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

----------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/m^2 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/m^2 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)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.12, 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)

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

Revised: 2/2020

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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/m^2 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/m^2 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:

  New dose* = current dose x (target concentration divided by 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 *[see Warnings and Precautions (5.1)]*	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 *[see Warnings and Precautions (5.5)]*	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) *[see Warnings and Precautions (5.9)]*	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 *[see Warnings and Precautions (5.10)]*	Grade 2	Withhold until improvement to Grade 0 or 1. Resume at same dose.
	Grade 3 **OR** 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 *[see Warnings and Precautions (5.10)]*	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.

Adverse Reaction	Severity	Dosage Modification
Febrile neutropenia *[see Warnings and Precautions (5.10)]*	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.
	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	• 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	• Severe hepatic impairment (Child-Pugh class C) – 2.5 mg/m^2 orally once daily. • Adjust dose based on everolimus trough concentrations as recommended *[see Dosage and Administration (2.8)]*.

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	• 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	• 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 Dosage and Administration (2.8)]*.

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	• 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	• 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 *[see Dosage and Administration (2.8)]*. • 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 ≥ 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 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)]*.

Laboratory Parameter	AFINITOR with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
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]
Hypokalemia	29	4	7	1[b]
Increased creatinine	24	2	13	0

Grading according to NCI CTCAE Version 3.0.

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

[b]No Grade 4 laboratory abnormalities were reported.

Topical Prophylaxis for Stomatitis

In a single arm study (SWISH; N = 92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily), patients started dexamethasone 0.5 mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with AFINITOR and exemestane. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone mouthwash. The primary objective of this study was to assess the incidence of Grade 2 to 4 stomatitis within 8 weeks. The incidence of Grade 2 to 4 stomatitis within 8 weeks was 2%, which was lower than the 33% reported in the BOLERO-2 trial. The incidence of Grade 1 stomatitis was 19%. No cases of Grade 3 or 4 stomatitis were reported. Oral candidiasis was reported in 2% of patients in this study compared to 0.2% in the BOLERO-2 trial.

Coadministration of AFINITOR/AFINITOR DISPERZ and dexamethasone alcohol-free oral solution has not been studied in pediatric patients.

Pancreatic Neuroendocrine Tumors (PNET)

In a randomized, controlled trial (RADIANT-3) of AFINITOR (n = 204) vs. placebo (n = 203) in patients with advanced PNET the median age of patients was 58 years (20 to 87 years), 79% were White, and 55% were male. Patients on the placebo arm could cross over to open-label AFINITOR upon disease progression.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common Grade 3-4 adverse reactions (incidence ≥ 5%) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hyperglycemia, increased alkaline phosphatase, hypercholesterolemia, decreased bicarbonate, and increased AST. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 3%) were hyperglycemia, lymphopenia, anemia, hypophosphatemia, increased alkaline phosphatase, neutropenia, increased AST, hypokalemia, and thrombocytopenia.

Deaths during double-blind treatment where an adverse reaction was the primary cause occurred in seven patients on AFINITOR. Causes of death on the AFINITOR arm included one case of each of the following: acute renal failure, acute

respiratory distress, cardiac arrest, death (cause unknown), hepatic failure, pneumonia, and sepsis. After cross-over to open-label AFINITOR, there were three additional deaths, one due to hypoglycemia and cardiac arrest in a patient with insulinoma, one due to myocardial infarction with congestive heart failure, and the other due to sudden death. The rate of adverse reactions resulting in permanent discontinuation was 20% for the AFINITOR group. Dose delay or reduction was necessary in 61% of AFINITOR patients. Grade 3-4 renal failure occurred in six patients in the AFINITOR arm. Thrombotic events included five patients with pulmonary embolus in the AFINITOR arm as well as three patients with thrombosis in the AFINITOR arm.

Table 8 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR vs. placebo. Laboratory abnormalities are summarized in Table 9. The median duration of treatment in patients who received AFINITOR was 37 weeks.

In female patients aged 18 to 55 years, irregular menstruation occurred in 5 of 46 (11%) AFINITOR-treated females.

