, decreased hemoglobin, hypophosphatemia, increased alkaline phosphatase, neutropenia, increased aspartate transaminase (AST), potassium decreased, and thrombocytopenia. Deaths during double-blind treatment where an adverse event was the primary cause occurred in 7 patients on AFINITOR and 1 patient on placebo. Causes of death on the AFINITOR arm included one case of each of the following: acute renal failure, acute respiratory distress, cardiac arrest, death (cause unknown), hepatic failure, pneumonia, and sepsis. There was 1 death due to pulmonary embolism on the placebo arm. After cross-over to open-label AFINITOR, there were 3 additional deaths, one due to hypoglycemia and cardiac arrest in a patient with insulinoma, one due to MI with CHF, and the other due to sudden death. The rates of treatment-emergent adverse events resulting in permanent discontinuation were 20% and 6% for the AFINITOR and placebo treatment groups, respectively. Dose delay or reduction was necessary in 61% of everolimus patients and 29% of placebo patients. grade 3-4 renal failure occurred in 6 patients in the everolimus arm and 3 patients in the placebo arm. Thrombotic events included 5 patients with pulmonary embolus in the everolimus arm and 1 in the placebo arm as well as 3 patients with thrombosis in the everolimus arm and 2 in the placebo arm.

Table 4 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 4: Adverse Reactions Reported ≥ 10% of Patients with Advanced PNET

	AFINITOR N=204			Placebo N=203		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Any adverse reaction	**100**	**49**	**13**	**98**	**32**	**8**
Gastrointestinal disorders						
Stomatitis[a]	70	7	0	20	0	0
Diarrhea[b]	50	5	0.5	25	3	0
Abdominal pain	36	4	0	32	6	1
Nausea	32	2	0	33	2	0
Vomiting	29	1	0	21	2	0
Constipation	14	0	0	13	0.5	0
Dry mouth	11	0	0	4	0	0
General disorders and administration site conditions						
Fatigue/malaise	45	3	0.5	27	2	0.5
Edema (general and peripheral)	39	1	0.5	12	1	0
Fever	31	0.5	0.5	13	0.5	0
Asthenia	19	3	0	20	3	0
Infections and infestations						
Nasopharyngitis/rhinitis/URI	25	0	0	13	0	0
Urinary tract infection	16	0	0	6	0.5	0
Investigations						
Weight decreased	28	0.5	0	11	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	18	1	0
Diabetes mellitus	10	2	0	0.5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	1	0.5	7	0.5	0
Back pain	15	1	0	11	1	0
Pain in extremity	14	0.5	0	6	1	0
Muscle spasms	10	0	0	4	0	0
Nervous system disorders						
Headache/migraine	30	0.5	0	15	1	0
Dysgeusia	19	0	0	5	0	0
Dizziness	12	0.5	0	7	0	0
Psychiatric disorders						
Insomnia	14	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough/productive cough	25	0.5	0	13	0	0
Epistaxis	22	0	0	1	0	0
Dyspnea/dyspnea exertional	20	2	0.5	7	0.5	0
Pneumonitis[c]	17	3	0.5	0	0	0
Oropharyngeal pain	11	0	0	6	0	0
Skin and subcutaneous disorders						
Rash	59	0.5	0	19	0	0
Nail disorders	22	0.5	0	2	0	0

	AFINITOR N=204			Placebo N=203		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Pruritus/pruritus generalized	21	0	0	13	0	0
Dry skin/xeroderma	13	0	0	6	0	0
Vascular disorders						
Hypertension	13	1	0	6	1	0
Median duration of treatment (wks)		**37**			**16**	

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[a] Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

[b] Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

[c] Includes pneumonitis, interstitial lung disease, pulmonary fibrosis and restrictive pulmonary disease.

Key observed laboratory abnormalities are presented in Table 5.

Table 5: Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced PNET

Laboratory parameter	AFINITOR N=204		Placebo N=203	
	All grades %	Grade 3-4 %	All grades %	Grade 3-4 %
Hematology				
Hemoglobin decreased	86	15	63	1
Lymphocytes decreased	45	16	22	4
Platelets decreased	45	3	11	0
WBC decreased	43	2	13	0
Neutrophils decreased	30	4	17	2
Clinical chemistry				
Alkaline phosphatase increased	74	8	66	8
Glucose (fasting) increased	75	17	53	6
Cholesterol increased	66	0.5	22	0
Bicarbonate decreased	56	0	40	0
Aspartate transaminase (AST) increased	56	4	41	4
Alanine transaminase (ALT) increased	48	2	35	2
Phosphate decreased	40	10	14	3
Triglycerides increased	39	0	10	0
Calcium decreased	37	0.5	12	0
Potassium decreased	23	4	5	0
Creatinine increased	19	2	14	0
Sodium decreased	16	1	16	1
Albumin decreased	13	1	8	0
Bilirubin increased	10	1	14	2
Potassium increased	7	0	10	0.5

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6.3 Clinical Study Experience in Advanced Renal Cell Carcinoma

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study

treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 6 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 6: Adverse Reactions Reported in at least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)		**141**			**60**	

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[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table 7.

Table 7: Key Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

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[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

6.4 Clinical Study Experience in Renal Angiomyolipoma with Tuberous Sclerosis Complex

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial of AFINITOR in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (n=5). The median age of patients was 31 years (range 18 to 61 years), 89% were Caucasian, and 34% were male. The median duration of blinded study treatment was 48 weeks (range 2 to 115 weeks) for patients receiving AFINITOR and 45 weeks (range 9 to 115 weeks) for those receiving placebo.

The most common adverse reaction reported for AFINITOR (incidence ≥ 30%) was stomatitis. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis and amenorrhea. The most common laboratory

abnormalities (incidence ≥ 50%) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was hypophosphatemia.

The rate of adverse reactions resulting in permanent discontinuation was 3.8% in the AFINITOR-treated patients. Adverse reactions leading to permanent discontinuation in the AFINITOR arm were hypersensitivity/angioedema/bronchospasm, convulsion, and hypophosphatemia. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 52% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Table 8 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 9.

Table 8: Adverse Reactions Reported in ≥ 10% of AFINITOR-treated Patients with Renal Angiomyolipoma

	AFINITOR N=79			Placebo N=39		
	All grades %	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Any adverse reaction	**100**	**25**	**5**	**97**	**8**	**5**
Gastrointestinal disorders						
Stomatitis[a]	78	6	0	23	0	0
Vomiting	15	0	0	5	0	0
Diarrhea	14	0	0	5	0	0
General disorders and administration site conditions						
Peripheral edema	13	0	0	8	0	0
Infections and infestations						
Upper respiratory tract infection	11	0	0	5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	20	0	0	13	0	0
Skin and subcutaneous tissue disorders						
Acne	22	0	0	5	0	0

Grading according to CTCAE Version 3.0
[a] Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.

Amenorrhea occurred in 15% of AFINITOR-treated females (8 of 52) and 4% (1 of 26) of females in the placebo group. Other adverse reactions involving the female reproductive system were menorrhagia (10%), menstrual irregularities (10%), and vaginal hemorrhage (8%).

The following additional adverse reactions occurred: epistaxis (9%), decreased appetite (6%), otitis media (6%), depression (5%), abnormal taste (5%), hypersensitivity (3%), and pneumonitis (1%).

Table 9: Key Laboratory Abnormalities Reported in AFINITOR-treated Patients with Renal Angiomyolipoma

	AFINITOR N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology						
Anemia	61	0	0	49	0	0
Leucopenia	37	0	0	21	0	0
Neutropenia	25	0	1	26	0	0
Lymphopenia	20	1	0	8	0	0
Thrombocytopenia	19	0	0	3	0	0
Clinical chemistry						
Hypercholesterolemia	85	1	0	46	0	0
Hypertriglyceridemia	52	0	0	10	0	0
Hypophosphatemia	49	5	0	15	0	0
Alkaline phosphatase increased	32	1	0	10	0	0
Elevated aspartate transaminase (AST)	23	1	0	8	0	0
Elevated alanine transaminase (ALT)	20	1	0	15	0	0
Fasting hyperglycemia	14	0	0	8	0	0

Grading according to CTCAE Version 3.0

6.5 Clinical Study Experience in Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (Study 1) of AFINITOR in 117 patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC). The median age of patients was 9.5 years (range 0.8 to 26 years), 93% were Caucasian, and 57% were male. The median duration of blinded study treatment was 52 weeks (range 24 to 89 weeks) for patients receiving AFINITOR and 47 weeks (range 14 to 88 weeks) for those receiving placebo.

The most common adverse reactions reported for AFINITOR (incidence ≥ 30%) were stomatitis and respiratory tract infection. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pyrexia, pneumonia, gastroenteritis, aggression, agitation, and amenorrhea. The most common key laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia.

There were no adverse reactions resulting in permanent discontinuation. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 55% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Table 10 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 11.

Table 10: Adverse Reactions Reported in ≥10% of AFINITOR-treated Patients with SEGA in Study 1

	AFINITOR N=78			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**97**	**36**	**3**	**92**	**23**	**3**
Gastrointestinal disorders						
Stomatitis[a]	62	9	0	26	3	0
Vomiting	22	1	0	13	0	0
Diarrhea	17	0	0	5	0	0
Constipation	10	0	0	3	0	0
Infections and infestations						
Respiratory tract infection[b]	31	1	1	23	0	0
Gastroenteritis[c]	10	4	1	3	0	0
Pharyngitis streptococcal	10	0	0	3	0	0
General disorders and administration site conditions						
Pyrexia	23	6	0	18	3	0
Fatigue	14	0	0	3	0	0
Psychiatric disorders						
Anxiety, aggression or other behavioral disturbance[d]	21	5	0	3	0	0
Skin and subcutaneous tissue disorders						
Rash[e]	21	0	0	8	0	0
Acne	10	0	0	5	0	0

Grading according to CTCAE Version 3.0

[a] Includes mouth ulceration, stomatitis, and lip ulceration

[b] Includes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral

[c] Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection

[d] Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder

[e] Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria

Amenorrhea occurred in 17% of AFINITOR-treated females aged 10 to 55 years (3 of 18) and none of the females in the placebo group. For this same group of AFINITOR-treated females, the following menstrual abnormalities were reported: dysmenorrhea (6%), menorrhagia (6%), metrorrhagia (6%), and unspecified menstrual irregularity (6%).

The following additional adverse reactions occurred in AFINITOR-treated patients: nausea (8%), pain in extremity (8%), insomnia (6%), pneumonia (6%), epistaxis (5%), hypersensitivity (3%), and pneumonitis (1%).

Table 11: Key Laboratory Abnormalities Reported in AFINITOR-treated Patients with SEGA in Study 1

	AFINITOR N=78			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology						
Elevated partial thromboplastin time	72	3	0	44	5	0
Neutropenia	46	9	0	41	3	0
Anemia	41	0	0	21	0	0
Clinical chemistry						
Hypercholesterolemia	81	0	0	39	0	0
Elevated aspartate transaminase (AST)	33	0	0	0	0	0
Hypertriglyceridemia	27	0	0	15	0	0
Elevated alanine transaminase (ALT)	18	0	0	3	0	0
Hypophosphatemia	9	1	0	3	0	0

Grading according to CTCAE Version 3.0

Longer-term follow-up of 34.2 months (range 4.7 to 47.1 months) from a non-randomized, open-label, 28-patient trial resulted in the following additional notable adverse reactions and key laboratory abnormalities: cellulitis (29%), hyperglycemia (25%), and elevated creatinine (14%).

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- 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.

Concomitant strong inhibitors of CYP3A4 should not be used *[see Dosage and Administration (2.2, 2.5) and Warnings and Precautions (5.7)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4 and/or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose *[see Dosage and Administration (2.2, 2.5) and Warnings and Precautions (5.7)]*.

7.2 Agents That May Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2, 2.5)]*.

7.3 Drugs That May Have Their Plasma Concentrations 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.

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

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. 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, HER2-negative advanced breast cancer receiving the combination.

Coadministration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.10)]*.

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. 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.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure ($AUC_{0\text{-}24h}$) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Pediatric use of AFINITOR Tablets and AFINITOR DISPERZ is recommended for patients 1 year of age and older with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The safety and effectiveness of AFINITOR Tablets and AFINITOR DISPERZ have not been established in pediatric patients with renal angiomyolipoma with TSC in the absence of SEGA.

The effectiveness of AFINITOR in pediatric patients with SEGA was demonstrated in two clinical trials based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume *[see Clinical Studies (14.5)]*. Improvement in disease-related symptoms and overall survival in pediatric patients with SEGA has not been demonstrated. The long term effects of AFINITOR on growth and pubertal development are unknown.

