

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR/AFINITOR DISPERZ safely and effectively. See full prescribing information for AFINITOR/AFINITOR DISPERZ.

AFINITOR® (everolimus) tablets, for oral use

AFINITOR DISPERZ® (everolimus tablets for oral suspension)

Initial U.S. Approval: 2009

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

Warnings and Precautions, Risk of Impaired Wound Healing (5.7) 2/2020

Warnings and Precautions, Radiation Sensitization and Radiation Recall (5.12) 4/2021

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

AFINITOR is a kinase inhibitor indicated for the treatment of:

- Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole. (1.1)
- Adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic.
Limitations of Use: AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors. (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. (1.4)

AFINITOR and AFINITOR DISPERZ are kinase inhibitors indicated for the treatment of adult and pediatric patients aged 1 year and older with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. (1.5)

AFINITOR DISPERZ is a kinase inhibitor indicated for the adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures. (1.6)

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

Do not combine AFINITOR and AFINITOR DISPERZ to achieve the total daily dose. (2.1)

Modify the dose for patients with hepatic impairment or for patients taking drugs that inhibit or induce P-glycoprotein (P-gp) and CYP3A4. (2.1)

Breast Cancer:

- 10 mg orally once daily. (2.2)

NET:

- 10 mg orally once daily. (2.3)

RCC:

- 10 mg orally once daily. (2.4)

TSC-Associated Renal Angiomyolipoma:

- 10 mg orally once daily. (2.5)

TSC-Associated SEGA:

- 4.5 mg/m² orally once daily; adjust dose to attain trough concentrations of 5-15 ng/mL. (2.6, 2.8)

TSC-Associated Partial-Onset Seizures:

- 5 mg/m² orally once daily; adjust dose to attain trough concentrations of 5-15 ng/mL. (2.7, 2.8)

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

- AFINITOR: 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets (3)
- AFINITOR DISPERZ: 2 mg, 3 mg, and 5 mg tablets (3)

-----CONTRAINDICATIONS-----

Clinically significant hypersensitivity to everolimus or to other rapamycin derivatives. (4)

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

- Non-Infectious Pneumonitis: Monitor for clinical symptoms or radiological changes. Withhold or permanently discontinue based on severity. (2.9, 5.1)

- Infections: Monitor for signs and symptoms of infection. Withhold or permanently discontinue based on severity. (2.9, 5.2)
- Severe Hypersensitivity Reactions: Permanently discontinue for clinically significant hypersensitivity. (5.3)
- Angioedema: Patients taking concomitant angiotensin-converting-enzyme (ACE) inhibitors may be at increased risk for angioedema. Permanently discontinue for angioedema. (5.4, 7.2)
- Stomatitis: Initiate dexamethasone alcohol-free mouthwash when starting treatment. (5.5, 6.1)
- Renal Failure: Monitor renal function prior to treatment and periodically thereafter. (5.6)
- Risk of Impaired Wound Healing: Withhold for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of treatment after resolution of wound healing complications has not been established. (5.7)
- Geriatric Patients: Monitor and adjust dose for adverse reactions. (5.8)
- Metabolic Disorders: Monitor serum glucose and lipids prior to treatment and periodically thereafter. Withhold or permanently discontinue based on severity. (2.9, 5.9)
- Myelosuppression: Monitor hematologic parameters prior to treatment and periodically thereafter. Withhold or permanently discontinue based on severity. (2.9, 5.10)
- Risk of Infection or Reduced Immune Response with Vaccination: Avoid live vaccines and close contact with those who have received live vaccines. Complete recommended childhood vaccinations prior to starting treatment. (5.11)
- Radiation Sensitization and Radiation Recall: Severe radiation reactions may occur. (5.12, 6.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.13, 8.1, 8.3)

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

- Breast cancer, NET, 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)
- TSC-Associated Renal Angiomyolipoma: Most common adverse reaction (incidence ≥ 30%) is stomatitis. (6.1)
- TSC-Associated SEGA: Most common adverse reactions (incidence ≥ 30%) are stomatitis and respiratory tract infection. (6.1)
- TSC-Associated Partial-Onset Seizures: Most common adverse reaction (incidence ≥ 30%) is stomatitis. (6.1)

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-----

- P-gp and strong CYP3A4 inhibitors: Avoid concomitant use. (2.11, 7.1)
- P-gp and moderate CYP3A4 inhibitors: Reduce the dose as recommended. (2.11, 7.1)
- P-gp and strong CYP3A4 inducers: Increase the dose as recommended. (2.12, 7.1)

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

- For breast cancer, NET, RCC, or TSC-associated renal angiomyolipoma patients with hepatic impairment, reduce the dose. (2.10, 8.6)
- For patients with TSC-associated SEGA or TSC-associated partial-onset seizures and severe hepatic impairment, reduce the starting dose and adjust dose to attain target trough concentrations. (2.8, 2.10, 8.6)

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Revised: 4/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer

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

1.2 Neuroendocrine Tumors (NET)

AFINITOR is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease.

AFINITOR is indicated for the treatment of adult patients with progressive, well-differentiated, non-functional NET of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease.

Limitations of Use: AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors [*see Clinical Studies (14.2)*].

1.3 Renal Cell Carcinoma (RCC)

AFINITOR is indicated for the treatment of adult patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

1.4 Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

AFINITOR is indicated for the treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery.

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

AFINITOR and AFINITOR DISPERZ® are indicated in adult and pediatric patients aged 1 year and older with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected.

1.6 Tuberous Sclerosis Complex (TSC)-Associated Partial-Onset Seizures

AFINITOR DISPERZ is indicated for the adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- AFINITOR and AFINITOR DISPERZ are two different dosage forms. Select the recommended dosage form based on the indication [*see Indications and Usage (1)*]. Do not combine AFINITOR and AFINITOR DISPERZ to achieve the total dose.
- Modify the dosage for patients with hepatic impairment or for patients taking drugs that inhibit or induce P-glycoprotein (P-gp) and CYP3A4 [*see Dosage and Administration (2.10, 2.11, 2.12)*].

2.2 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer

The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for Neuroendocrine Tumors (NET)

The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.

2.4 Recommended Dosage for Renal Cell Carcinoma (RCC)

The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.

2.5 Recommended Dosage for Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

The recommended dosage of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.

2.6 Recommended Dosage for Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA)

The recommended starting dosage of AFINITOR/AFINITOR DISPERZ is 4.5 mg/m² orally once daily until disease progression or unacceptable toxicity [see *Dosage and Administration* (2.8)].

2.7 Recommended Dosage for Tuberous Sclerosis Complex (TSC)-Associated Partial-Onset Seizures

The recommended starting dosage of AFINITOR DISPERZ is 5 mg/m² orally once daily until disease progression or unacceptable toxicity [see *Dosage and Administration* (2.8)].

2.8 Therapeutic Drug Monitoring (TDM) and Dose Titration for Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA) and TSC-Associated Partial-Onset Seizures

- Monitor everolimus whole blood trough concentrations at time points recommended in Table 1.
- Titrate the dose to attain trough concentrations of 5 ng/mL to 15 ng/mL.
- Adjust the dose using the following equation:

$$\text{New dose}^* = \text{current dose} \times (\text{target concentration} \div \text{current concentration})$$

*The maximum dose increment at any titration must not exceed 5 mg. Multiple dose titrations may be required to attain the target trough concentration.

- When possible, use the same assay and laboratory for TDM throughout treatment.

Table 1: Recommended Timing of Therapeutic Drug Monitoring

Event	When to Assess Trough Concentrations After Event
Initiation of AFINITOR/AFINITOR DISPERZ	1 to 2 weeks
Modification of AFINITOR/AFINITOR DISPERZ dose	1 to 2 weeks
Switch between AFINITOR and AFINITOR DISPERZ	1 to 2 weeks
Initiation or discontinuation of P-gp and moderate CYP3A4 inhibitor	2 weeks
Initiation or discontinuation of P-gp and strong CYP3A4 inducer	2 weeks
Change in hepatic function	2 weeks
Stable dose with changing body surface area (BSA)	Every 3 to 6 months
Stable dose with stable BSA	Every 6 to 12 months

Abbreviation: P-gp, P-glycoprotein.

2.9 Dosage Modifications for Adverse Reactions

Table 2 summarizes recommendations for dosage modifications of AFINITOR/AFINITOR DISPERZ for the management of adverse reactions.