Table 8: Adverse Reactions Reported in ≥ 10% of Patients with PNET in RADIANT-3

	AFINITOR N = 204		Placebo N = 203	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal				
Stomatitis[a]	70	7[d]	20	0
Diarrhea[b]	50	6	25	3[d]
Abdominal pain	36	4[d]	32	7
Nausea	32	2[d]	33	2[d]
Vomiting	29	1[d]	21	2[d]
Constipation	14	0	13	0.5[d]
Dry mouth	11	0	4	0
General				
Fatigue/malaise	45	4	27	3
Edema (general and peripheral)	39	2	12	1[d]
Fever	31	1	13	0.5[d]
Asthenia	19	3[d]	20	3[d]
Infections				
Nasopharyngitis/rhinitis/URI	25	0	13	0
Urinary tract infection	16	0	6	0.5[d]
Investigations				
Weight loss	28	0.5[d]	11	0
Metabolism and nutrition				
Decreased appetite	30	1[d]	18	1[d]
Diabetes mellitus	10	2[d]	0.5	0
Musculoskeletal and connective tissue				
Arthralgia	15	1	7	0.5[d]
Back pain	15	1[d]	11	1[d]
Pain in extremity	14	0.5[d]	6	1[d]
Muscle spasms	10	0	4	0
Nervous system				
Headache/migraine	30	0.5[d]	15	1[d]
Dysgeusia	19	0	5	0

	AFINITOR N = 204		Placebo N = 203	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Dizziness	12	0.5[d]	7	0
Psychiatric				
Insomnia	14	0	8	0
Respiratory, thoracic and mediastinal				
Cough/productive cough	25	0.5[d]	13	0
Epistaxis	22	0	1	0
Dyspnea/dyspnea exertional	20	3	7	0.5[d]
Pneumonitis[c]	17	4	0	0
Oropharyngeal pain	11	0	6	0
Skin and subcutaneous				
Rash	59	0.5	19	0
Nail disorders	22	0.5	2	0
Pruritus/pruritus generalized	21	0	13	0
Dry skin/xeroderma	13	0	6	0
Vascular				
Hypertension	13	1	6	1[d]

Grading according to NCI CTCAE Version 3.0.
[a]Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.
[b]Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.
[c]Includes pneumonitis, interstitial lung disease, pulmonary fibrosis, and restrictive pulmonary disease.
[d]No Grade 4 adverse reactions were reported.

Table 9: Selected Laboratory Abnormalities Reported in ≥ 10% of Patients with PNET in RADIANT-3

Laboratory parameter	AFINITOR N = 204		Placebo N = 203	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
Anemia	86	15	63	1
Lymphopenia	45	16	22	4
Thrombocytopenia	45	3	11	0
Leukopenia	43	2	13	0
Neutropenia	30	4	17	2
Chemistry				
Hyperglycemia (fasting)	75	17	53	6
Increased alkaline phosphatase	74	8	66	8
Hypercholesterolemia	66	0.5	22	0
Bicarbonate decreased	56	0	40	0
Increased AST	56	4	41	4
Increased ALT	48	2	35	2
Hypophosphatemia	40	10	14	3

Laboratory parameter	AFINITOR N = 204		Placebo N = 203	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hypertriglyceridemia	39	0	10	0
Hypocalcemia	37	0.5	12	0
Hypokalemia	23	4	5	0
Increased creatinine	19	2	14	0
Hyponatremia	16	1	16	1
Hypoalbuminemia	13	1	8	0
Hyperbilirubinemia	10	1	14	2
Hyperkalemia	7	0	10	0.5

Grading according to NCI CTCAE Version 3.0.

Neuroendocrine Tumors (NET) of Gastrointestinal (GI) or Lung Origin

In a randomized, controlled trial (RADIANT-4) of AFINITOR (n = 202 treated) vs. placebo (n = 98 treated) in patients with advanced non-functional NET of GI or lung origin, the median age of patients was 63 years (22-86 years), 76% were White, and 53% were female. The median duration of exposure to AFINITOR was 9.3 months; 64% of patients were treated for ≥ 6 months and 39% were treated for ≥ 12 months. AFINITOR was discontinued for adverse reactions in 29% of patients, dose reduction or delay was required in 70% of AFINITOR-treated patients.

Serious adverse reactions occurred in 42% of AFINITOR-treated patients and included 3 fatal events (cardiac failure, respiratory failure, and septic shock). Adverse reactions occurring at an incidence of ≥ 10% and at ≥ 5% absolute incidence over placebo (all Grades) or ≥ 2% higher incidence over placebo (Grade 3 and 4) are presented in Table 10. Laboratory abnormalities are presented in Table 11.

Table 10: Adverse Reactions in ≥ 10% of AFINITOR-Treated Patients with Non-Functional NET of GI or Lung Origin in RADIANT-4

	AFINITOR N = 202		Placebo N = 98	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal				
Stomatitis[a]	63	9[d]	22	0
Diarrhea	41	9	31	2[d]
Nausea	26	3	17	1[d]
Vomiting	15	4[d]	12	2[d]
General				
Peripheral edema	39	3[d]	6	1[d]
Fatigue	37	5	36	1[d]
Asthenia	23	3	8	0
Pyrexia	23	2	8	0
Infections				
Infections[b]	58	11	29	2
Investigations				
Weight loss	22	2[d]	11	1[d]

	AFINITOR N = 202		Placebo N = 98	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Metabolism and nutrition				
Decreased appetite	22	1[d]	17	1[d]
Nervous system				
Dysgeusia	18	1[d]	4	0
Respiratory, thoracic and mediastinal				
Cough	27	0	20	0
Dyspnea	20	3[d]	11	2
Pneumonitis[c]	16	2[d]	2	0
Epistaxis	13	1[d]	3	0
Skin and subcutaneous				
Rash	30	1[d]	9	0
Pruritus	17	1[d]	9	0

Grading according to NCI CTCAE Version 4.03.
[a]Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration, and mucosal inflammation.
[b]Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock and viral myocarditis.
[c]Includes pneumonitis and interstitial lung disease.
[d]No Grade 4 adverse reactions were reported.