Study 1 was a randomized, double-blind, multicenter trial comparing AFINITOR (n=78) to placebo (n=39) in pediatric and adult patients. The median age was 9.5 years (range 0.8 to 26 years). At the time of randomization, a total of 20 patients were < 3 years of age, 54 patients were 3 to < 12 years of age, 27 patients were 12 to < 18 years of age, and 16 patients were ≥ 18 years of age. The overall nature, type, and frequency of adverse reactions across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious adverse events in patients < 3 years of age. A total of 6 of 13 patients (46%) < 3 years of age had at least one serious adverse event due to infection, compared to 2 of 7 patients (29%) treated with placebo. No patient in any age group discontinued AFINITOR due to infection *[see Adverse Reactions (6.5)]*. Subgroup analyses showed reduction in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Study 2 was an open-label, single-arm, single-center trial of AFINITOR (N=28) in patients aged ≥ 3 years; median age was 11 years (range 3 to 34 years). A total of 16 patients were 3 to < 12 years, 6 patients were 12 to < 18 years, and 6 patients were ≥ 18 years. The frequency of adverse reactions across the age groups was generally similar *[see Adverse Reactions (6.5)]*. Subgroup analyses showed reductions in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Everolimus clearance normalized to body surface area was higher in pediatric patients than in adults with SEGA *[see Clinical Pharmacology (12.3)]*.The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 5 to 15 ng/mL are the same for adult and pediatric patients with SEGA *[see Dosage and Administration (2.3, 2.4)]*.

8.5 Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 and over. No overall differences in effectiveness were observed between elderly and younger subjects. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 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 ≥ 65 years of age compared to 17% in patients < 65 years of age *[see Warnings and Precautions (5.5)]*.

In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger subjects. In the randomized advanced RCC study, 41% of AFINITOR treated patients were ≥ 65 years of age, while 7% were 75 and over. In the randomized advanced PNET study, 30% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 and over.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3)]*.

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2)]*.

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

10 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 2000 mg/kg (limit test).

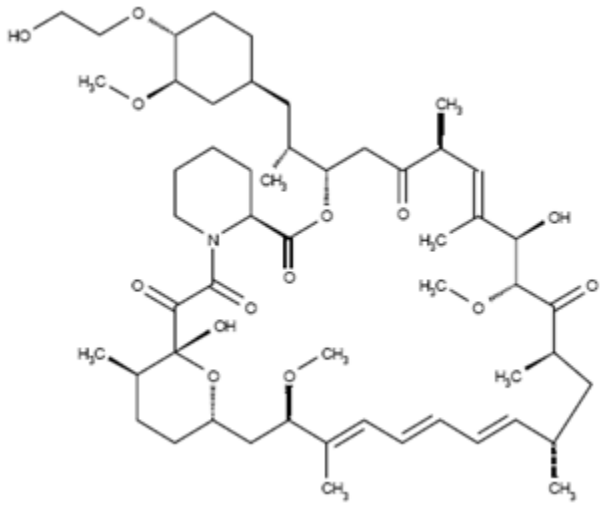
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

11 DESCRIPTION

AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is:



AFINITOR Tablets are supplied for oral administration and contain 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus. The tablets also contain anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate as inactive ingredients.

AFINITOR DISPERZ (everolimus tablets for oral suspension) is supplied for oral administration and contains 2 mg, 3 mg, or 5 mg of everolimus. The tablets for oral suspension also contain butylated hydroxytoluene, colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol, and microcrystalline cellulose as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular

protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *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.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.

12.2 Pharmacodynamics

Exposure Response Relationships

Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose.

In patients with SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, as responses have been observed at trough concentrations as low as 5 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

12.3 Pharmacokinetics

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

Dose Proportionality in Patients with SEGA and TSC: In patients with SEGA and TSC, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.

Food effect: In healthy subjects, high fat meals reduced systemic exposure to AFINITOR 10 mg tablet (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.

Relative bioavailability of AFINITOR DISPERZ (everolimus tablets for oral suspension): The $AUC_{0-\infty}$ of AFINITOR DISPERZ was equivalent to that of AFINITOR Tablets; the C_{max} of this dosage form was 20-36% lower than that of AFINITOR Tablets. The predicted trough concentrations at steady-state were similar after daily administration.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 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.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus.

These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [^{14}C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25–178 mL/min) was detected on oral clearance (CL/F) of everolimus *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects (N=13), there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in exposure (i.e. AUC) for subjects with mild (Child-Pugh class A, N=6), moderate (Child-Pugh class B, N=9), and severe (Child-Pugh class C, N=6) hepatic impairment, respectively. In another study, the average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with moderate or mild hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2)]*.

For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

In patients with SEGA, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 to 18 years were lower by 54% and 40%, respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults.

Ethnicity

Based on a cross-study comparison, Japanese patients (n=6) had on average exposures that were higher than non-Japanese patients receiving the same dose.

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

The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

12.6 QT/QTc Prolongation Potential

In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of AFINITOR in single doses up to 50 mg.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure ($AUC_{0\text{-}24h}$) at the 10 mg daily human dose.

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella,* mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m^2/day, approximately 255-fold the 10 mg daily human dose, and 103-fold the maximum dose administered to patients with SEGA, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with 5 mg/kg. These doses result in exposures which are 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 resulted in infertility in the rats at 5 mg/kg. Effects on male fertility occurred at the $AUC_{0\text{-}24h}$ values below that of therapeutic exposure (approximately 10%-81% of the $AUC_{0\text{-}24h}$ in patients receiving the 10 mg daily dose). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).

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 increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus *[see Use in Specific Populations (8.1)]*.

13.2 Animal Toxicology and/or Pharmacology

In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day.

14 CLINICAL STUDIES

14.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer

A randomized, double-blind, multicenter study of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER 2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. 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. Patients were permitted to have received 0-1 prior lines of chemotherapy for advanced disease.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on investigator (local radiology) assessment. Other endpoints included overall survival (OS), objective response rate (ORR), and safety.

Patients were randomly allocated in a 2:1 ratio to AFINITOR 10 mg/day plus exemestane 25 mg/day (n = 485) or to placebo plus exemestane 25 mg/day (n = 239). The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Patients were not permitted to cross over to AFINITOR at the time of disease progression.

The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the AFINITOR and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank p < 0.0001] (see Table 12 and Figure 1). The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.

Objective response rate was 12.6% (95% CI: 9.8, 15.9) in the AFINITOR plus exemestane arm vs. 1.7% (95% CI: 0.5, 4.2) in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the AFINITOR plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm.

The overall survival results were not mature at the time of the interim analysis, and no statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)].

Table 12: Progression-free Survival Results

Analysis	AFINITOR + exemestane[a] N = 485	Placebo + exemestane[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45[b] (0.38 to 0.54)	<0.0001[c]
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38[b] (0.3 to 0.5)	<0.0001[c]
Best overall response (%, 95% CI)				
Objective response rate (ORR)[d]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[e]	

[a] Exemestane (25 mg/day)

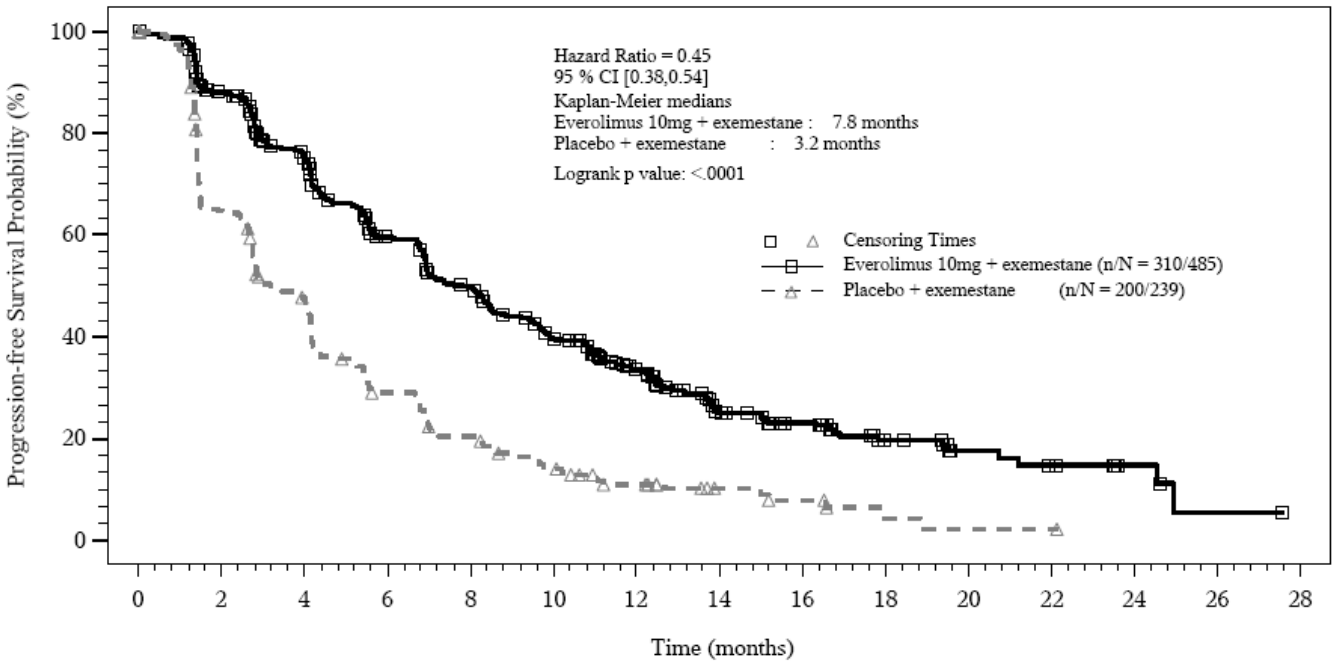
[b] Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis

[c] p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis

[d] Objective response rate = proportion of patients with CR or PR

[e] not applicable

Figure 1: Kaplan-Meier Progression-free Survival Curves (Investigator Radiological Review)



14.2 Advanced Neuroendocrine Tumors

Locally Advanced or Metastatic Advanced Pancreatic Neuroendocrine Tumors (PNET)

A randomized, double-blind, multi-center trial of AFINITOR plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (PNET) and disease progression 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 progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors). After documented radiological progression, patients could be unblinded by the investigator; those randomized to placebo were then able to receive open-label AFINITOR. Other endpoints included safety, objective response rate [ORR (complete response (CR) or partial response (PR)], response duration, and overall survival.

Patients were randomized 1:1 to receive either AFINITOR 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 79% Caucasian). Crossover from placebo to open-label AFINITOR occurred in 73% (148/203) of patients.

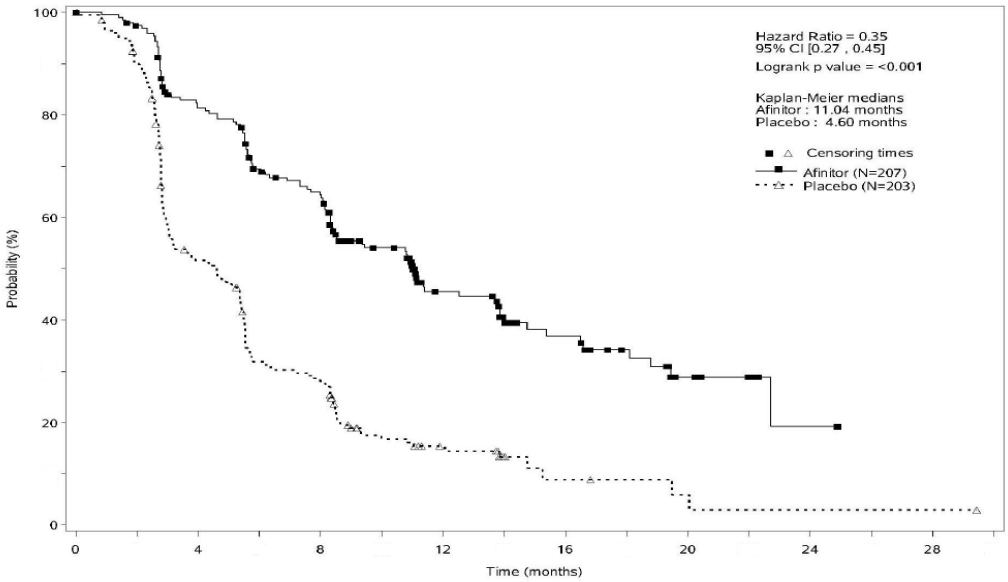
The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95%CI: 0.27 to 0.45; p<0.001) (see Table 13 and Figure 2). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analog use. The PFS results by investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 13.

Table 13: Progression-free Survival Results

Analysis	N	AFINITOR N=207	Placebo N=203	Hazard Ratio (95%CI)	p-value
	410	Median progression-free survival (months) (95% CI)			
Investigator radiological review		11.0 (8.4 to 13.9)	4.6 (3.1 to 5.4)	0.35 (0.27 to 0.45)	<0.001
Central radiological review		13.7 (11.2 to 18.8)	5.7 (5.4 to 8.3)	0.38 (0.28 to 0.51)	<0.001
Adjudicated radiological review[a]		11.4 (10.8 to 14.8)	5.4 (4.3 to 5.6)	0.34 (0.26 to 0.44)	<0.001

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

Figure 2: Kaplan-Meier Investigator-Determined Progression-free Survival Curves



Investigator-determined response rate was low (4.8%) in the AFINITOR arm and there were no complete responses. The overall survival results are not yet mature and no statistically significant treatment-related difference in OS was noted [HR=1.05 (95% CI: 0.71 to 1.55)].