Table 2: Recommended Dosage Modifications for AFINITOR/AFINITOR DISPERZ for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Non-infectious pneumonitis <i>[see Warnings and Precautions (5.1)]</i>	Grade 2	Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. Permanently discontinue if toxicity does not resolve or improve to Grade 1 within 4 weeks.
	Grade 3	Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If toxicity recurs at Grade 3, permanently discontinue.
	Grade 4	Permanently discontinue.
Stomatitis <i>[see Warnings and Precautions (5.5)]</i>	Grade 2	Withhold until improvement to Grade 0 or 1. Resume at same dose. If recurs at Grade 2, withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 3	Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 4	Permanently discontinue.
Metabolic events (e.g., hyperglycemia, dyslipidemia) <i>[see Warnings and Precautions (5.9)]</i>	Grade 3	Withhold until improvement to Grade 0, 1, or 2. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 4	Permanently discontinue.
Other non-hematologic toxicities	Grade 2	If toxicity becomes intolerable, withhold until improvement to Grade 0 or 1. Resume at same dose. If toxicity recurs at Grade 2, withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 3	Withhold until improvement to Grade 0 or 1. Consider resuming at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If recurs at Grade 3, permanently discontinue.
	Grade 4	Permanently discontinue.
Thrombocytopenia <i>[see Warnings and Precautions (5.10)]</i>	Grade 2	Withhold until improvement to Grade 0 or 1. Resume at same dose.
	Grade 3 OR	Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
	Grade 4	Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
Neutropenia <i>[see Warnings and Precautions (5.10)]</i>	Grade 3	Withhold until improvement to Grade 0, 1, or 2. Resume at same dose.
	Grade 4	Withhold until improvement to Grade 0, 1, or 2. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
Febrile neutropenia <i>[see Warnings and Precautions (5.10)]</i>	Grade 3	Withhold until improvement to Grade 0, 1, or 2, and no fever. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.

Adverse Reaction	Severity	Dosage Modification
	Grade 4	Permanently discontinue.

2.10 Dosage Modifications for Hepatic Impairment

The recommended dosages of AFINITOR/AFINITOR DISPERZ for patients with hepatic impairment are described in Table 3 [see *Use in Specific Populations (8.6)*]:

Table 3: Recommended Dosage Modifications for Patients with Hepatic Impairment

Indication	Dose Modification for AFINITOR/AFINITOR DISPERZ
Breast Cancer, NET, RCC, and TSC-Associated Renal Angiomyolipoma	<ul style="list-style-type: none"> Mild hepatic impairment (Child-Pugh class A) – 7.5 mg orally once daily; decrease the dose to 5 mg orally once daily if a dose of 7.5 mg once daily is not tolerated. Moderate hepatic impairment (Child-Pugh class B) – 5 mg orally once daily; decrease the dose to 2.5 mg orally once daily if a dose of 5 mg once daily is not tolerated. Severe hepatic impairment (Child-Pugh class C) – 2.5 mg orally once daily if the desired benefit outweighs the risk; do not exceed a dose of 2.5 mg once daily.
TSC-Associated SEGA and TSC-Associated Partial-Onset Seizures	<ul style="list-style-type: none"> Severe hepatic impairment (Child-Pugh class C) – 2.5 mg/m² orally once daily. Adjust dose based on everolimus trough concentrations as recommended [see <i>Dosage and Administration (2.8)</i>].

Abbreviations: NET, Neuroendocrine Tumors; RCC, Renal Cell Carcinoma; SEGA, Subependymal Giant Cell Astrocytoma; TSC, Tuberous Sclerosis Complex.

2.11 Dosage Modifications for P-gp and CYP3A4 Inhibitors

- Avoid the concomitant use of P-gp and strong CYP3A4 inhibitors [see *Drug Interactions (7.1)*].
- Avoid ingesting grapefruit and grapefruit juice.
- Reduce the dose for patients taking AFINITOR/AFINITOR DISPERZ with a P-gp and moderate CYP3A4 inhibitor as recommended in Table 4 [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

Table 4: Recommended Dosage Modifications for Concurrent Use of AFINITOR/AFINITOR DISPERZ with a P-gp and Moderate CYP3A4 Inhibitor

Indication	Dose Modification for AFINITOR/AFINITOR DISPERZ
Breast Cancer, NET, RCC, and TSC-Associated Renal Angiomyolipoma	<ul style="list-style-type: none"> Reduce dose to 2.5 mg once daily. May increase dose to 5 mg once daily if tolerated. Resume dose administered prior to inhibitor initiation, once the inhibitor is discontinued for 3 days.
TSC-Associated SEGA and TSC-Associated Partial-Onset Seizures	<ul style="list-style-type: none"> Reduce the daily dose by 50%. Change to every other day dosing if the reduced dose is lower than the lowest available strength. Resume dose administered prior to inhibitor initiation, once the inhibitor is discontinued for 3 days. Assess trough concentrations when initiating and discontinuing the inhibitor [see <i>Dosage and Administration (2.8)</i>].

2.12 Dosage Modifications for P-gp and CYP3A4 Inducers

- Avoid concomitant use of St. John's Wort (*Hypericum perforatum*).
- Increase the dose for patients taking AFINITOR/AFINITOR DISPERZ with a P-gp and strong CYP3A4 inducer as recommended in Table 5 [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*].

Table 5: Recommended Dosage Modifications for Concurrent Use of AFINITOR/AFINITOR DISPERZ with P-gp and Strong CYP3A4 Inducers

Indication	Dose Modification for AFINITOR/AFINITOR DISPERZ
Breast Cancer, NET, RCC, and TSC-Associated Renal Angiomyolipoma	<ul style="list-style-type: none">• Avoid coadministration where alternatives exist.• If coadministration cannot be avoided, double the daily dose using increments of 5 mg or less. Multiple increments may be required.• Resume the dose administered prior to inducer initiation, once an inducer is discontinued for 5 days.
TSC-Associated SEGA and TSC-Associated Partial-Onset Seizures	<ul style="list-style-type: none">• Double the daily dose using increments of 5 mg or less. Multiple increments may be required.• Addition of another strong CYP3A4 inducer in a patient already receiving treatment with a strong CYP3A4 inducer may not require additional dosage modification.• Assess trough concentrations when initiating and discontinuing the inducer [<i>see Dosage and Administration (2.8)</i>].• Resume the dose administered before starting any inducer, once all inducers are discontinued for 5 days.

2.13 Administration and Preparation

- Administer AFINITOR/AFINITOR DISPERZ at the same time each day.
- Administer AFINITOR/AFINITOR DISPERZ consistently either with or without food [*see Clinical Pharmacology (12.3)*].
- If a dose of AFINITOR/AFINITOR DISPERZ is missed, it can be administered up to 6 hours after the time it is normally administered. After more than 6 hours, the dose should be skipped for that day. The next day, AFINITOR/AFINITOR DISPERZ should be administered at its usual time. Double doses should not be administered to make up for the dose that was missed.

AFINITOR

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

AFINITOR DISPERZ

- Wear gloves to avoid possible contact with everolimus when preparing suspensions of AFINITOR DISPERZ for another person.
- Administer as a suspension only.
- Administer suspension immediately after preparation. Discard suspension if not administered within 60 minutes after preparation.
- Prepare suspension in water only.

Using an Oral Syringe to Prepare Oral Suspension:

- Place the prescribed dose 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 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 to Prepare Oral Suspension:

- Place the prescribed dose into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg 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

AFINITOR

Tablets, white to slightly yellow and elongated with a bevelled edge:

- 2.5 mg: engraved with “LCL” on one side and “NVR” on the other.
- 5 mg: engraved with “5” on one side and “NVR” on the other.
- 7.5 mg: engraved with “7P5” on one side and “NVR” on the other.
- 10 mg: engraved with “UHE” on one side and “NVR” on the other.

AFINITOR DISPERZ

Tablets for oral suspension, white to slightly yellowish, round, and flat with a bevelled edge:

- 2 mg: engraved with “D2” on one side and “NVR” on the other.
- 3 mg: engraved with “D3” on one side and “NVR” on the other.
- 5 mg: engraved with “D5” on one side and “NVR” on the other.