Table 11: Selected Laboratory Abnormalities in ≥ 10% of AFINITOR-Treated Patients with Non-Functional NET of GI or Lung Origin in RADIANT-4

	AFINITOR N = 202		Placebo N = 98	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
Anemia	81	5[a]	41	2[a]
Lymphopenia	66	16	32	2[a]
Leukopenia	49	2[a]	17	0
Thrombocytopenia	33	2	11	0
Neutropenia	32	2[a]	15	3[a]
Chemistry				
Hypercholesterolemia	71	0	37	0
Increased AST	57	2	34	2[a]
Hyperglycemia (fasting)	55	6[a]	36	1[a]
Increased ALT	46	5	39	1[a]
Hypophosphatemia	43	4[a]	15	2[a]
Hypertriglyceridemia	30	3	8	1[a]
Hypokalemia	27	6	12	3[a]
Hypoalbuminemia	18	0	8	0

Grading according to NCI CTCAE Version 4.03.
[a]No Grade 4 laboratory abnormalities were reported.

Renal Cell Carcinoma (RCC)

The data described below reflect exposure to AFINITOR (n = 274) and placebo (n = 137) in a randomized, controlled trial (RECORD-1) in patients with metastatic RCC who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (27 to 85 years), 88% were White, and 78% were male. The median duration of blinded study treatment was 141 days (19 to 451 days) for patients receiving AFINITOR.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia.

Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm. The rate of adverse reactions resulting in permanent discontinuation was 14% for the AFINITOR group. The most common adverse reactions leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR vs. placebo are presented in Table 12. Laboratory abnormalities are presented in Table 13.

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

	AFINITOR N = 274		Placebo N = 137	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
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.

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

[b]Includes all reported infections including, but not limited to, respiratory tract (upper and lower) infections, urinary tract infections, and skin infections.

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

[d]No 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%), onychoclasis (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 increased	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.

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

[b]No 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 lymphangioleiomyomatosis (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 ≥ 30%) was stomatitis. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis and amenorrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was hypophosphatemia.

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

Adverse reactions reported with an incidence of ≥ 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 ≥ 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.
[a]Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.
[b]No 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
Thrombocytopenia	19	0	3	0
Chemistry				
Hypercholesterolemia	85	1[a]	46	0
Hypertriglyceridemia	52	0	10	0
Hypophosphatemia	49	5[a]	15	0

	AFINITOR N = 79		Placebo N = 39	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
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.
[a]No 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 ≥ 30%) were stomatitis and respiratory tract infection. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pyrexia, pneumonia, gastroenteritis, aggression, agitation, and amenorrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia.

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

Adverse reactions reported with an incidence of ≥ 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 ≥ 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
General				

	AFINITOR N = 78		Placebo N = 39	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
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.

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

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

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

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

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

[f]No 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.

[a]No 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

	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 %

[a]Includes stomatitis, mouth ulceration, aphthous ulcer, lip ulceration, tongue ulceration, mucosal inflammation, gingival pain.
[b]No 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.
[a]No 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

- 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).

Who should not take AFINITOR or AFINITOR DISPERZ?

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.

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

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

- Have or have had kidney problems
- Have or have had liver problems
- Have diabetes or high blood sugar
- Have high blood cholesterol levels
- Have any infections
- Previously had hepatitis B
- Are scheduled to receive any vaccinations. You should not receive a “live vaccine” or be around people who have recently received a “live vaccine” during your treatment with AFINITOR or AFINITOR DISPERZ. If you are not sure about the type of immunization or vaccine, ask your healthcare provider. 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. If you are a female who is able to become pregnant you should use effective birth control during treatment and for 8 weeks after your last dose of AFINITOR or AFINITOR DISPERZ. If you are a male 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?"**

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.
- When you start treatment with AFINITOR, your healthcare provider may also prescribe a 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.
- 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.

AFINITOR:

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

AFINITOR DISPERZ:

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

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

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.

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:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. When you start treatment with AFINITOR, 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.

- 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:

- Mouth ulcers. AFINITOR and AFINITOR DISPERZ can cause mouth ulcers and sores. 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.
- 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 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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