Locally Advanced or Metastatic Carcinoid Tumors

In a randomized, double-blind, multi-center trial in 429 patients with carcinoid tumors, AFINITOR plus depot octreotide (Sandostatin LAR®) was compared to placebo plus depot octreotide. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR plus depot octreotide. The study did not meet the primary efficacy endpoint (PFS) and the OS interim analysis numerically favored the placebo plus depot octreotide arm. Therefore, the use of AFINITOR in patients with carcinoid tumors remains investigational.

14.3 Advanced Renal Cell Carcinoma

An international, multi-center, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted. Randomization was stratified according to prognostic score and prior anticancer therapy *[see References (15)]*.

Progression-free survival (PFS), documented using Response Evaluation Criteria in Solid Tumors (RECIST) was assessed via a blinded, independent, central radiologic review. 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 daily.

In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

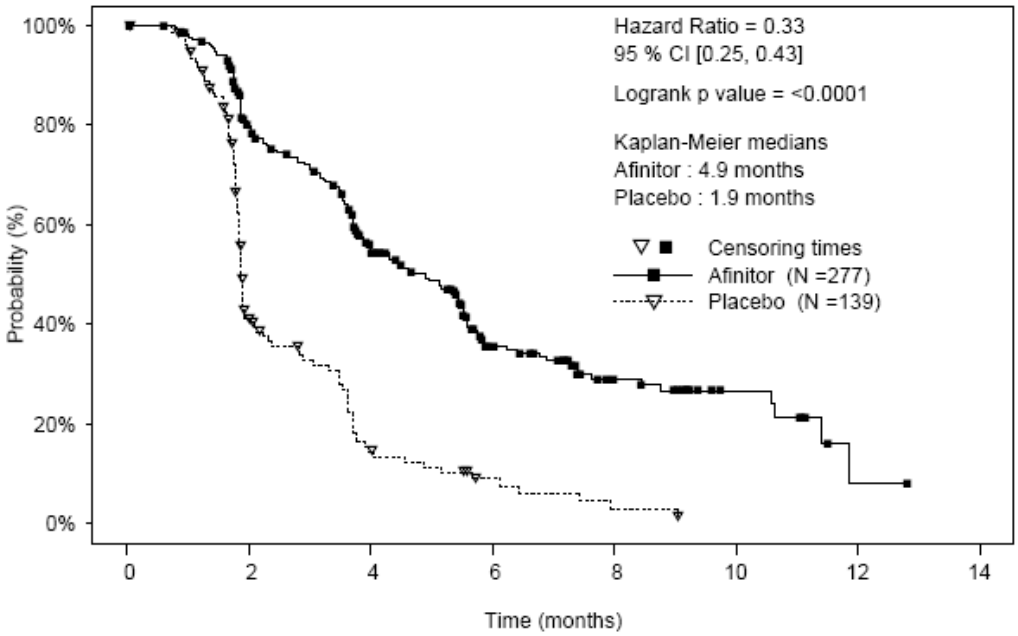
AFINITOR was superior to placebo for PFS (see Table 14 and Figure 3). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. Final overall survival (OS) results yield a hazard ratio of 0.90 (95% CI: 0.71 to 1.14), with no statistically significant difference between the two treatment groups. Planned crossover from placebo due to disease progression to open label AFINITOR occurred in 111 of the 139 patients (79.9%) and may have confounded the OS benefit.

Table 14: Efficacy Results by Central Radiologic Review

	AFINITOR N=277	Placebo N=139	Hazard Ratio (95% CI)	p-value [a]
Median Progression-free Survival (95% CI)	4.9 months (4.0 to 5.5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.0001
Objective Response Rate	2%	0%	n/a [b]	n/a [b]

[a] Log-rank test stratified by prognostic score.
[b] Not applicable.

Figure 3: Kaplan-Meier Progression-free Survival Curves



14.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex

A randomized (2:1), double-blind, placebo-controlled trial of AFINITOR was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (n=5).

The key eligibility requirements for this trial were at least one angiomyolipoma of ≥ 3 cm in longest diameter on CT/MRI based on local radiology assessment, no immediate indication for surgery, and age ≥ 18 years. Patients received daily oral AFINITOR 10 mg or matching placebo until disease progression or unacceptable toxicity. CT or MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks and annually thereafter. Clinical and photographic assessment of skin lesions were conducted at baseline and every 12 weeks thereafter until treatment discontinuation. The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review, which was defined as a ≥ 50% reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of

kidney volume increase ≥ 20%, and no angiomyolipoma related bleeding of ≥ grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. Analyses of efficacy outcome measures were limited to the blinded treatment period which ended 6 months after the last patient was randomized. The comparative angiomyolipoma response rate analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Of the 118 patients enrolled, 79 were randomized to AFINITOR and 39 to placebo. The median age was 31 years (range 18 to 61 years), 34% were male, and 89% were Caucasian. At baseline, 17% of patients were receiving EIAEDs. On central radiology review at baseline, 92% of patients had at least one angiomyolipoma of ≥ 3 cm in longest diameter, 29% had angiomyolipomas ≥ 8 cm, 78% had bilateral angiomyolipomas, and 97% had skin lesions. The median values for the sum of all target renal angiomyolipoma lesions at baseline were 85 cm^3 (range 9 to 1612 cm^3) and 120 cm^3 (range 3 to 4520 cm^3) in the AFINITOR and placebo arms respectively. Forty-six (39%) patients had prior renal embolization or nephrectomy. The median duration of follow-up was 8.3 months (range 0.7 to 24.8 months).

The renal angiomyolipoma response rate was statistically significantly higher in AFINITOR-treated patients; there were 33 (41.8%) patients with angiomyolipoma responses in the AFINITOR arm as compared to none in the placebo arm. Results are displayed in Table 15. The median response duration is 5.3+ months (range 2.3+ to 19.6+ months).

Table 15: Angiomyolipoma Response

	AFINITOR N=79	**Placebo N=39**	**p-value**
Primary analysis			
Angiomyolipoma response rate[a] - %	**41.8**	**0**	**<0.0001**
95% CI	(30.8, 53.4)	(0.0, 9.0)	

[a] Per independent central radiology review

There were 3 patients in the AFINITOR arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review. The time to angiomyolipoma progression was statistically significantly longer in the AFINITOR arm (HR 0.08 [95% CI: 0.02, 0.37]; p <0.0001).

Skin lesion response rates were assessed by local investigators in 77 patients in the AFINITOR arm and 37 patients in the placebo arm with skin lesions at study entry. The skin lesion response rate was statistically significantly higher in the AFINITOR arm (26% vs. 0, p=0.0011); all skin lesion responses were partial responses, defined as visual improvement in 50%-99% skin lesions, considering all skin lesions, durable for at least eight weeks (Physician's Global Assessment of Clinical Condition).

14.5 Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex

Study 1 was a randomized (2:1), double-blind, placebo-controlled trial of AFINITOR Tablets conducted in 117 pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC). Eligible patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter on MRI based on local radiology assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received AFINITOR Tablets at a starting dose of 4.5 mg/m^2 daily, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL as tolerated. AFINITOR/matched placebo treatment continued until disease progression or unacceptable toxicity. MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter.

The main efficacy outcome measure was SEGA response rate based on independent central radiology review. SEGA response was defined as a ≥ 50% reduction in the sum of SEGA volume relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, and new or worsening hydrocephalus. Analysis of SEGA response rate was limited to the blinded treatment period which ended 6 months after the last patient was randomized. The analysis of SEGA response rate was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Of the 117 patients enrolled, 78 were randomized to AFINITOR and 39 to placebo. The median age was 9.5 years (range 0.8 to 26 years; 69% were 3 to < 18 years at enrollment; 17% were < 3 years at enrollment), 57% were male, and 93% were Caucasian. At baseline, 18% of patients were receiving EIAEDs. Based on central radiology review at baseline, 98% of patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter, 79% had bilateral SEGAs, 43% had ≥ 2 target SEGA lesions, 26% had growth in or into the inferior surface of the ventricle, 9% had evidence of growth beyond the

subependymal tissue adjacent to the ventricle, and 7% had radiographic evidence of hydrocephalus. The median values for the sum of all target SEGA lesions at baseline were 1.63 cm^3 (range 0.18 to 25.15 cm^3) and 1.30 cm^3 (range 0.32 to 9.75 cm^3) in the AFINITOR and placebo arms respectively. Eight (7%) patients had prior SEGA-related surgery. The median duration of follow-up was 8.4 months (range 4.6 to 17.2 months).

The SEGA response rate was statistically significantly higher in AFINITOR-treated patients. There were 27 (35%) patients with SEGA responses in the AFINITOR arm and no SEGA responses in the placebo arm. Results are displayed in Table 16. At the time of the final analysis, all SEGA responses were ongoing and the median duration of response was 5.3 months (range 2.1 to 8.4 months). No patient in either treatment arm required surgical intervention during the course of Study 1.

Table 16: SEGA response

	AFINITOR N=78	**Placebo N=39**	**p-value**
Final analysis			
SEGA response rate[a] - (%)	**35**	**0**	**<0.0001**
95% CI	24, 46	0, 9	

[a] Per independent central radiology review

With a median follow-up of 8.4 months, SEGA progression was detected in 6 of 39 (15.4%) patients randomized to receive placebo and none of the 78 patients randomized to receive AFINITOR.

Study 2 was an open-label, single-arm trial conducted to evaluate the safety and efficacy of AFINITOR in patients with SEGA and TSC. Serial radiological evidence of SEGA growth was required for entry. Change in SEGA volume at the end of the core 6-month treatment phase was assessed via independent central radiology review. In total, 28 patients received treatment with AFINITOR; median age was 11 years (range 3-34), 61% male, 86% Caucasian. Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving AFINITOR treatment. After the core treatment phase, patients could continue to receive AFINITOR treatment as part of an extension treatment phase where SEGA volume was assessed every 6 months. The median duration of treatment was 34.2 months (range 4.7-47.1 months).

At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. The median duration of response for these 9 patients was 11.8 months (range 3.2 to 39.1 months). Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff.

Three of 4 patients who had prior surgery experienced a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions.

15 REFERENCES

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- Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

AFINITOR (everolimus) Tablets

2.5 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “LCL” on one side and “NVR” on the other; available in:
Blisters of 28 tablets……NDC 0078-0594-51
Each carton contains 4 blister cards of 7 tablets each

5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other; available in:
Blisters of 28 tablets……NDC 0078-0566-51
Each carton contains 4 blister cards of 7 tablets each

7.5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “7P5” on one side and “NVR” on the other; available in:
Blisters of 28 tablets.....NDC 0078-0620-51
Each carton contains 4 blister cards of 7 tablets each

10 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other; available in:
Blisters of 28 tablets……NDC 0078-0567-51
Each carton contains 4 blister cards of 7 tablets each

AFINITOR DISPERZ (everolimus tablets for oral suspension)

2 mg tablets for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and no score, engraved with “D2” on one side and “NVR” on the other; available in:
Blisters of 28 tablets.....NDC 0078-0626-51
Each carton contains 4 blister cards of 7 tablets each

3 mg tablets for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and no score, engraved with “D3” on one side and “NVR” on the other; available in:
Blisters of 28 tablets.....NDC 0078-0627-51
Each carton contains 4 blister cards of 7 tablets each

5 mg tablets for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and no score, engraved with “D5” on one side and “NVR” on the other; available in:
Blisters of 28 tablets.....NDC 0078-0628-51
Each carton contains 4 blister cards of 7 tablets each

Store AFINITOR (everolimus) Tablets and AFINITOR DISPERZ (everolimus tablets for oral suspension) at 25°C (77°F); excursions permitted between 15°–30°C (59°–86°F). See USP Controlled Room Temperature. Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken.

17 PATIENT COUNSELING INFORMATION

17.1 Non-infectious Pneumonitis

Warn patients of the possibility of developing non-infectious pneumonitis. In clinical studies, some non-infectious pneumonitis cases have been severe and occasionally fatal. Advise patients to report promptly any new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

17.2 Infections

Inform patients that they are more susceptible to infections while being treated with AFINITOR and that cases of hepatitis B reactivation have been associated with AFINITOR treatment. In clinical studies, some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Patients should be aware of the signs and symptoms of infection and should report any such signs or symptoms promptly to their physician *[see Warnings and Precautions (5.2)]*.

17.3 Oral Ulceration

Inform patients of the possibility of developing mouth ulcers, stomatitis, and oral mucositis. In such cases, mouthwashes and/or topical treatments are recommended, but these should not contain alcohol, peroxide, iodine, or thyme *[see Warnings and Precautions (5.3)]*.