4 CONTRAINDICATIONS

AFINITOR/AFINITOR DISPERZ is contraindicated in patients with clinically significant hypersensitivity to everolimus or to other rapamycin derivatives [see *Warnings and Precautions* (5.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR/AFINITOR DISPERZ in clinical trials, some cases were reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. The incidence of Grade 3 and 4 non-infectious pneumonitis was up to 4% and up to 0.2%, respectively [see *Adverse Reactions* (6.1)]. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms. Consider opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

Continue AFINITOR/AFINITOR DISPERZ without dose alteration in patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms. Imaging appears to overestimate the incidence of clinical pneumonitis.

For Grade 2 to 4 non-infectious pneumonitis, withhold or permanently discontinue AFINITOR/AFINITOR DISPERZ based on severity [see *Dosage and Administration* (2.9)]. Corticosteroids may be indicated until clinical symptoms resolve. Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR/AFINITOR DISPERZ has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens [see *Adverse Reactions (6.1)*]. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections (e.g., aspergillosis, candidiasis, or PJP), and viral infections (e.g., reactivation of hepatitis B virus) have occurred. Some of these infections have been severe (e.g., sepsis, septic shock, or resulting in multisystem organ failure) or fatal. The incidence of Grade 3 and 4 infections was up to 10% and up to 3%, respectively. The incidence of serious infections was reported at a higher frequency in patients < 6 years of age [see *Use in Specific Populations (8.4)*].

Complete treatment of preexisting invasive fungal infections prior to starting treatment. Monitor for signs and symptoms of infection. Withhold or permanently discontinue AFINITOR/AFINITOR DISPERZ based on severity of infection [see *Dosage and Administration (2.9)*].

Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.3 Severe Hypersensitivity Reactions

Hypersensitivity reactions to AFINITOR/AFINITOR DISPERZ have been observed and include anaphylaxis, dyspnea, flushing, chest pain, and angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) [see *Contraindications (4)*]. The incidence of Grade 3 hypersensitivity reactions was up to 1%. Permanently discontinue AFINITOR/AFINITOR DISPERZ for the development of clinically significant hypersensitivity.

5.4 Angioedema with Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors

Patients taking concomitant ACE inhibitors with AFINITOR/AFINITOR DISPERZ may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment). In a pooled analysis of randomized double-blind oncology clinical trials, the incidence of angioedema in patients taking AFINITOR with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor. Permanently discontinue AFINITOR/AFINITOR DISPERZ for angioedema.

5.5 Stomatitis

Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with AFINITOR/AFINITOR DISPERZ at an incidence ranging from 44% to 78% across clinical trials. Grades 3-4 stomatitis was reported in 4% to 9% of patients [see *Adverse Reactions (6.1)*]. Stomatitis most often occurs within the first 8 weeks of treatment. When starting AFINITOR/AFINITOR DISPERZ, initiating dexamethasone alcohol-free oral solution as a swish and spit mouthwash reduces the incidence and severity of stomatitis [see *Adverse Reactions (6.1)*]. If stomatitis does occur, mouthwashes and/or other topical treatments are recommended. Avoid alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products, as they may exacerbate the condition. Do not administer antifungal agents, unless fungal infection has been diagnosed.

5.6 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have occurred in patients taking AFINITOR. Elevations of serum creatinine and proteinuria have been reported in patients taking AFINITOR/AFINITOR DISPERZ [see *Adverse Reactions (6.1)*]. The incidence of Grade 3 and 4 elevations of serum creatinine was up to 2% and up to 1%, respectively. The incidence of Grade 3 and 4 proteinuria was up to 1% and up to 0.5%, respectively. Monitor renal function prior to starting AFINITOR/AFINITOR DISPERZ and annually thereafter. Monitor renal function at least every 6 months in patients who have additional risk factors for renal failure.

5.7 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, AFINITOR/AFINITOR DISPERZ have the potential to adversely affect wound healing.

Withhold AFINITOR/AFINITOR DISPERZ for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of treatment upon resolution of wound healing complications has not been established.

5.8 Geriatric Patients

In the randomized hormone receptor-positive, HER2-negative breast cancer study (BOLERO-2), the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients \geq 65 years of age compared to 2% in

patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 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 (2.9)*, *Use in Specific Populations (8.5)*].

5.9 Metabolic Disorders

Hyperglycemia, hypercholesterolemia, and hypertriglyceridemia have been reported in patients taking AFINITOR/AFINITOR DISPERZ at an incidence up to 75%, 86%, and 73%, respectively. The incidence of these Grade 3 and 4 laboratory abnormalities was up to 15% and up to 0.4%, respectively [see *Adverse Reactions (6.1)*]. In non-diabetic patients, monitor fasting serum glucose prior to starting AFINITOR/AFINITOR DISPERZ and annually thereafter. In diabetic patients, monitor fasting serum glucose more frequently as clinically indicated. Monitor lipid profile prior to starting AFINITOR/AFINITOR DISPERZ and annually thereafter. When possible, achieve optimal glucose and lipid control prior to starting AFINITOR/AFINITOR DISPERZ. For Grade 3 to 4 metabolic events, withhold or permanently discontinue AFINITOR/AFINITOR DISPERZ based on severity [see *Dosage and Administration (2.9)*].

5.10 Myelosuppression

Anemia, lymphopenia, neutropenia, and thrombocytopenia have been reported in patients taking AFINITOR/AFINITOR DISPERZ. The incidence of these Grade 3 and 4 laboratory abnormalities was up to 16% and up to 2%, respectively [see *Adverse Reactions (6.1)*]. Monitor complete blood count (CBC) prior to starting AFINITOR/AFINITOR DISPERZ every 6 months for the first year of treatment and annually thereafter. Withhold or permanently discontinue AFINITOR/AFINITOR DISPERZ based on severity [see *Dosage and Administration (2.9)*].

5.11 Risk of Infection or Reduced Immune Response with Vaccination

The safety of immunization with live vaccines during AFINITOR/AFINITOR DISPERZ therapy has not been studied. Due to the potential increased risk of infection, avoid the use of live vaccines and close contact with individuals who have received live vaccines during treatment with AFINITOR/AFINITOR DISPERZ. Due to the potential increased risk of infection or reduced immune response with vaccination, complete the recommended childhood series of vaccinations according to American Council on Immunization Practices (ACIP) guidelines prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

5.12 Radiation Sensitization and Radiation Recall

Radiation sensitization and recall, in some cases severe, involving cutaneous and visceral organs (including radiation esophagitis and pneumonitis) have been reported in patients treated with radiation prior to, during, or subsequent to AFINITOR/AFINITOR DISPERZ treatment [see *Adverse Reactions (6.2)*].

Monitor patients closely when AFINITOR/AFINITOR DISPERZ is administered during or sequentially with radiation treatment.

5.13 Embryo-Fetal Toxicity

Based on animal studies and the mechanism of action, AFINITOR/AFINITOR DISPERZ can cause fetal harm when administered to a pregnant woman. In animal studies, everolimus caused embryo-fetal toxicities in rats when administered during the period of organogenesis at maternal exposures that were lower than human exposures at the clinical dose of 10 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use effective contraception during treatment with AFINITOR/AFINITOR DISPERZ and for 8 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR/AFINITOR DISPERZ and for 4 weeks after the last dose [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Non-Infectious Pneumonitis [see *Warnings and Precautions (5.1)*].
- Infections [see *Warnings and Precautions (5.2)*].
- Severe Hypersensitivity Reactions [see *Warnings and Precautions (5.3)*].
- Angioedema with Concomitant Use of ACE inhibitors [see *Warnings and Precautions (5.4)*].
- Stomatitis [see *Warnings and Precautions (5.5)*].
- Renal Failure [see *Warnings and Precautions (5.6)*].

- Impaired Wound Healing [see Warnings and Precautions (5.7)].
- Metabolic Disorders [see Warnings and Precautions (5.9)].
- Myelosuppression [see Warnings and Precautions (5.10)].
- Radiation Sensitization and Radiation Recall [see Warnings and Precautions (6.2)].

6.1 Clinical Trials Experience

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.

Hormone Receptor-Positive, HER2-Negative Breast Cancer

The safety of AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily) (n = 485) vs. placebo in combination with exemestane (n = 239) was evaluated in a randomized, controlled trial (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (28 to 93 years), and 75% were White. The median follow-up was approximately 13 months.