17.4 Renal Failure

Inform patients of the possibility of developing kidney failure. In some cases kidney failure has been severe and occasionally fatal. Inform patients of the need for the healthcare provider to monitor kidney function, especially in patients with risk factors that may impair kidney function *[see Warnings and Precautions (5.4)]*.

17.5 Laboratory Tests and Monitoring

Inform patients of the need to monitor blood chemistry and hematology prior to the start of AFINITOR therapy and periodically thereafter *[see Warnings and Precautions (5.6)]*.

17.6 Drug-drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements. Inform the patients to avoid concomitant administration of strong CYP3A4 inhibitors or inducers while on AFINITOR treatment *[see Dosage and Administration (2.2, 2.5), Warnings and Precautions (5.7), Drug Interactions (7.1, 7.2)]*.

17.7 Vaccinations

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines *[see Warnings and Precautions (5.9)]*.

17.8 Embryo-fetal Toxicity

Advise female patients of childbearing potential that AFINITOR may cause fetal harm and that a highly effective method of contraception should be used during therapy with AFINITOR and for 8 weeks after ending treatment *[see Warnings and Precautions (5.10)]*.

17.9 Safe Handling Practices for AFINITOR DISPERZ

Advise patients and their caregivers to read and carefully follow the FDA approved AFINITOR DISPERZ “Instructions for Use” to minimize unintended exposure to AFINITOR.

17.10 Dosing Instructions

Advise patients that AFINITOR is available in two dosage forms: tablets (AFINITOR Tablets) and tablets for oral suspension (AFINITOR DISPERZ). AFINITOR DISPERZ is recommended only for the treatment of patients with SEGA and TSC in conjunction with therapeutic drug monitoring *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

Inform patients to take AFINITOR Tablets orally once daily at the same time every day, either consistently with food or consistently without food. Inform patients that AFINITOR Tablets should be swallowed whole with a glass of water.

Inform patients that AFINITOR DISPERZ should be taken as a suspension only and should not be swallowed whole. The suspension should be taken orally once daily at the same time every day, either consistently with food or consistently without food. Review the procedures for preparation of the AFINITOR DISPERZ suspension with patients *[see Dosage and Administration (2.7)]*. Refer patients to the "Instructions for Use" pamphlet for additional information regarding these procedures.

Instruct patients that if they miss a dose of AFINITOR, they may still take it up to 6 hours after the time they would normally take it. If more than 6 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take AFINITOR at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

PATIENT INFORMATION
AFINITOR® (a-fin-it-or)
(everolimus)
Tablets

AFINITOR® DISPERZ (a-fin-it-or dis-perz)
(everolimus tablets for oral suspension)

Read this Patient Information leaflet that comes with AFINITOR or AFINITOR DISPERZ before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AFINITOR and AFINITOR DISPERZ?

AFINITOR and AFINITOR DISPERZ can cause serious side effects. These serious side effects include:

1. **You may develop lung or breathing problems.** In some people lung or breathing problems may be severe, and can even lead to death. Tell your healthcare provider right away if you have any of these symptoms:
   - New or worsening cough
   - Shortness of breath
   - Chest pain
   - Difficulty breathing or wheezing

2. **You may be more likely to develop an infection,** such as pneumonia, or a bacterial, fungal or viral infection. Viral infections may include active hepatitis B in people who have had hepatitis B in the past (reactivation). In some people these infections may be severe, and can even lead to death. You may need to be treated as soon as possible.

   Tell your healthcare provider right away if you have a temperature of 100.5°F or above, chills, or do not feel well.

   Symptoms of hepatitis B or infection may include the following:
   - Fever
   - Chills
   - Skin rash
   - Joint pain and inflammation
   - Tiredness
   - Loss of appetite
   - Nausea
   - Pale stools or dark urine
   - Yellowing of the skin
   - Pain in the upper right side of the stomach

3. **You may develop kidney failure.** In some people this may be severe and can even lead to death. Your healthcare provider should do tests to check your kidney function before and during your treatment with AFINITOR or AFINITOR DISPERZ.

If you have any of the serious side effects listed above, you may need to stop taking AFINITOR or AFINITOR DISPERZ for a while or use a lower dose. Follow your healthcare provider's instructions.

What is AFINITOR?

AFINITOR is a prescription medicine used to treat:

- advanced hormone receptor-positive, HER2-negative breast cancer, along with the medicine exemestane, in postmenopausal women who have already received certain other medicines for their cancer.
- adults with a type of pancreatic cancer known as pancreatic neuroendocrine tumor (PNET), that has progressed and cannot be treated with surgery.
  It is not known if AFINITOR is safe and effective in people with carcinoid tumors.
- adults with advanced kidney cancer (renal cell carcinoma or RCC) when certain other medicines have not worked.
- people with the following types of tumors that are seen with a genetic condition called tuberous sclerosis complex (TSC):
  - adults with a kidney tumor called angiomyolipoma, when their kidney tumor does not require surgery right away.
  - adults and children with a brain tumor called subependymal giant cell astrocytoma (SEGA) when the tumor cannot be removed completely by surgery.

What is AFINITOR DISPERZ?

AFINITOR DISPERZ is a prescription medicine used to treat:

- adults and children with a genetic condition called tuberous sclerosis complex (TSC) who have a brain tumor called subependymal giant cell astrocytoma (SEGA) when the tumor cannot be removed completely by surgery.

Who should not take AFINITOR or AFINITOR DISPERZ?

Do not take AFINITOR or AFINITOR DISPERZ if you are allergic to everolimus or to any of the ingredients in AFINITOR or AFINITOR DISPERZ. See the end of this leaflet for a complete list of ingredients in AFINITOR and AFINITOR DISPERZ.

Talk to your healthcare provider before taking this medicine if you are allergic to:

- sirolimus (Rapamune®)
- temsirolimus (Torisel®)

Ask your healthcare provider if you do not know.

What should I tell my healthcare provider before taking AFINITOR or AFINITOR DISPERZ?

Before taking AFINITOR or AFINITOR DISPERZ, tell your healthcare provider about all of your medical conditions, including if you:

- Have or have had kidney problems
- Have or have had liver problems
- Have diabetes or high blood sugar
- Have high blood cholesterol levels
- Have any infections
- Previously had hepatitis B

- Are scheduled to receive any vaccinations. You should not receive a "live vaccine" or be around people who have recently received a "live vaccine" during your treatment with AFINITOR or AFINITOR DISPERZ. If you are not sure about the type of immunization or vaccine, ask your healthcare provider.
- Have other medical conditions
- Are pregnant, or could become pregnant. AFINITOR or AFINITOR DISPERZ can cause harm to your unborn baby. You should use effective birth control while using AFINITOR or AFINITOR DISPERZ and for 8 weeks after stopping treatment.
- Are breastfeeding or plan to breastfeed. It is not known if AFINITOR or AFINITOR DISPERZ passes into your breast milk. You and your healthcare provider should decide if you will take AFINITOR or AFINITOR DISPERZ, or breastfeed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

AFINITOR or AFINITOR DISPERZ may affect the way other medicines work, and other medicines can affect how AFINITOR or AFINITOR DISPERZ work. Using AFINITOR or AFINITOR DISPERZ with other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine. Especially tell your healthcare provider if you take:
- St. John's Wort (Hypericum perforatum)
- Medicine for:
    - Fungal infections
    - Bacterial infections
    - Tuberculosis
    - Seizures
    - HIV-AIDS
    - Heart conditions or high blood pressure
- Medicines that weaken your immune system (your body's ability to fight infections and other problems)

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of those taken for the conditions listed above. If you are taking any medicines for the conditions listed above, your healthcare provider might need to prescribe a different medicine or your dose of AFINITOR or AFINITOR DISPERZ may need to be changed. You should also tell your healthcare provider before you start taking any new medicine.

How should I take AFINITOR or AFINITOR DISPERZ?
- Your healthcare provider will prescribe the dose of AFINITOR or AFINITOR DISPERZ that is right for you.
- Take AFINITOR or AFINITOR DISPERZ exactly as your healthcare provider tells you to.
- Your healthcare provider may change your dose of AFINITOR or AFINITOR DISPERZ if needed.
- Use scissors to open the blister pack.

AFINITOR:

- Swallow AFINITOR tablets whole with a glass of water. Do not take any tablet that is broken or crushed.

AFINITOR DISPERZ:

- If your healthcare provider prescribes AFINITOR DISPERZ for you, see the "Instructions for Use" that come with your medicine for instructions on how to prepare and take your dose.
- Each dose of AFINITOR DISPERZ must be prepared as a suspension before it is given.
- AFINITOR DISPERZ can cause harm to an unborn baby. When possible, the suspension should be prepared by an adult who is not pregnant or planning to become pregnant.
- Anyone who prepares suspensions of AFINITOR DISPERZ for another person should wear gloves to avoid possible contact with the medicine.

- Take AFINITOR or AFINITOR DISPERZ one time each day at about the same time.
- Take AFINITOR or AFINITOR DISPERZ the same way each time, either with food or without food.
- If you take too much AFINITOR or AFINITOR DISPERZ contact your healthcare provider or go to the nearest hospital emergency department right away. Take the pack of AFINITOR or AFINITOR DISPERZ with you.
- If you miss a dose of AFINITOR or AFINITOR DISPERZ, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your AFINITOR or AFINITOR DISPERZ, skip the dose for that day. The next day, take AFINITOR or AFINITOR DISPERZ at your usual time. Do not take 2 doses to make up for the one that you missed. If you are not sure about what to do, call your healthcare provider.
- You should have blood tests before you start AFINITOR or AFINITOR DISPERZ and as needed during your treatment. These will include tests to check your blood cell count, kidney and liver function, cholesterol, and blood sugar levels.
- If you take AFINITOR or AFINITOR DISPERZ to treat SEGA, you will also need to have blood tests regularly to measure how much medicine is in your blood. This will help your healthcare provider decide how much AFINITOR or AFINITOR DISPERZ you need to take.

What should I avoid while taking AFINITOR or AFINITOR DISPERZ?

You should not drink grapefruit juice or eat grapefruit during your treatment with AFINITOR or AFINITOR DISPERZ. It may make the amount of AFINITOR in your blood increase to a harmful level.

What are the possible side effects of AFINITOR or AFINITOR DISPERZ?

AFINITOR and AFINITOR DISPERZ can cause serious side effects.

- **See "What is the most important information I should know about AFINITOR and AFINITOR DISPERZ?" for more information.**

Common side effects of AFINITOR in people with advanced hormone receptor-positive, HER 2-negative breast cancer, advanced pancreatic neuroendocrine tumors, and advanced kidney cancer include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol, peroxide, iodine, or thyme.
- Infections
- Feeling weak or tired

- Cough, shortness of breath
- Diarrhea and constipation
- Rash, dry skin, and itching
- Nausea and vomiting
- Fever
- Loss of appetite, weight loss
- Swelling of arms, hands, feet, ankles, face or other parts of the body
- Abnormal taste
- Dry mouth
- Inflammation of lining of the digestive system
- Headache
- Nose bleeds
- Pain in arms and legs, mouth and throat, back or joints
- High blood glucose
- High blood pressure
- Difficulty sleeping
- Hair loss
- Muscle spasms
- Feeling dizzy
- Nail disorders

Common side effects of AFINITOR and AFINITOR DISPERZ in people who have SEGA or renal angiomyolipoma with TSC include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol, peroxide iodine, or thyme.
- Infections
- Nausea and vomiting
- Diarrhea and constipation
- Swelling of your hands, arms, legs, and feet
- Joint pain
- Cough
- Skin problems (such as rash, acne, or dry skin)
- Fever
- Feeling tired
- Anxiety, aggression, and other abnormal behaviors
- Absence of menstrual periods (menstruation). You may miss one or more menstrual periods. Tell your healthcare provider if this happens.
- Low red blood cells, white blood cells or platelets
- Increased blood cholesterol level and certain other blood tests
- Increased blood sugar levels
- Decreased blood phosphate levels

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of AFINITOR and AFINITOR DISPERZ. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AFINITOR or AFINITOR DISPERZ?

- Store AFINITOR or AFINITOR DISPERZ at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep AFINITOR or AFINITOR DISPERZ in the pack it comes in.
- Open the blister pack just before taking AFINITOR or AFINITOR DISPERZ.
- Keep AFINITOR or AFINITOR DISPERZ dry and away from light.
- Do not use AFINITOR or AFINITOR DISPERZ that is out of date or no longer needed.

Keep AFINITOR or AFINITOR DISPERZ and all medicines out of the reach of children.

General information about AFINITOR and AFINITOR DISPERZ

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AFINITOR or AFINITOR DISPERZ for a condition for which it was not prescribed. Do not give AFINITOR or AFINITOR DISPERZ to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about AFINITOR and AFINITOR DISPERZ. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information written for healthcare professionals.

For more information call 1-888-423-4648 or go to www.AFINITOR.com.

What are the ingredients in AFINITOR?

Active ingredient: everolimus.
Inactive ingredients: anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate.

What are the ingredients in AFINITOR DISPERZ?

Active ingredient: everolimus.
Inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol, and microcrystalline cellulose.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Revised August 2012

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T2012-/T2012-

Instructions For Use
AFINITOR® (a-fin-it-or) DISPERZ™ (dis-perz)
(everolimus tablets for oral suspension)

Read these Instructions for Use for AFINITOR DISPERZ before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Important Information:

- **Take AFINITOR DISPERZ as a suspension only**. AFINITOR DISPERZ is prepared as a suspension of un-dissolved medicine that is mixed with water, and then it is taken by mouth. Do not chew, crush, or swallow AFINITOR DISPERZ whole.

- **AFINITOR DISPERZ can cause harm to an unborn baby**. When possible, the suspension should be prepared by an adult who is not pregnant or planning to become pregnant.

- Keep AFINITOR DISPERZ and the prepared suspension out of the reach of children.

- Anyone who prepares suspensions of AFINITOR DISPERZ for another person should wear gloves to avoid possible contact with the drug.

- Only use water with AFINITOR DISPERZ to prepare the suspension. Do not prepare the suspension with juice or any other liquids.

- The suspension must be given right away. If you do not give the dose within 60 minutes after it has been prepared, throw away the dose and prepare a new dose of AFINITOR DISPERZ.

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

Supplies needed to prepare the suspension in an oral syringe:

- Blister card with AFINITOR DISPERZ
- Scissors to open the blister card
- Disposable gloves (for one time use)
- 2 clean drinking glasses
- Approximately 30 mL of water
- 10 mL oral syringe (for one time use) (see Figure A)
- Paper towels

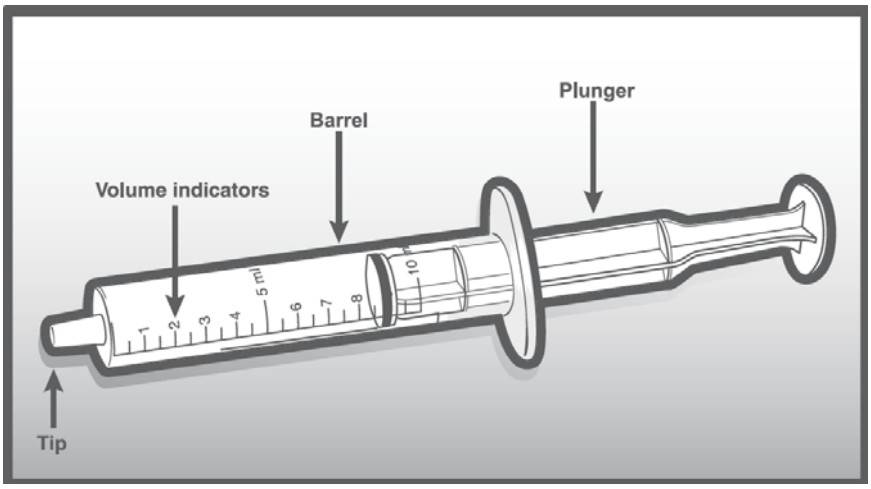

Figure A

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

- Blister card with AFINITOR DISPERZ
- Scissors to open the blister card
- Disposable gloves (for one time use)
- 30 mL dose cup for measuring water (you can ask your pharmacist for this)
- 1 clean drinking glass (maximum size 100 mL)
- Water to prepare the suspension
- Spoon for stirring
- Paper towels

Preparing a dose of AFINITOR DISPERZ suspension using an oral syringe:

Step 1: Prepare a clean, flat work surface that is away from where you prepare and eat food. Place a clean paper towel on the work surface. Place the needed supplies on the paper towel.

Step 2: Wash and dry your hands well before preparing the medicine (see Figure B).

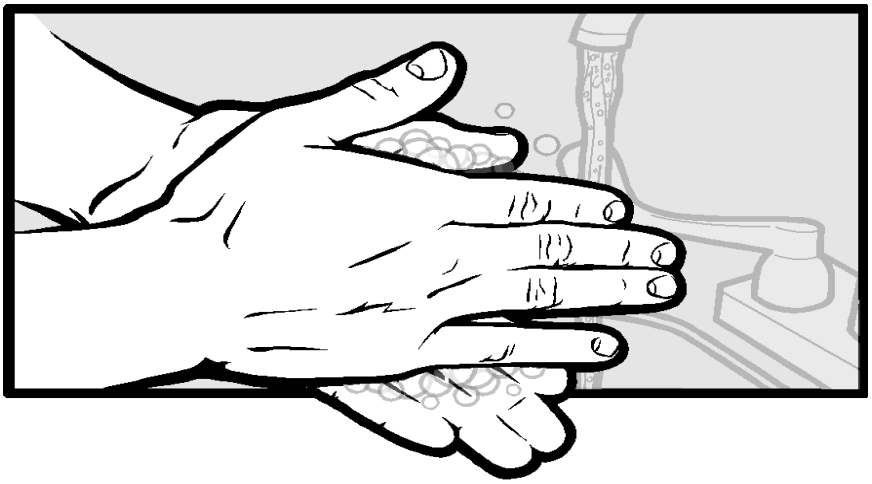

Figure B

Step 3: If preparing the AFINITOR DISPERZ suspension for another person, put on disposable gloves (see Figure C).

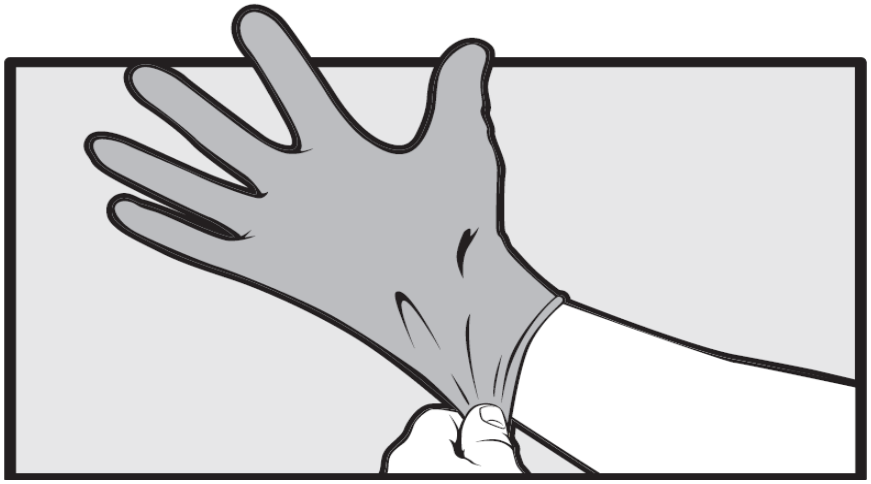

Figure C

Step 4: Take a 10 mL oral syringe and pull back on the plunger. Remove the plunger from the barrel of the syringe (see Figure D).

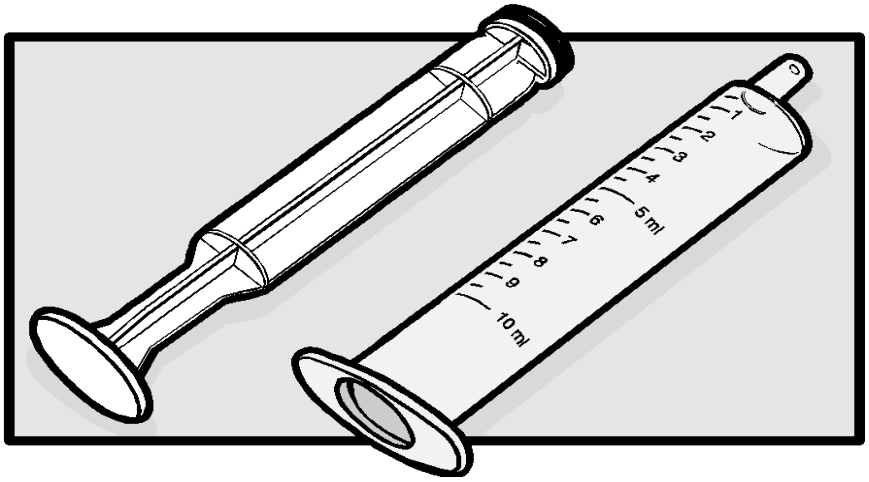

Figure D

Step 5: Use scissors to open the blister card along the dotted line (see Figure E) and remove the prescribed number of AFINITOR DISPERZ tablets for oral suspension from the blister card. Place them into the barrel of the oral syringe (see Figure F).

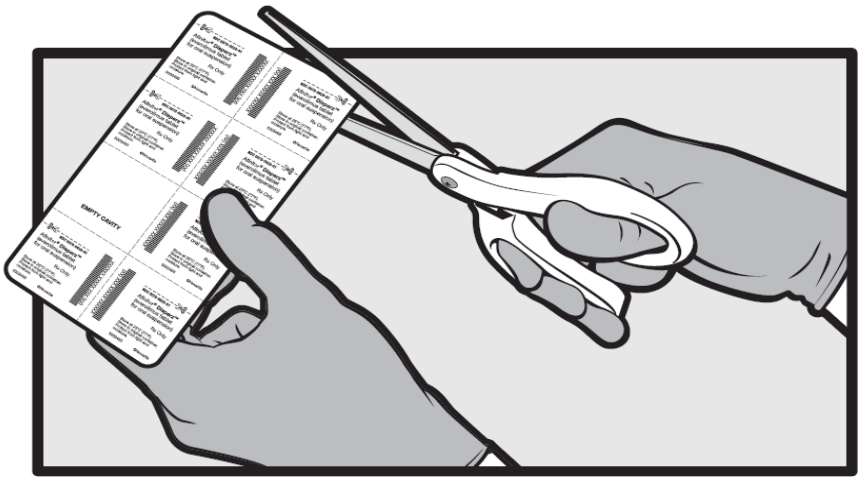

Figure E

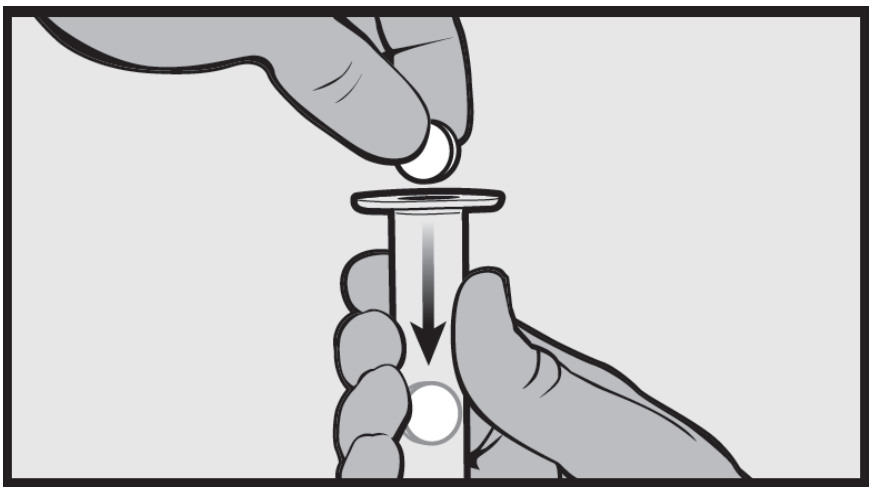

Figure F

- Doses of up to 10 mg can be prepared with the oral syringe. **If your total prescribed dose is more than 10 mg, you will need to split the dose. Follow steps 4 through 17 for the first half of the dose. Then repeat steps 4 through 17 for the second half of the dose. Do not prepare a dose of more than 10 mg in one syringe.** Ask your pharmacist or healthcare provider if you are not sure what to do.

Step 6: Re-insert the plunger into the barrel of the oral syringe (see Figure G) and push the plunger in until it comes into contact with the AFINITOR DISPERZ tablets for oral suspension (see Figure H).