The most common adverse reactions (incidence $\geq 30\%$) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common Grade 3-4 adverse reactions (incidence $\geq 2\%$) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence $\geq 50\%$) were hypercholesterolemia, hyperglycemia, increased aspartate transaminase (AST), anemia, leukopenia, thrombocytopenia, lymphopenia, increased alanine transaminase (ALT), and hypertriglyceridemia. The most common Grade 3-4 laboratory abnormalities (incidence $\geq 3\%$) were lymphopenia, hyperglycemia, anemia, hypokalemia, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred in 2% of patients who received AFINITOR. The rate of adverse reactions resulting in permanent discontinuation was 24% for the AFINITOR arm. Dose adjustments (interruptions or reductions) occurred in 63% of patients in the AFINITOR arm.

Adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving AFINITOR vs. placebo are presented in Table 6. Laboratory abnormalities are presented in Table 7. The median duration of treatment with AFINITOR was 23.9 weeks; 33% were exposed to AFINITOR for a period of ≥ 32 weeks.

Table 6: Adverse Reactions Reported in $\geq 10\%$ of Patients with Hormone Receptor-Positive Breast Cancer in BOLERO-2

	AFINITOR with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal				
Stomatitis ^a	67	8 ^d	11	0.8
Diarrhea	33	2	18	0.8
Nausea	29	0.4	28	1
Vomiting	17	1	12	0.8
Constipation	14	0.4 ^d	13	0.4
Dry mouth	11	0	7	0
General				
Fatigue	36	4	27	1 ^d
Edema peripheral	19	1 ^d	6	0.4 ^d
Pyrexia	15	0.2 ^d	7	0.4 ^d
Asthenia	13	2	4	0
Infections				
Infections ^b	50	6	25	2 ^d
Investigations				
Weight loss	25	1 ^d	6	0
Metabolism and nutrition				
Decreased appetite	30	1 ^d	12	0.4 ^d

	AFINITOR with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	%	%	%	%
Hyperglycemia	14	5	2	0.4 ^d
Musculoskeletal and connective tissue				
Arthralgia	20	0.8 ^d	17	0
Back pain	14	0.2 ^d	10	0.8 ^d
Pain in extremity	9	0.4 ^d	11	2 ^d
Nervous system				
Dysgeusia	22	0.2 ^d	6	0
Headache	21	0.4 ^d	14	0
Psychiatric				
Insomnia	13	0.2 ^d	8	0
Respiratory, thoracic and mediastinal				
Cough	24	0.6 ^d	12	0
Dyspnea	21	4	11	1
Epistaxis	17	0	1	0
Pneumonitis ^c	19	4	0.4	0
Skin and subcutaneous tissue				
Rash	39	1 ^d	6	0
Pruritus	13	0.2 ^d	5	0
Alopecia	10	0	5	0
Vascular				
Hot flush	6	0	14	0

Grading according to NCI CTCAE Version 3.0.

^aIncludes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis, and lip ulceration.

^bIncludes all reported infections including, but not limited to, urinary tract infections, respiratory tract (upper and lower) infections, skin infections, and gastrointestinal tract infections.

^cIncludes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

^dNo Grade 4 adverse reactions were reported.

Table 7: Selected Laboratory Abnormalities Reported in ≥ 10% of Patients with Hormone Receptor-Positive Breast Cancer in BOLERO-2

Laboratory Parameter	AFINITOR with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	%	%	%	%
Hematology^a				
Anemia	68	6	40	1
Leukopenia	58	2 ^b	28	6
Thrombocytopenia	54	3	5	0.4
Lymphopenia	54	12	37	6
Neutropenia	31	2 ^b	11	2
Chemistry				
Hypercholesterolemia	70	1	38	2
Hyperglycemia	69	9	44	1
Increased AST	69	4	45	3
Increased ALT	51	4	29	5 ^b
Hypertriglyceridemia	50	0.8 ^b	26	0
Hypoalbuminemia	33	0.8 ^b	16	0.8 ^b

Table 12: Adverse Reactions Reported in ≥ 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm in RECORD-1

	AFINITOR N = 274		Placebo N = 137	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal				
Stomatitis ^a	44	4	8	0
Diarrhea	30	2 ^d	7	0
Nausea	26	2 ^d	19	0
Vomiting	20	2 ^d	12	0
Infections^b	37	10	18	2
General				
Asthenia	33	4	23	4
Fatigue	31	6 ^d	27	4
Edema peripheral	25	< 1 ^d	8	< 1 ^d
Pyrexia	20	< 1 ^d	9	0
Mucosal inflammation	19	2 ^d	1	0
Respiratory, thoracic and mediastinal				
Cough	30	< 1 ^d	16	0
Dyspnea	24	8	15	3 ^d
Epistaxis	18	0	0	0
Pneumonitis ^c	14	4 ^d	0	0
Skin and subcutaneous tissue				
Rash	29	1 ^d	7	0
Pruritus	14	< 1 ^d	7	0
Dry skin	13	< 1 ^d	5	0
Metabolism and nutrition				
Anorexia	25	2 ^d	14	< 1 ^d
Nervous system				
Headache	19	1	9	< 1 ^d
Dysgeusia	10	0	2	0
Musculoskeletal and connective tissue				
Pain in extremity	10	1 ^d	7	0

Grading according to NCI CTCAE Version 3.0.

^aStomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

^bIncludes all reported infections including, but not limited to, respiratory tract (upper and lower) infections, urinary tract infections, and skin infections.

^cIncludes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

^dNo Grade 4 adverse reactions were reported.

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

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

General: Weight loss (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

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

Skin and subcutaneous tissue: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasia (4%), skin lesion (4%), acneiform dermatitis (3%), angioedema (< 1%)

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

Psychiatric: Insomnia (9%)

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

Ocular: Eyelid edema (4%), conjunctivitis (2%)

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

Renal and urinary: Renal failure (3%)

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

Musculoskeletal and connective tissue: Jaw pain (3%)

Hematologic: Hemorrhage (3%)

Table 13: Selected Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm Than the Placebo Arm in RECORD-1

Laboratory parameter	AFINITOR N = 274		Placebo N = 137	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology^a				
Anemia	92	13	79	6
Lymphopenia	51	18	28	5 ^b
Thrombocytopenia	23	1 ^b	2	< 1
Neutropenia	14	< 1	4	0
Chemistry				
Hypercholesterolemia	77	4 ^b	35	0
Hypertriglyceridemia	73	< 1 ^b	34	0
Hyperglycemia	57	16	25	2 ^b
Increased creatinine	50	2 ^b	34	0
Hypophosphatemia	37	6 ^b	8	0
Increased AST	25	1	7	0
Increased ALT	21	1 ^b	4	0
Hyperbilirubinemia	3	1	2	0

Grading according to NCI CTCAE Version 3.0.

^aReflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

^bNo Grade 4 laboratory abnormalities were reported.

Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

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

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

(incidence \geq 50%) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3-4 laboratory abnormality (incidence \geq 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.

Adverse reactions reported with an incidence of \geq 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo are presented in Table 14. Laboratory abnormalities are presented in Table 15.

Table 14: Adverse Reactions Reported in \geq 10% of AFINITOR-Treated Patients with TSC-Associated Renal Angiomyolipoma in EXIST-2

	AFINITOR N = 79		Placebo N = 39	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal				
Stomatitis ^a	78	6 ^b	23	0
Vomiting	15	0	5	0
Diarrhea	14	0	5	0
General				
Peripheral edema	13	0	8	0
Infections				
Upper respiratory tract infection	11	0	5	0
Musculoskeletal and connective tissue				
Arthralgia	13	0	5	0
Respiratory, thoracic and mediastinal				
Cough	20	0	13	0
Skin and subcutaneous tissue				
Acne	22	0	5	0

Grading according to NCI CTCAE Version 3.0.

^aIncludes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.

^bNo Grade 4 adverse reactions were reported.

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

The following additional adverse reactions occurred in less than 10% of AFINITOR-treated patients: epistaxis (9%), decreased appetite (6%), otitis media (6%), depression (5%), abnormal taste (5%), increased blood luteinizing hormone (LH) levels (4%), increased blood follicle stimulating hormone (FSH) levels (3%), hypersensitivity (3%), ovarian cyst (3%), pneumonitis (1%), and angioedema (1%).