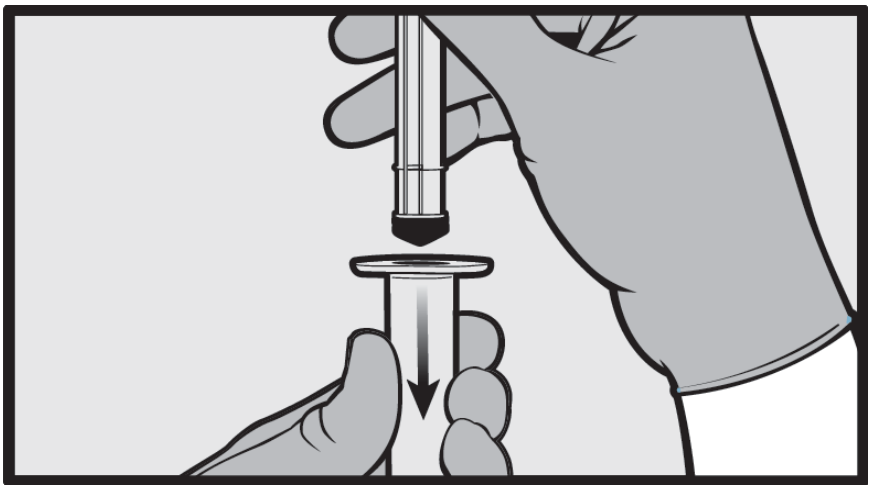

Figure G

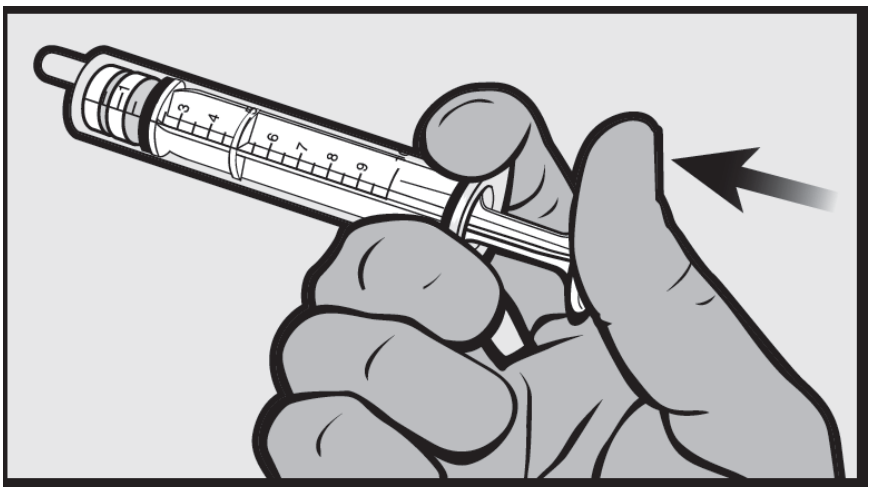

Figure H

Step 7: Fill a small drinking glass with about 30 mL of water. Insert the tip of the oral syringe into the water. Then slowly pull back on the plunger until the syringe is about half full of water and all the tablets are covered by water (see Figure I).

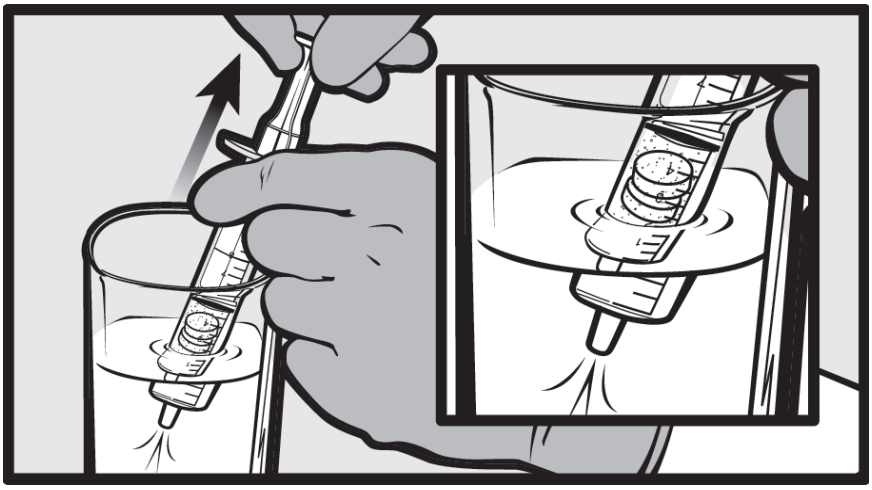

Figure I

Step 8: Hold the oral syringe with the tip pointing up. Pull back on the plunger to draw back about 4 mL of air (see Figure J).

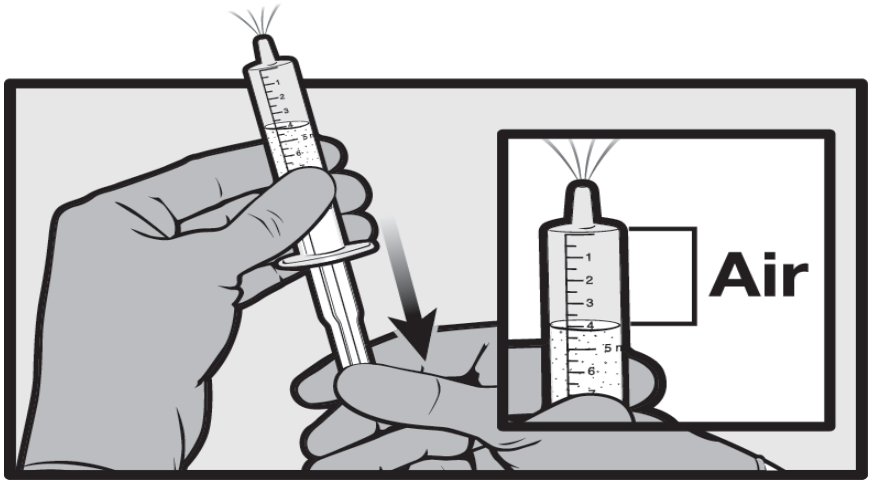

Figure J

Step 9: Place the filled oral syringe in the clean, empty glass with the tip pointing up. Wait **3 minutes** to allow AFINITOR DISPERZ to break apart (see Figure K).

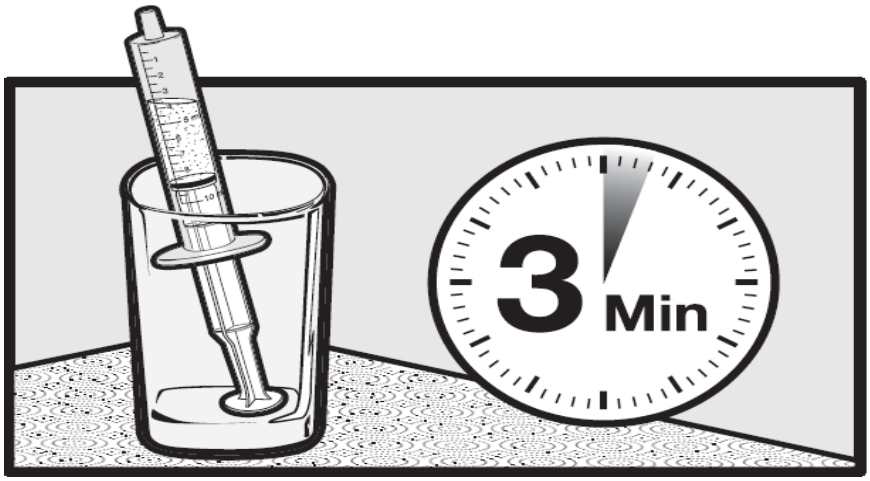

Figure K

Step 10: Slowly turn the oral syringe up and down five times just before giving the dose (see Figure L). **Do not shake** the syringe.

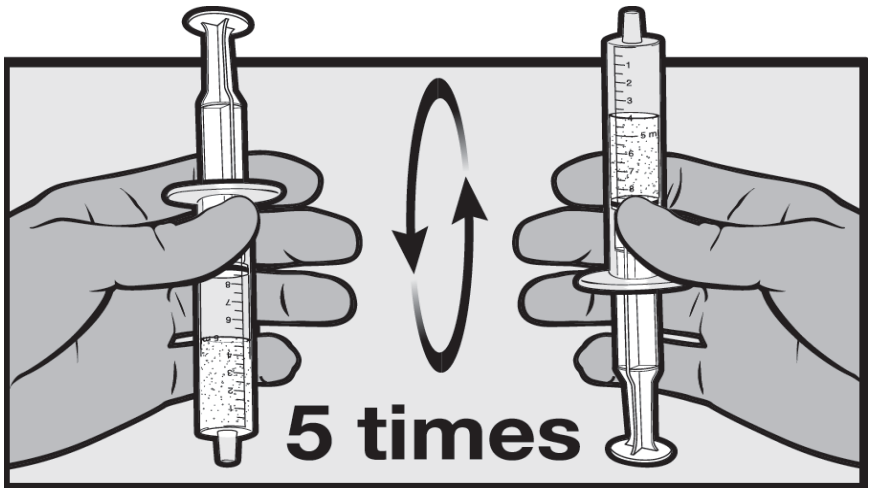

Figure L

Step 11: Hold the oral syringe in an upright position (with the tip up). Carefully remove most of the air by pushing up gently on the plunger (see Figure M).

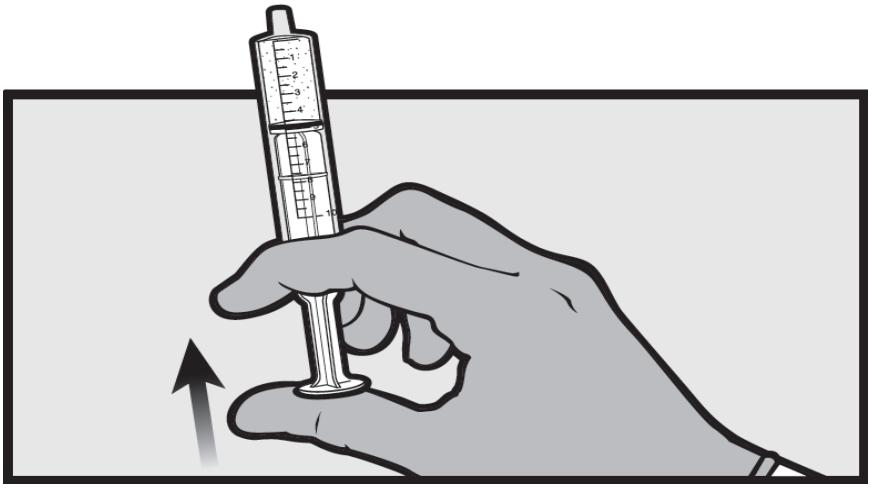

Figure M

Step 12: Give the full contents of the oral syringe slowly and gently into the mouth right away, within 60 minutes of preparing it (see Figure N). Carefully remove the syringe from the mouth. Continue with steps 13 through 17 to make sure that the entire dose of medicine is given.

(b) (4)

Figure N

Step 13: Insert the tip of the oral syringe into the drinking glass that is filled with water, and pull up about 5 mL of water by slowly pulling back on the plunger (see Figure O).

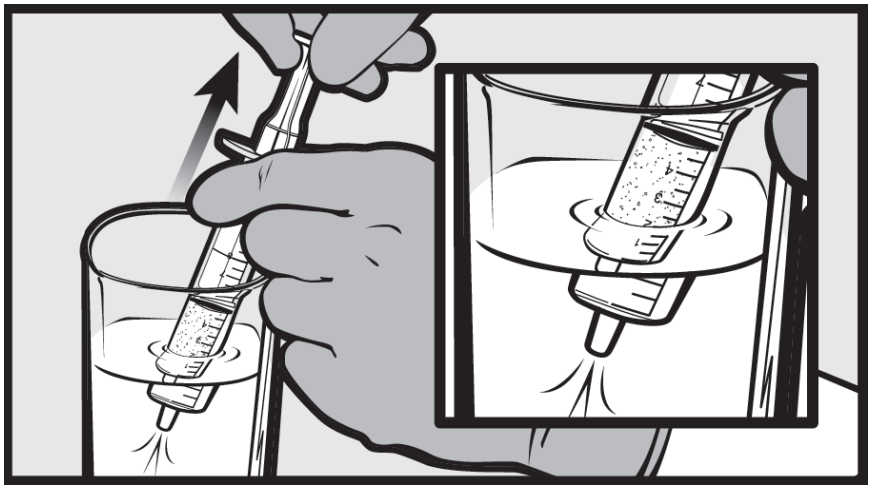

Figure O

Step 14: Hold the oral syringe with the tip pointing up and use the plunger to draw back about 4 mL of air (see Figure P).

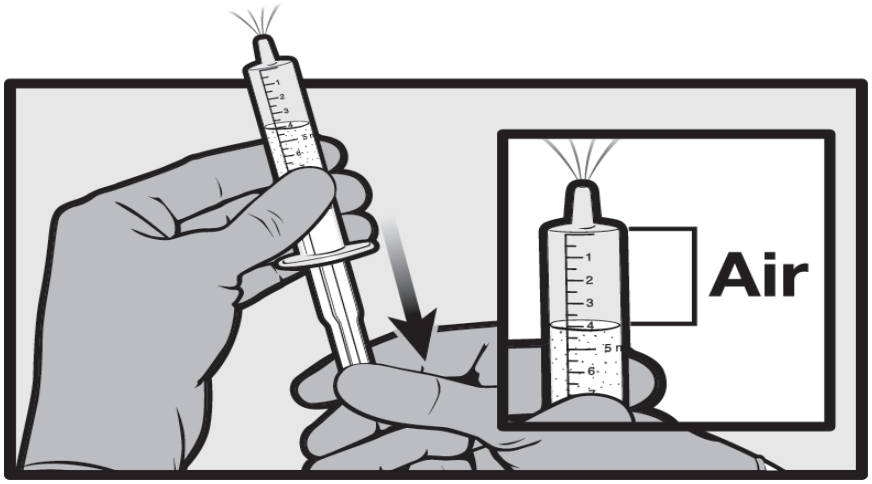

Figure P

Step 15: With the tip of the syringe still pointing up, swirl the contents by gently rotating the syringe in a circular motion (see Figure Q).

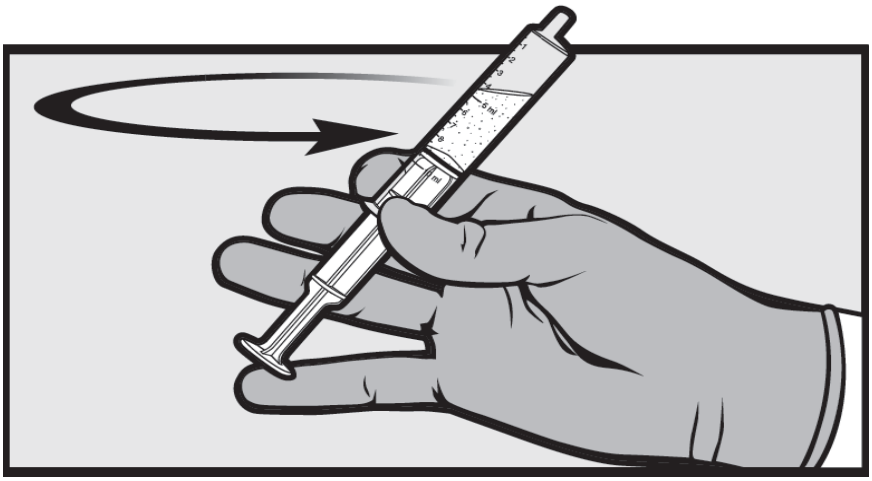

Figure Q

Step 16: Hold the oral syringe in an upright position (with the tip up). Carefully remove most of the air by pushing up gently on the plunger (see Figure R).

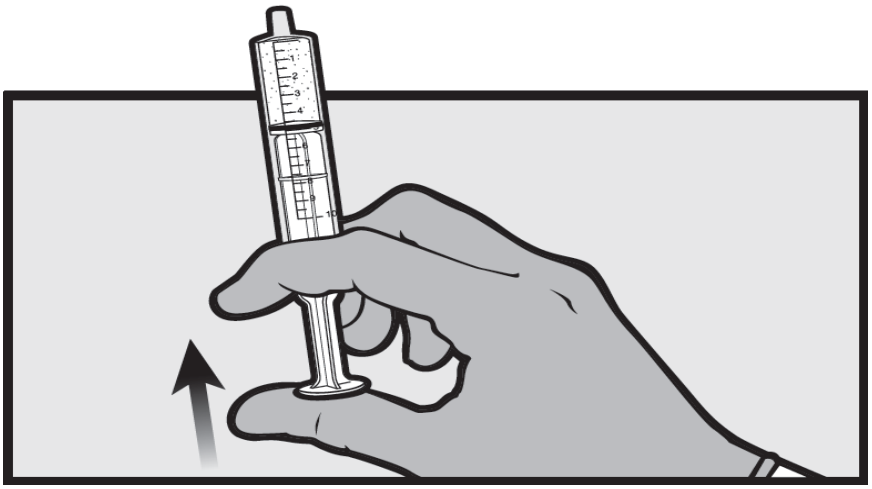

Figure R

Step 17: Give the full contents of the oral syringe slowly and gently into the mouth by pushing on the plunger (see Figure S). Carefully remove the syringe from the mouth.

(b) (4)

Figure S

If the total prescribed dose is more than 10 mg, repeat steps 4 through 17 to finish giving the dose.

Step 18: Throw away the oral syringe, paper towel, and used gloves in your household trash.

Step 19: Wash your hands.

Preparing a dose of AFINITOR DISPERZ suspension using a small drinking glass:

Step 1: Prepare a clean, flat work surface that is away from where you prepare and eat food. Place a clean paper towel on the work surface. Place the needed supplies on the paper towel.

Step 2: Wash and dry your hands before preparing the medicine (See Figure T).

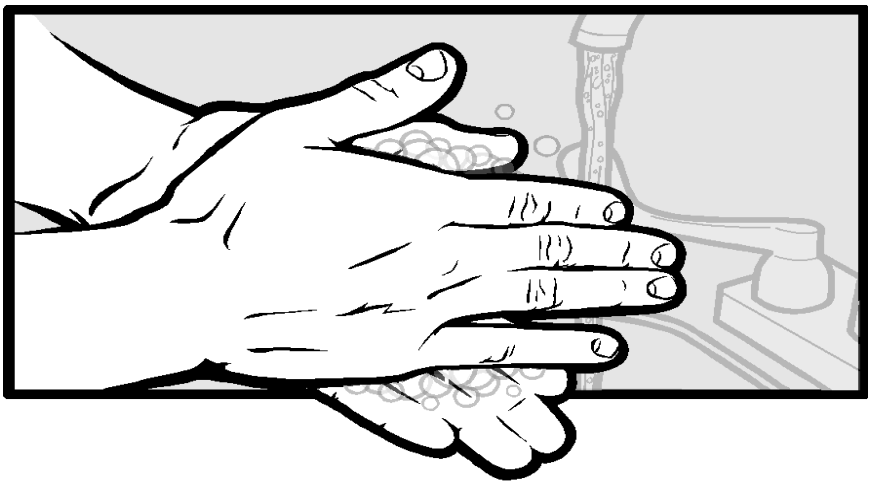

Figure T

Step 3: If preparing the AFINITOR DISPERZ suspension for another person, put on disposable gloves (see Figure U).

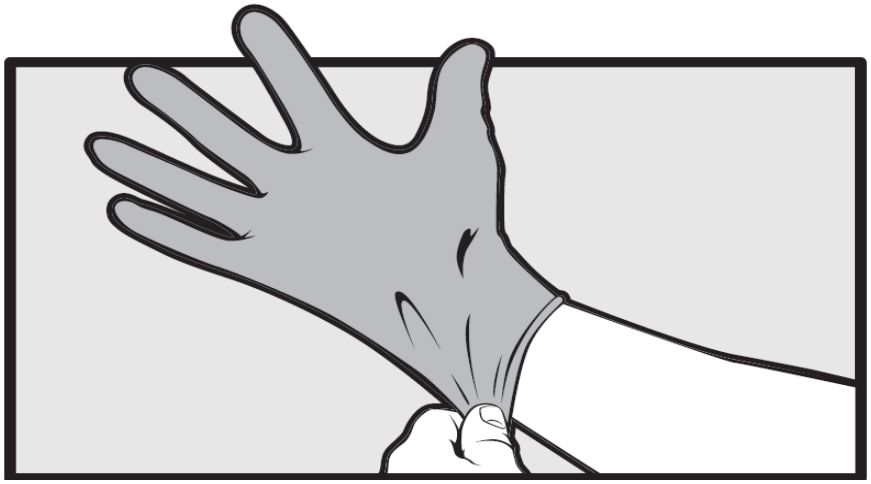

Figure U

Step 4: Add about 25 mL of water to the 30 mL dose cup. The amount of water added does not need to be exact (see Figure V).

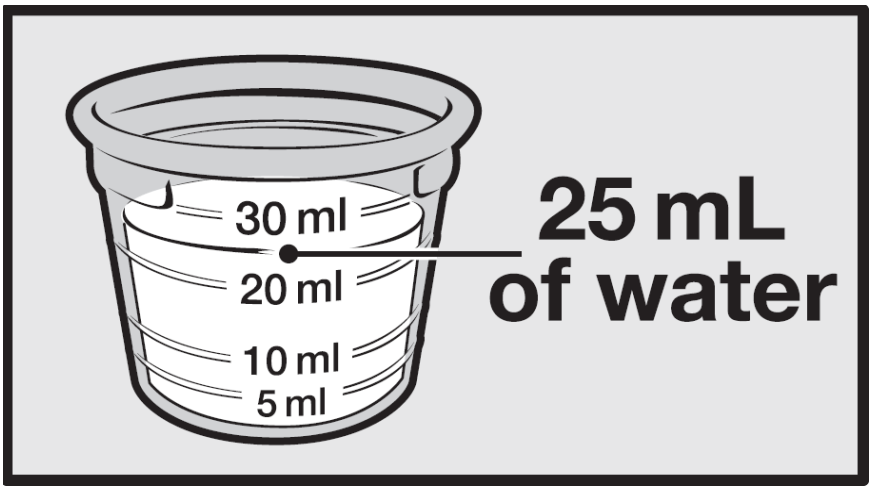

Figure V

Step 5: Pour the water from the dose cup into a small drinking glass (maximum size 100 mL) (see Figure W).

Figure W

- Doses up to 10 mg can be prepared in the small drinking glass. If your total prescribed dose is more than 10 mg you will need to split the dose. **Follow steps 4 through 10 for the first half of the dose. Then repeat steps 4 through 10 for the second half of the dose.** Ask your pharmacist or healthcare provider if you are not sure what to do.

Step 6: Use scissors to open the blister card along the dotted line (see Figure X) and remove the prescribed number of AFINITOR DISPERZ tablets for oral suspension from the blister card.

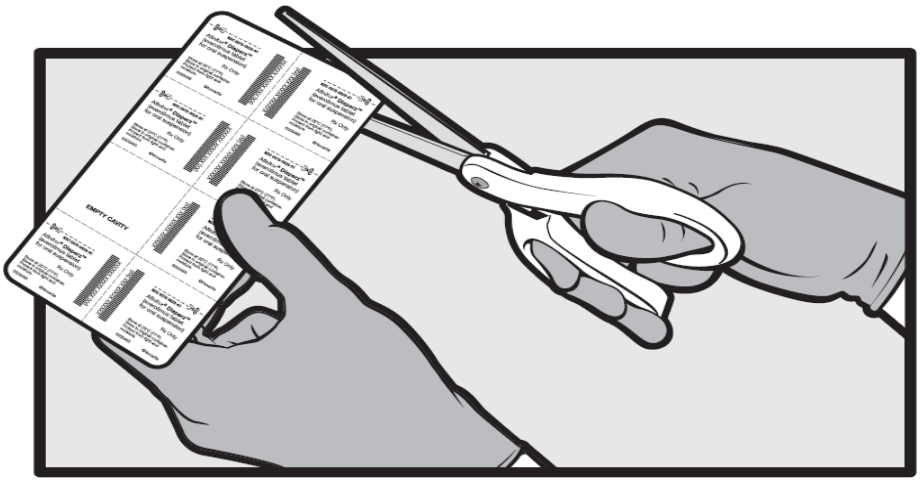

Figure X

Step 7: Add the prescribed number of AFINITOR DISPERZ tablets for oral suspension into the water (see Figure Y).

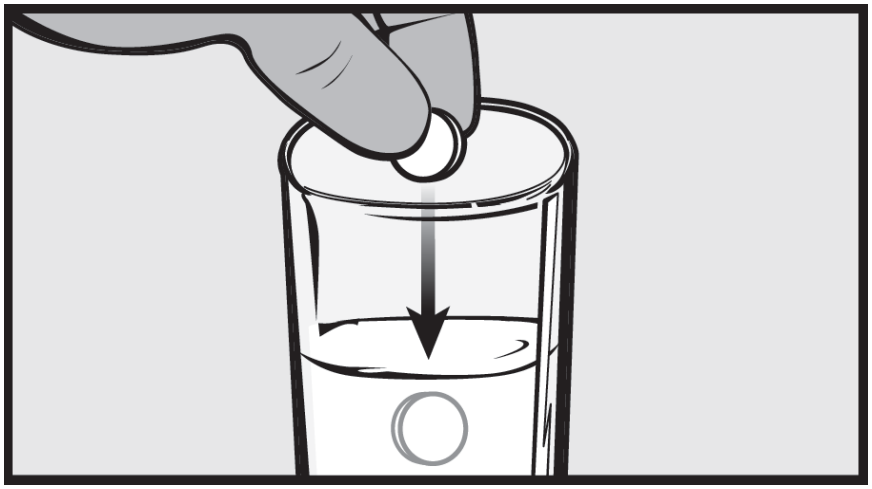

Figure Y

Step 8: Wait **3 minutes** to allow AFINITOR DISPERZ tablets for oral suspension to break apart (see Figure Z).