Table 15: Selected Laboratory Abnormalities Reported in AFINITOR-Treated Patients with TSC-Associated Renal Angiomyolipoma in EXIST-2

	AFINITOR N = 79		Placebo N = 39	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
Anemia	61	0	49	0
Leukopenia	37	0	21	0
Neutropenia	25	1	26	0
Lymphopenia	20	1 ^a	8	0

	AFINITOR N = 79		Placebo N = 39	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Thrombocytopenia	19	0	3	0
Chemistry				
Hypercholesterolemia	85	1 ^a	46	0
Hypertriglyceridemia	52	0	10	0
Hypophosphatemia	49	5 ^a	15	0
Increased alkaline phosphatase	32	1 ^a	10	0
Increased AST	23	1 ^a	8	0
Increased ALT	20	1 ^a	15	0
Hyperglycemia (fasting)	14	0	8	0

Grading according to NCI CTCAE Version 3.0.

^aNo Grade 4 laboratory abnormalities were reported.

Updated safety information from 112 patients treated with AFINITOR for a median duration of 3.9 years identified the following additional adverse reactions and selected laboratory abnormalities: increased partial thromboplastin time (63%), increased prothrombin time (40%), decreased fibrinogen (38%), urinary tract infection (31%), proteinuria (18%), abdominal pain (16%), pruritus (12%), gastroenteritis (12%), myalgia (11%), and pneumonia (10%).

TSC-Associated Subependymal Giant Cell Astrocytoma (SEGA)

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (EXIST-1) of AFINITOR in 117 patients with SEGA and TSC. The median age of patients was 9.5 years (0.8 to 26 years), 93% were White, and 57% were male. The median duration of blinded study treatment was 52 weeks (24 to 89 weeks) for patients receiving AFINITOR.

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

Adverse reactions reported with an incidence of \geq 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo are reported in Table 16. Laboratory abnormalities are presented in Table 17.

Table 16: Adverse Reactions Reported in \geq 10% of AFINITOR-Treated Patients with TSC-Associated SEGA in EXIST-1

	AFINITOR N = 78		Placebo N = 39	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal				
Stomatitis ^a	62	9 ^f	26	3 ^f
Vomiting	22	1 ^f	13	0
Diarrhea	17	0	5	0
Constipation	10	0	3	0
Infections				
Respiratory tract infection ^b	31	3	23	0
Gastroenteritis ^c	10	5	3	0
Pharyngitis streptococcal	10	0	3	0

	AFINITOR N = 78		Placebo N = 39	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	%	%	%	%
General				
Pyrexia	23	6 ^f	18	3 ^f
Fatigue	14	0	3	0
Psychiatric				
Anxiety, aggression or other behavioral disturbance ^d	21	5 ^f	3	0
Skin and subcutaneous tissue				
Rash ^e	21	0	8	0
Acne	10	0	5	0

Grading according to NCI CTCAE Version 3.0.

^aIncludes mouth ulceration, stomatitis, and lip ulceration.

^bIncludes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral.

^cIncludes gastroenteritis, gastroenteritis viral, and gastrointestinal infection.

^dIncludes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

^eIncludes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria.

^fNo Grade 4 adverse reactions were reported.

Amenorrhea occurred in 17% of AFINITOR-treated females aged 10 to 55 years (3 of 18). 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 less than 10% of AFINITOR-treated patients: nausea (8%), pain in extremity (8%), insomnia (6%), pneumonia (6%), epistaxis (5%), hypersensitivity (3%), increased blood luteinizing hormone (LH) levels (1%), and pneumonitis (1%).

Table 17: Selected Laboratory Abnormalities Reported in AFINITOR-Treated Patients with TSC-Associated SEGA in EXIST-1

	AFINITOR N = 78		Placebo N = 39	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	%	%	%	%
Hematology				
Elevated partial thromboplastin time	72	3 ^a	44	5 ^a
Neutropenia	46	9 ^a	41	3 ^a
Anemia	41	0	21	0
Chemistry				
Hypercholesterolemia	81	0	39	0
Elevated AST	33	0	0	0
Hypertriglyceridemia	27	0	15	0
Elevated ALT	18	0	3	0
Hypophosphatemia	9	1 ^a	3	0

Grading according to NCI CTCAE Version 3.0.

^aNo Grade 4 laboratory abnormalities were reported.

Updated safety information from 111 patients treated with AFINITOR for a median duration of 47 months identified the following additional notable adverse reactions and selected laboratory abnormalities: decreased appetite (14%), hyperglycemia (13%), hypertension (11%), urinary tract infection (9%), decreased fibrinogen (8%), cellulitis (6%), abdominal pain (5%), decreased weight (5%), elevated creatinine (5%), and azoospermia (1%).

TSC-Associated Partial-Onset Seizures

The data described below are based on the 18-week Core phase of a randomized, double-blind, multicenter, three-arm trial (EXIST-3) comparing two everolimus trough levels (3-7 ng/mL and 9-15 ng/mL) to placebo as adjunctive antiepileptic therapy in patients with TSC-associated partial-onset seizures. A total of 366 patients were randomized to AFINITOR DISPERZ low trough (LT) (n = 117), AFINITOR DISPERZ high trough (HT) (n = 130), or placebo (n = 119). The median age of patients was 10 years (2.2 to 56 years; 28% were < 6 years, 31% were 6 to < 12 years, 22% were 12 to < 18 years, and 18% were ≥ 18 years), 65% were White, and 52% were male. Patients received between one and three concomitant antiepileptic drugs.

The most common adverse reaction reported for AFINITOR DISPERZ in both arms (incidence ≥ 30%) was stomatitis. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pneumonia, and irregular menstruation. The most common laboratory abnormality (incidence ≥ 50%) was hypercholesterolemia. The most common Grade 3-4 laboratory abnormality (incidence ≥ 2%) was neutropenia.

Adverse reactions leading to study drug discontinuation occurred in 5% and 3% of patients in the LT and HT arms, respectively. The most common adverse reaction (incidence ≥ 1%) leading to discontinuation was stomatitis. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 24% and 35% of patients in the LT and HT arms, respectively. The most common adverse reactions (incidence ≥ 3%) leading to dose adjustments in the AFINITOR DISPERZ arms were stomatitis, pneumonia, and pyrexia.

Adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR DISPERZ are presented in Table 18. Laboratory abnormalities are presented in Table 19.

Table 18: Adverse Reactions Reported in ≥ 10% of AFINITOR DISPERZ-Treated Patients with TSC-Associated Partial-Onset Seizures in EXIST-3

	AFINITOR DISPERZ				Placebo	
	Target of 3-7 ng/mL N = 117		Target of 9-15 ng/mL N = 130		N = 119	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal						
Stomatitis ^a	55	3 ^b	64	4 ^b	9	0
Diarrhea	17	0	22	0	5	0
Vomiting	12	0	10	2 ^b	9	0
Infections						
Nasopharyngitis	14	0	16	0	16	0
Upper respiratory tract infection	13	0	15	0	13	0.8 ^b
General						
Pyrexia	20	0	14	0.8 ^b	5	0
Respiratory, thoracic and mediastinal						
Cough	11	0	10	0	3	0
Skin and subcutaneous tissue						
Rash	6	0	10	0	3	0

^aIncludes stomatitis, mouth ulceration, aphthous ulcer, lip ulceration, tongue ulceration, mucosal inflammation, gingival pain.

^bNo Grade 4 adverse reactions were reported.

The following additional adverse reactions occurred in < 10% of AFINITOR DISPERZ treated patients (% AFINITOR DISPERZ LT, % AFINITOR DISPERZ HT): decreased appetite (9%, 7%), pneumonia (2%, 4%), aggression (2%, 0.8%), proteinuria (0%, 2%), menorrhagia (0.9%, 0.8%), and pneumonitis (0%, 0.8%).

Table 19: Selected Laboratory Abnormalities Reported in ≥ 10% AFINITOR DISPERZ-Treated Patients with TSC-Associated Partial-Onset Seizures

	AFINITOR DISPERZ				Placebo	
	Target of 3-7 ng/mL N = 117		Target of 9-15 ng/mL N = 130		N = 119	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology						
Neutropenia	25	4 ^a	37	6	23	7 ^a
Anemia	27	0.9 ^a	30	0	21	0.8 ^a
Thrombocytopenia	12	0	15	0	6	0
Chemistry						
Hypercholesterolemia	86	0	85	0.8 ^a	58	0
Hypertriglyceridemia	43	2 ^a	39	2	22	0
Increased ALT	17	0	22	0	6	0
Increased AST	13	0	19	0	4	0
Hyperglycemia	19	0	18	0	17	0
Increased alkaline phosphatase	24	0	16	0	29	0
Hypophosphatemia	9	0.9 ^a	16	2	3	0

Grading according to NCI CTCAE version 4.03.