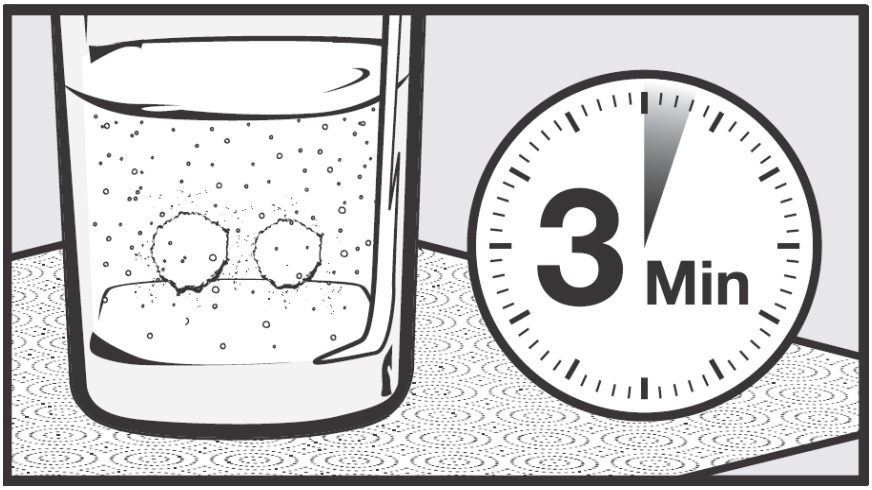

Figure Z

Step 9: Gently stir the contents of the glass with a spoon and place the spoon back on the paper towel (see Figure AA). Drink the full amount of the suspension right away, within 60 minutes of preparing it (see Figure BB).

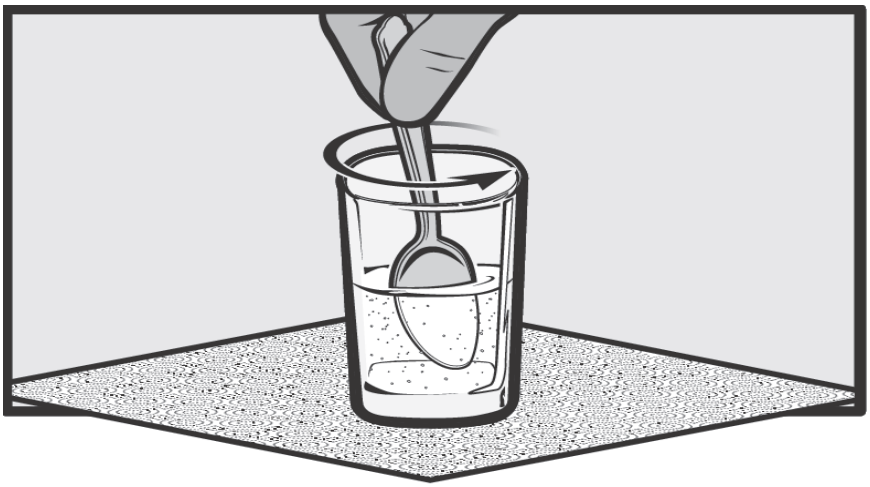

Figure AA

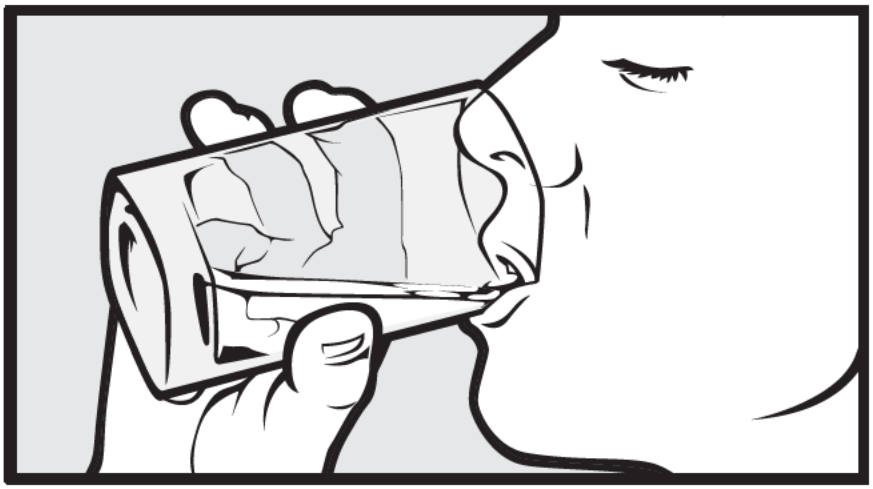

Figure BB

Step 10: Refill the glass with the same amount of water (about 25 mL). Stir the contents with the same spoon and place the spoon back on the paper towel (see Figure CC). Drink the full amount right away so that you take any remaining medicine (see Figure DD).

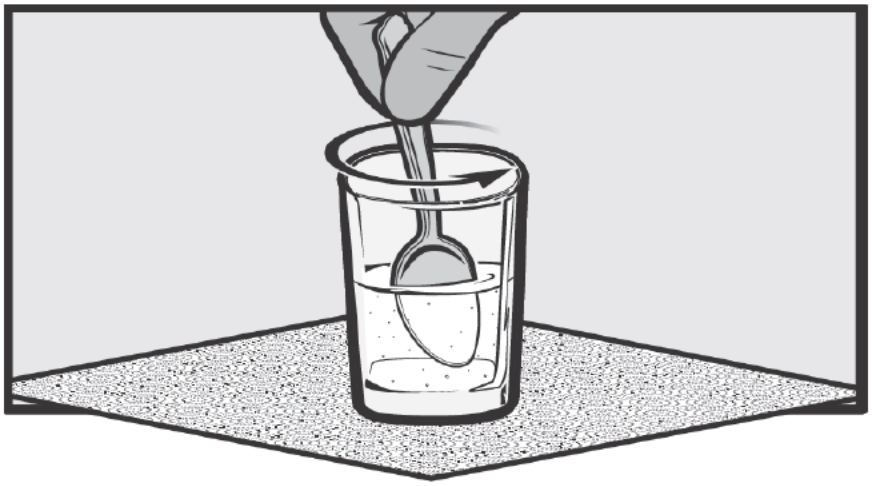

Figure CC

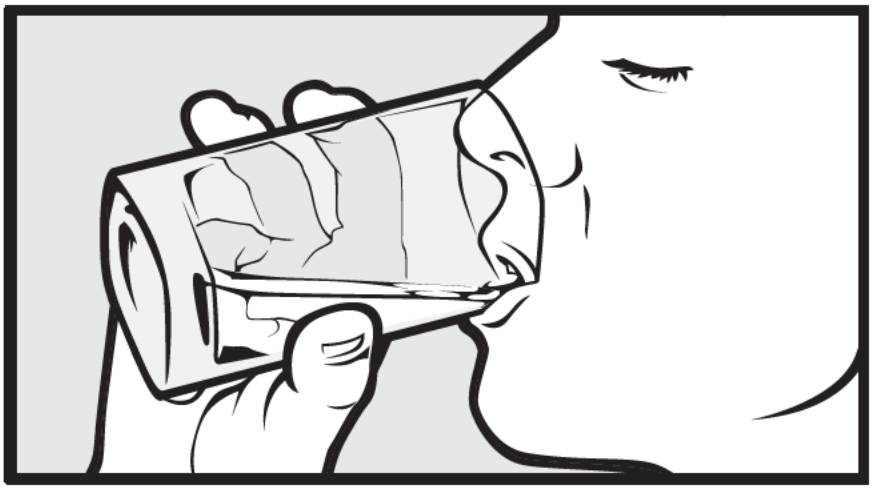

Figure DD

If your total prescribed dose is more than 10 mg, repeat steps 4 through 10 to finish taking your dose.

Step 11: Wash the glass and the spoon thoroughly with water. Wipe the glass and spoon with a clean paper towel and store them in a dry and clean place until your next dose of AFINITOR DISPERZ (see Figure EE).

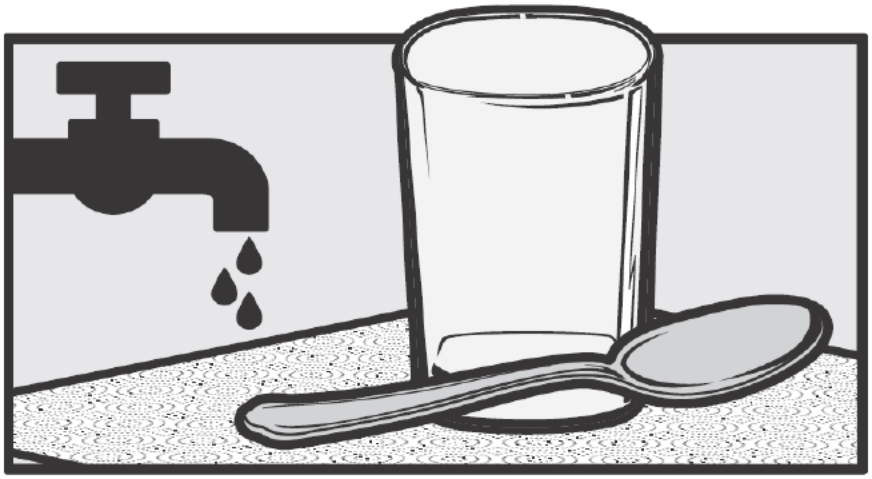

Figure EE

Step 12: Throw away the used paper towel and gloves in your household trash.

Step 13: Wash your hands.

How should I store AFINITOR DISPERZ?

- Store AFINITOR at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep AFINITOR DISPERZ in the pack it comes in.
- Open the blister pack just before taking AFINITOR DISPERZ.
- Keep AFINITOR DISPERZ dry and away from light.
- Do not use AFINITOR DISPERZ that is out of date or no longer needed.

Keep AFINITOR DISPERZ and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
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East Hanover, New Jersey 07936

Issued August 2012

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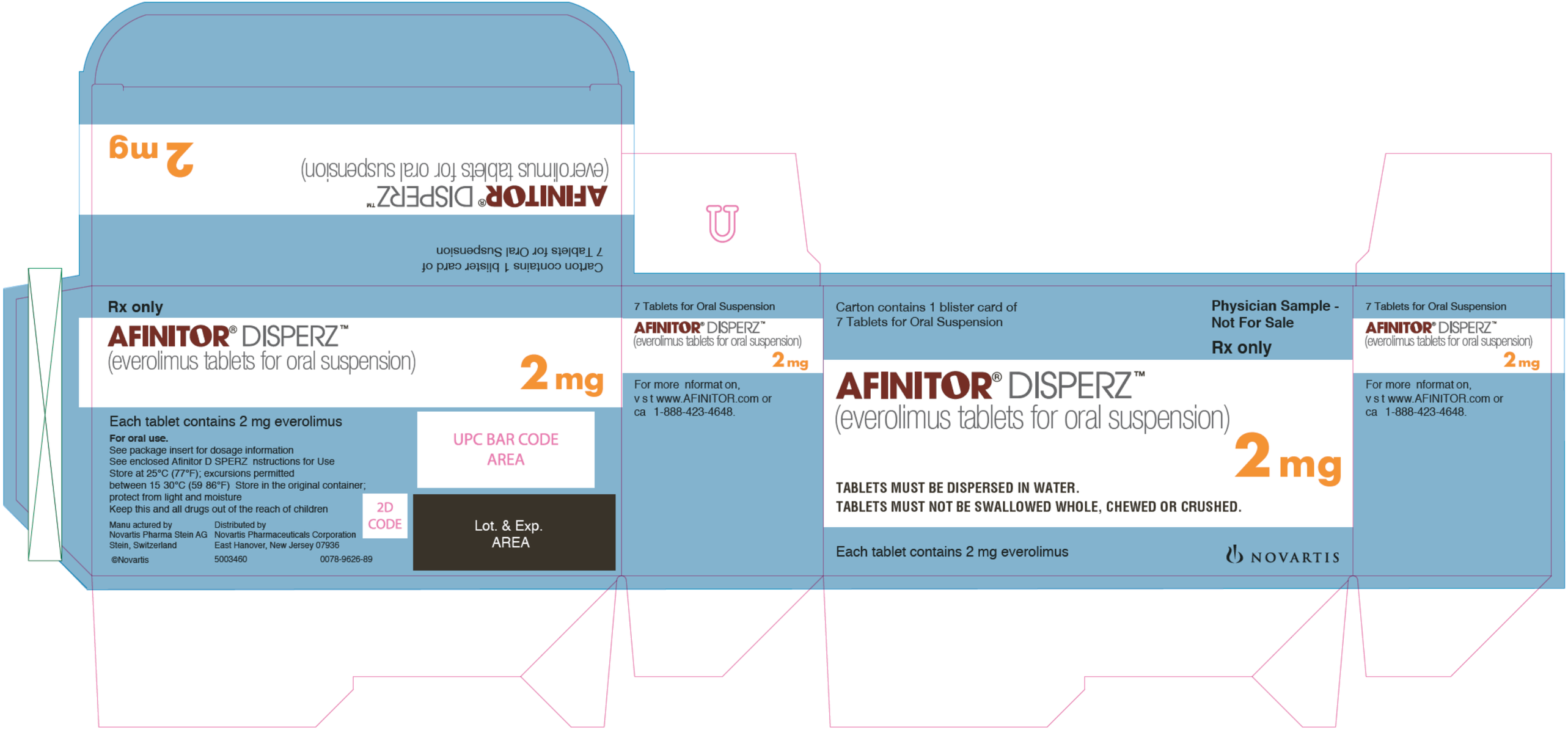
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