^aNo Grade 4 laboratory abnormalities were reported.

Updated safety information from 357 patients treated with AFINITOR DISPERZ for a median duration of 48 weeks identified the following additional notable adverse reactions: hypersensitivity (0.6%), angioedema (0.3%), and ovarian cyst (0.3%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AFINITOR/AFINITOR DISPERZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure:

- *Blood and lymphatic disorders:* Thrombotic microangiopathy
- *Cardiac:* Cardiac failure with some cases reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event
- *Gastrointestinal:* Acute pancreatitis
- *Hepatobiliary:* Cholecystitis and cholelithiasis
- *Infections:* Sepsis and septic shock
- *Nervous System:* Reflex sympathetic dystrophy
- *Vascular:* Arterial thrombotic events
- *Injury, poisoning and procedural complications:* Radiation Sensitization and Radiation Recall
- 7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on AFINITOR/AFINITOR DISPERZ

Inhibitors

Avoid the concomitant use of P-gp and strong CYP3A4 inhibitors [see *Dosage and Administration (2.11)*, *Clinical Pharmacology (12.3)*].

Reduce the dose for patients taking AFINITOR/AFINITOR DISPERZ with a P-gp and moderate CYP3A4 inhibitor as recommended [see *Dosage and Administration (2.11)*, *Clinical Pharmacology (12.3)*].

Inducers

Increase the dose for patients taking AFINITOR/AFINITOR DISPERZ with a P-gp and strong CYP3A4 inducer as recommended [see *Dosage and Administration (2.12)*, *Clinical Pharmacology (12.3)*].

7.2 Effects of Combination Use of Angiotensin Converting Enzyme (ACE) Inhibitors

Patients taking concomitant ACE inhibitors with AFINITOR/AFINITOR DISPERZ may be at increased risk for angioedema. Avoid the concomitant use of ACE inhibitors with AFINITOR/AFINITOR DISPERZ [see *Warnings and Precautions (5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and the mechanism of action [see *Clinical Pharmacology (12.1)*], AFINITOR/AFINITOR DISPERZ can cause fetal harm when administered to a pregnant woman. There are limited case reports of AFINITOR use in pregnant women; however, these reports are not sufficient to inform about risks of birth defects or miscarriage. In animal studies, everolimus caused embryo-fetal toxicities in rats when administered during the period of organogenesis at maternal exposures that were lower than human exposures at the recommended dose of AFINITOR 10 mg orally once daily (see *Data*). Advise pregnant women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2% to 4% and 15% to 20% of clinically recognized pregnancies, respectively.

Data

Animal Data

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/m²) with resulting exposures of approximately 4% of the human exposure at the recommended dose of AFINITOR 10 mg orally once daily based on area under the curve (AUC). In rabbits, embryo-toxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m²), approximately 1.6 times the recommended dose of AFINITOR 10 mg orally once daily or the median dose administered to patients with tuberous sclerosis complex (TSC)-associated subependymal giant cell astrocytoma (SEGA), and 1.3 times the median dose administered to patients with TSC-associated partial-onset seizures based on BSA. 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/m²), 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.

8.2 Lactation

Risk Summary

There are no data on the presence of everolimus or its metabolites in human milk, the effects of everolimus on the breastfed infant or on milk production. Everolimus and its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because of the potential for serious adverse reactions in breastfed infants from everolimus, advise women not to breastfeed during treatment with AFINITOR/AFINITOR DISPERZ and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting AFINITOR/AFINITOR DISPERZ [see *Use in Specific Populations (8.1)*].

Contraception

AFINITOR/AFINITOR DISPERZ can cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*].

Females: Advise female patients of reproductive potential to use effective contraception during treatment with AFINITOR/AFINITOR DISPERZ and for 8 weeks after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR/AFINITOR DISPERZ and for 4 weeks after the last dose.

Infertility

Females: Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking AFINITOR/AFINITOR DISPERZ. Based on these findings, AFINITOR/AFINITOR DISPERZ may impair fertility in female patients [*see Adverse Reactions (6.1), Nonclinical Toxicology (13.1)*].

Males: Cases of reversible azoospermia have been reported in male patients taking AFINITOR. In male rats, sperm motility, sperm count, plasma testosterone levels and fertility were diminished at AUC similar to those of the clinical dose of AFINITOR 10 mg orally once daily. Based on these findings, AFINITOR/AFINITOR DISPERZ may impair fertility in male patients [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

TSC-Associated SEGA

The safety and effectiveness of AFINITOR/AFINITOR DISPERZ have been established in pediatric patients age 1 year and older with TSC-associated SEGA that requires therapeutic intervention but cannot be curatively resected. Use of AFINITOR/AFINITOR DISPERZ for this indication is supported by evidence from a randomized, double-blind, placebo-controlled trial in adult and pediatric patients (EXIST-1); an open-label, single-arm trial in adult and pediatric patients (Study 2485); and additional pharmacokinetic data in pediatric patients [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.5)*]. The safety and effectiveness of AFINITOR/AFINITOR DISPERZ have not been established in pediatric patients less than 1 year of age with TSC-associated SEGA.

In EXIST-1, the incidence of infections and serious infections were reported at a higher frequency in patients < 6 years of age. Ninety-six percent of 23 AFINITOR-treated patients < 6 years had at least one infection compared to 67% of 55 AFINITOR-treated patients ≥ 6 years. Thirty-five percent of 23 AFINITOR-treated patients < 6 years of age had at least 1 serious infection compared to 7% of 55 AFINITOR-treated patients ≥ 6 years.

Although a conclusive determination cannot be made due to the limited number of patients and lack of a comparator arm in the open label follow-up periods of EXIST-1 and Study 2485, AFINITOR did not appear to adversely impact growth and pubertal development in the 115 pediatric patients treated with AFINITOR for a median duration of 4.1 years.

TSC-Associated Partial-Onset Seizures

The safety and effectiveness of AFINITOR DISPERZ has been established for the adjunctive treatment of pediatric patients aged 2 years and older with TSC-associated partial-onset seizures. Use of AFINITOR DISPERZ for this indication is supported by evidence from a randomized, double-blind, placebo-controlled trial in adult and pediatric patients (EXIST-3) with additional pharmacokinetic data in pediatric patients [*see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.6)*]. The safety and effectiveness of AFINITOR DISPERZ and AFINITOR have not been established for the adjunctive treatment of pediatric patients less than 2 years of age with TSC-associated partial-onset seizures.

The incidence of infections and serious infections were reported at a higher frequency in patients < 6 years of age compared to patients ≥ 6 years old. Seventy-seven percent of 70 AFINITOR DISPERZ-treated patients < 6 years had at least one infection, compared to 53% of 177 AFINITOR DISPERZ-treated patients ≥ 6 years. Sixteen percent of 70 AFINITOR DISPERZ-treated patients < 6 years of age had at least 1 serious infection, compared to 4% of 177 AFINITOR DISPERZ-treated patients ≥ 6 years of age. Two fatal cases due to infections were reported in pediatric patients.

Other Indications

The safety and effectiveness of AFINITOR/AFINITOR DISPERZ in pediatric patients have not been established in:

- Hormone receptor-positive, HER2-negative breast cancer
- Neuroendocrine tumors (NET)
- Renal cell carcinoma (RCC)
- TSC-associated renal angiomyolipoma

8.5 Geriatric Use

In BOLERO-2, 40% of patients with breast cancer treated with AFINITOR were ≥ 65 years of age, while 15% were ≥ 75 years of age. No overall differences in effectiveness were observed between elderly and younger patients. 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.

In RECORD-1, 41% of patients with renal cell carcinoma treated with AFINITOR were ≥ 65 years of age, while 7% were ≥ 75 years of age. In RADIANT-3, 30% of patients with PNET treated with AFINITOR were ≥ 65 years of age, while 7% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients.

8.6 Hepatic Impairment

AFINITOR/AFINITOR DISPERZ exposure may increase in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

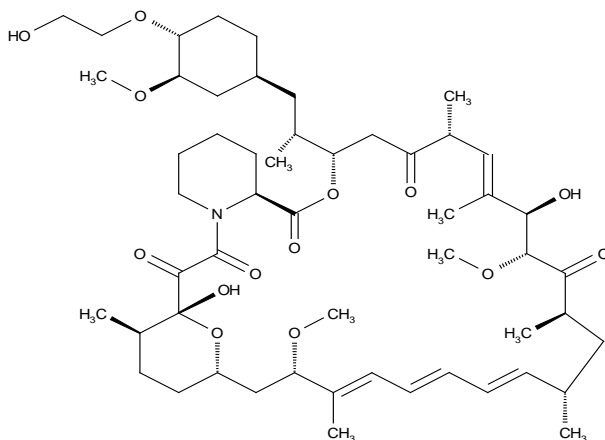
For patients with breast cancer, NET, RCC, and TSC-associated renal angiomyolipoma who have hepatic impairment, reduce the AFINITOR dose as recommended [see *Dosage and Administration (2.10)*].

For patients with TSC-associated SEGA and TSC-associated partial-onset seizures who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR/AFINITOR DISPERZ as recommended and adjust the dose based on everolimus trough concentrations [see *Dosage and Administration (2.8, 2.10)*].

11 DESCRIPTION

AFINITOR (everolimus) and AFINITOR DISPERZ (everolimus tablets for oral suspension) are kinase inhibitors.

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-dioxo-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 C₅₃H₈₃NO₁₄ and the molecular weight is 958.2 g/mol. The structural formula is:



AFINITOR for oral administration contains 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus and the following inactive ingredients: anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate.

AFINITOR DISPERZ for oral administration contains 2 mg, 3 mg, or 5 mg of everolimus and the following inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol, and microcrystalline cellulose.

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 and in tuberous sclerosis complex (TSC). 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 initiation 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 as well as seizures and epileptogenesis. Overactivation of mTOR results in neuronal dysplasia, aberrant axonogenesis and dendrite formation, increased excitatory synaptic currents, reduced myelination, and disruption of the cortical laminar structure causing abnormalities in neuronal development and function. Treatment with an mTOR inhibitor in animal models of mTOR dysregulation in the brain resulted in seizure suppression, prevention of the development of new-onset seizures, and prevention of premature death.

12.2 Pharmacodynamics

Exposure-Response Relationship

In patients with TSC-associated subependymal giant cell astrocytoma (SEGA), the magnitude of the reduction in SEGA volume was correlated with the everolimus trough concentration.

In patients with TSC-associated partial-onset seizures, the magnitude of the reduction in absolute seizure frequency was correlated with the everolimus trough concentration.

Cardiac Electrophysiology

In a randomized, placebo-controlled, cross-over study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. AFINITOR at single doses up to 50 mg did not prolong the QT/QTc interval.

12.3 Pharmacokinetics

Absorption

After administration of AFINITOR 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 with daily dosing between 5 mg and 10 mg. With single doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional; however, AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

In patients with TSC-associated SEGA, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m² to 14.4 mg/m².

Effect of Food: In healthy subjects, a high-fat meal (containing approximately 1000 calories and 55 grams of fat) reduced systemic exposure to AFINITOR 10 mg (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Light-fat meals (containing approximately 500 calories and 20 grams of fat) reduced AUC by 32% and C_{max} by 42%.

In healthy subjects who received 9 mg of AFINITOR DISPERZ, high-fat meals (containing approximately 1000 calories and 55 grams of fat) reduced everolimus AUC by 12% and C_{max} by 60% and low-fat meals (containing approximately 500 calories and 20 grams of fat) reduced everolimus AUC by 30% and C_{max} by 50%.

Relative Bioavailability: The AUC_{inf} of everolimus was equivalent between AFINITOR DISPERZ and AFINITOR; the C_{max} of everolimus in the AFINITOR DISPERZ dosage form was 20% to 36% lower than that of AFINITOR. 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 orally once daily. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Elimination

The mean elimination half-life of everolimus is approximately 30 hours.

Metabolism: Everolimus is a substrate of CYP3A4. 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.

Excretion: No specific elimination 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.

Specific Populations

No relationship was apparent between oral clearance and age or sex in patients with cancer.

Patients with Renal Impairment: No significant influence of creatinine clearance (25 to 178 mL/min) was detected on oral clearance (CL/F) of everolimus.

Patients with Hepatic Impairment: Compared to normal subjects, there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in AUC for subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment, respectively. In another study, the average AUC of everolimus in subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in subjects with normal hepatic function [see *Dosage and Administration (2.10), Use in Specific Populations (8.6)*].

Pediatric Patients: In patients with TSC-associated SEGA or TSC-associated partial-onset seizures, the mean C_{min} values normalized to mg/m² dose in pediatric patients (< 18 years of age) were lower than those observed in adults, suggesting that everolimus clearance adjusted to BSA was higher in pediatric patients as compared to adults.

Race or Ethnicity: Based on a cross-study comparison, Japanese patients had on average exposures that were higher than non-Japanese patients receiving the same dose. Oral clearance (CL/F) is on average 20% higher in Black patients than in White patients.

Drug Interaction Studies

Effect of CYP3A4 and P-glycoprotein (P-gp) Inhibitors on Everolimus: Everolimus exposure increased when AFINITOR was coadministered with:

- ketoconazole (a P-gp and strong CYP3A4 inhibitor) - C_{max} and AUC increased by 3.9- and 15-fold, respectively.
- erythromycin (a P-gp and moderate CYP3A4 inhibitor) - C_{max} and AUC increased by 2- and 4.4-fold, respectively.
- verapamil (a P-gp and moderate CYP3A4 inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Effect of CYP3A4 and P-gp Inducers on Everolimus: The coadministration of AFINITOR with rifampin, a P-gp and strong inducer of CYP3A4, decreased everolimus AUC by 63% and C_{max} by 58% compared to AFINITOR alone [see *Dosage and Administration (2.12)*].

Effect of Everolimus on CYP3A4 Substrates: No clinically significant pharmacokinetic interactions were observed between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate), pravastatin (a non-CYP3A4 substrate), and simvastatin (a CYP3A4 substrate).

The coadministration of an oral dose of midazolam (sensitive CYP3A4 substrate) with AFINITOR resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam AUC_{0-inf} .

The coadministration of AFINITOR with 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 2 treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

The coadministration of AFINITOR with long acting octreotide increased octreotide C_{min} by approximately 50%.

Effect of Everolimus on Antiepileptic drugs (AEDs): Everolimus increased pre-dose concentrations of the carbamazepine, clobazam, oxcarbazepine, and clobazam's metabolite N-desmethylclobazam by about 10%. Everolimus had no impact on pre-dose concentrations of AEDs that are substrates of CYP3A4 (e.g., clonazepam and zonisamide) or other AEDs, including valproic acid, topiramate, phenobarbital, and phenytoin.

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 human exposure based on AUC at the recommended dose of AFINITOR 10 mg orally once daily.

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/m²/day, approximately 255-fold the recommended dose of AFINITOR 10 mg orally once daily, and approximately 200-fold the median dose administered to patients with TSC-associated SEGA and TSC-associated partial-onset seizures, based on the BSA), administered as 2 doses, 24 hours apart.

Based on non-clinical findings, AFINITOR/AFINITOR DISPERZ may impair male fertility. In a 13-week male fertility study in rats, testicular morphology was affected at doses of 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with 5 mg/kg. The exposures at these doses (52 ng•hr/mL and 414 ng•hr/mL, respectively) were within the range of human exposure at the recommended dose of AFINITOR 10 mg orally once daily (560 ng•hr/mL) and resulted in infertility in the rats at 5 mg/kg. Effects on male fertility occurred at AUC_{0-24h} values 10% to 81% lower than human exposure at the recommended dose of AFINITOR 10 mg orally once daily. After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60%.

Oral doses of everolimus in female rats at doses ≥ 0.1 mg/kg (approximately 4% the human exposure based on AUC at the recommended dose of AFINITOR 10 mg orally once daily) resulted in increased incidence of pre-implantation loss, suggesting that the drug may reduce female fertility.

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 Hormone Receptor-Positive, HER2-Negative Breast Cancer

A randomized, double-blind, multicenter study (BOLERO-2, NCT00863655) of AFINITOR in combination with exemestane vs. placebo in combination with exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2-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 major efficacy outcome measure was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid

Tumors), based on investigator (local radiology) assessment. Other outcome measures included overall survival (OS) and objective response rate (ORR).

Patients were randomized 2:1 to AFINITOR 10 mg orally once daily in combination with exemestane 25 mg once daily (n = 485) or to placebo in combination with exemestane 25 mg orally once daily (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 trial demonstrated a statistically significant improvement in PFS by investigator assessment (Table 20 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.

ORR was higher in the AFINITOR in combination with exemestane arm vs. the placebo in combination with exemestane arm (Table 20). There were 3 complete responses (0.6%) and 58 partial responses (12%) in the AFINITOR arm. There were no complete responses and 4 partial responses (1.7%) in the placebo in combination with exemestane arm.

After a median follow-up of 39.3 months, there was no statistically significant difference in OS between the AFINITOR in combination with exemestane arm and the placebo in combination with exemestane arm [HR 0.89 (95% CI: 0.73, 1.10)].

Table 20: Efficacy Results in Hormone-Receptor Positive, HER-2 Negative Breast Cancer in BOLERO-2

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

^aHazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis.

^bp-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis.

^cObjective response rate = proportion of patients with CR or PR.

^dNot applicable.

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, including:

- 1. You may develop lung or breathing problems.** In some people lung or breathing problems may be severe and can 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 (including adults and children) these infections may be severe and can 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 swelling
 - Tiredness
 - Loss of appetite
 - Nausea
 - Pale stools or dark urine
 - Yellowing of the skin
 - Pain in the upper right side of the stomach
- 3. Severe allergic reactions.** Call your healthcare provider or get medical help right away if you get signs and symptoms of a severe allergic reaction including: rash, itching, hives, flushing, trouble breathing or swallowing, chest pain or dizziness.
- 4. Possible increased risk for a type of allergic reaction called angioedema,** in people who take an Angiotensin-Converting Enzyme (ACE) inhibitor medicine during treatment with AFINITOR or AFINITOR DISPERZ. Talk with your healthcare provider before taking AFINITOR or AFINITOR DISPERZ if you are not sure if you take an ACE inhibitor medicine. Get medical help right away if you have trouble breathing or develop swelling of your tongue, mouth, or throat during treatment with AFINITOR or AFINITOR DISPERZ.
- 5. Mouth ulcers and sores.** Mouth ulcers and sores are common during treatment with AFINITOR or AFINITOR DISPERZ but can also be severe. When you start treatment with AFINITOR or AFINITOR DISPERZ, your healthcare provider may tell you to also start a prescription mouthwash to reduce the likelihood of getting mouth ulcers or sores and to reduce their severity. Follow your healthcare provider's instructions on how to use this prescription mouthwash. If you develop pain, discomfort, or open sores in your mouth, tell your healthcare provider. Your healthcare provider may tell you to re-start this mouthwash or to use a special mouthwash or mouth gel that does not contain alcohol, peroxide, iodine, or thyme.
- 6. You may develop kidney failure.** In some people this may be severe and can 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.
- adults with a type of cancer known as neuroendocrine tumor (NET) of the stomach and intestine (gastrointestinal), or lung that has progressed and cannot be treated with surgery.

AFINITOR is not for use in people with carcinoid tumors that actively produce hormones.

- 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 1 year of age and older 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 1 year of age and older 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.
- adults and children 2 years of age and older with a genetic condition called tuberous sclerosis complex (TSC) who have certain types of seizures (epilepsy), as an added treatment to other antiepileptic medicines.

It is not known if AFINITOR and AFINITOR DISPERZ are safe and effective in children to treat:

- hormone receptor-positive, HER-2 negative breast cancer
- a type of cancer called neuroendocrine tumors (NET)
- kidney cancer (renal cell carcinoma)
- a kidney tumor called angiomyolipoma, that can happen in children with a genetic condition called tuberous sclerosis complex (TSC).

Do not take AFINITOR or AFINITOR DISPERZ if you have had a severe allergic reaction to everolimus.

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.

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. For children with TSC and SEGA or certain types of seizures, work with your healthcare provider to complete the recommended childhood series of vaccines before your child starts treatment with AFINITOR or AFINITOR DISPERZ.
- Are pregnant, can become pregnant, or have a partner who can become pregnant. AFINITOR or AFINITOR DISPERZ can cause harm to your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment with AFINITOR or AFINITOR DISPERZ.
- You should use effective birth control during treatment and for 8 weeks after your last dose of AFINITOR or AFINITOR DISPERZ.

Males with a female partner, you should use effective birth control during treatment and for 4 weeks after your last dose of AFINITOR or AFINITOR DISPERZ.

Talk to your healthcare provider about birth control methods that may be right for you during this time. If you become pregnant or think you are pregnant, tell your healthcare provider right away.

- Are breastfeeding or plan to breastfeed. It is not known if AFINITOR or AFINITOR DISPERZ passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of AFINITOR or AFINITOR DISPERZ.
- Are planning to have surgery or if you have had a recent surgery. You should stop taking AFINITOR or AFINITOR DISPERZ at least 1 week before planned surgery. See **“What are the possible side effects of AFINITOR and AFINITOR DISPERZ?”**

- Have received radiation therapy or are planning to receive radiation therapy in the future. See “**What are the possible side effects of AFINITOR and AFINITOR DISPERZ?**”

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter 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. Taking 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 or tell you to temporarily interrupt dosing, if needed.
- **Take only AFINITOR or AFINITOR DISPERZ. Do not mix AFINITOR and AFINITOR DISPERZ together.**
- Use scissors to open the blister pack.
- Take AFINITOR or AFINITOR DISPERZ 1 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 room right away. Take the pack of AFINITOR or AFINITOR DISPERZ with you.
- If you miss a dose of AFINITOR or AFINITOR DISPERZ, you may take it if it is **less than 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 a missed dose. 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 or AFINITOR DISPERZ to treat certain types of seizures with TSC, 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.

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 comes 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.
- Wear gloves to avoid possible contact with everolimus when preparing suspensions of AFINITOR DISPERZ for another person.

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 or AFINITOR DISPERZ 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.
- **Risk of wound healing problems.** Wounds may not heal properly during AFINITOR and AFINITOR DISPERZ treatment. Tell your healthcare provider if you plan to have any surgery before starting or during treatment with AFINITOR and AFINITOR DISPERZ.
 - You should stop taking AFINITOR and AFINITOR DISPERZ at least 1 week before planned surgery.
 - Your healthcare provider should tell you when you may start taking AFINITOR and AFINITOR DISPERZ again after surgery.
- **Increased blood sugar and fat (cholesterol and triglyceride) levels in the blood.** Your healthcare provider should do blood tests to check your fasting blood sugar, cholesterol, and triglyceride levels in the blood before you start and during treatment with AFINITOR or AFINITOR DISPERZ.
- **Decreased blood cell counts.** AFINITOR and AFINITOR DISPERZ can cause you to have decreased red blood cells, white blood cells, and platelets. Your healthcare provider should do blood tests to check your blood cell counts before you start and during treatment with AFINITOR or AFINITOR DISPERZ.
- **Worsening side effects from radiation treatment,** that can sometimes be severe. Tell your healthcare provider if you have had or are planning to receive radiation therapy.

The most common side effects of AFINITOR in people with advanced hormone receptor-positive, HER2-negative breast cancer, advanced neuroendocrine tumors of the pancreas, stomach and intestine (gastrointestinal) or lung, and advanced kidney cancer include:

- Infections
- Rash
- Feeling weak or tired
- Diarrhea
- Swelling of arms, hands, feet, ankles, face, or other parts of the body
- Stomach-area (abdominal) pain
- Nausea
- Fever
- Cough
- Headache
- Decreased appetite

The most common side effects of AFINITOR and AFINITOR DISPERZ in people who have SEGA, renal angiomyolipoma, or certain types of seizures with TSC include respiratory tract infections.

Other side effects that may occur with AFINITOR and AFINITOR DISPERZ:

- Absence of menstrual periods (menstruation). You may miss 1 or more menstrual periods. Tell your healthcare provider if this happens.
- AFINITOR and AFINITOR DISPERZ may affect fertility in females and may affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.
- AFINITOR and AFINITOR DISPERZ may affect fertility in males and may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

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 the safe and effective use of 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.

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

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

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