

EVEROLIMUS- everolimus tablet
EVEROLIMUS- everolimus tablet, for suspension
Breckenridge Pharmaceutical, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVEROLIMUS TABLETS/EVEROLIMUS TABLETS FOR ORAL SUSPENSION safely and effectively. See full prescribing information for EVEROLIMUS TABLETS/EVEROLIMUS TABLETS FOR ORAL SUSPENSION.

EVEROLIMUS tablets, for oral use
EVEROLIMUS tablets for oral suspension
Initial U.S. Approval: 2009

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

Everolimus tablets are 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: Everolimus tablets are 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)

Everolimus tablets and everolimus tablets for oral suspension 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)
Everolimus tablets for oral suspension 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 everolimus tablets and everolimus tablets for oral suspension 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** -----

- Everolimus Tablets: 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets with no score (3)
- Everolimus tablets for oral suspension: 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 \geq 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 \geq 30%) is stomatitis. (6.1)
- TSC-Associated SEGA: Most common adverse reactions (incidence \geq 30%) are stomatitis and respiratory tract infection. (6.1)
- TSC-Associated Partial-Onset Seizures: Most common adverse reaction (incidence \geq 30%) is stomatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Breckenridge Pharmaceutical, Inc. at 1-800-367-3395 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: 9/2025

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer

Everolimus tablets are 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)

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

Everolimus tablets are 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: Everolimus tablets are not indicated for the treatment of patients with functional carcinoid tumors [see *Clinical Studies (14.2)*].

1.3 Renal Cell Carcinoma (RCC)

Everolimus tablets are 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

Everolimus tablets are 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)

Everolimus tablets and Everolimus tablets for oral suspension 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

Everolimus tablets for oral suspension are 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

- Everolimus tablets and everolimus tablets for oral suspension are two different dosage forms. Select the recommended dosage form based on the indication [see *Indications and Usage (1)*]. Do not combine everolimus tablets and everolimus tablets for oral suspension 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 everolimus tablets is 10 mg orally once daily until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for Neuroendocrine Tumors (NET)

The recommended dosage of everolimus tablets 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets for oral suspension 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:

New dose¹ = current dose × (target concentration divided by current 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 everolimus tablets/everolimus tablets for oral suspension | 1 to 2 weeks |
| Modification of everolimus tablets/everolimus tablets for oral suspension dose | 1 to 2 weeks |
| Switch between everolimus tablets/everolimus tablets for oral suspension | 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.

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

2.9 Dosage Modifications for Adverse Reactions

Table 2 summarizes recommendations for dosage modifications of everolimus tablets/everolimus tablets for oral suspension for the management of adverse reactions.

Table 2: Recommended Dosage Modifications for Everolimus Tablets/Everolimus Tablets for Oral Suspension 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) [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 | 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 | |
| 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. |
| 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 everolimus tablets/everolimus tablets for oral suspension 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 Everolimus Tablets/Everolimus Tablets for Oral Suspension |
|--|---|
| 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, Tuberos 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 everolimus tablets/everolimus tablets for oral suspension 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 Everolimus Tablets/Everolimus Tablets for Oral Suspension With a P-gp and Moderate CYP3A4 Inhibitor

| Indication | Dose Modification for Everolimus Tablets/Everolimus Tablets for Oral Suspension |
|------------|---|
|------------|---|

| | |
|--|--|
| 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</i> (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 everolimus tablets/everolimus tablets for oral suspension 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 Everolimus Tablets/Everolimus Tablets for Oral Suspension With P-gp and Strong CYP3A4 Inducers

| Indication | Dose Modification for Everolimus Tablets/Everolimus Tablets for Oral Suspension |
|--|---|
| 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 [see <i>Dosage and Administration</i> (2.8)]. • Resume the dose administered before starting any inducer, once all inducers are discontinued |

| |
|-------------|
| for 5 days. |
|-------------|

2.13 Administration and Preparation

- Administer everolimus tablets/everolimus tablets for oral suspension at the same time each day.
- Administer everolimus tablets/everolimus tablets for oral suspension consistently either with or without food [see *Clinical Pharmacology (12.3)*].
- If a dose of everolimus tablets/everolimus tablets for oral suspension 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, everolimus tablets/everolimus tablets for oral suspension should be administered at its usual time. Double doses should not be administered to make up for the dose that was missed.

Everolimus Tablets

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

Everolimus Tablets for Oral Suspension

- Wear gloves to avoid possible contact with everolimus when preparing suspensions of everolimus tablets for oral suspension 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

Everolimus Tablets

2.5 mg: White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and '2.5' on the other side.

5 mg: White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and '5' on the other side.

7.5 mg: White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and '7.5' on the other side.

10 mg: White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and 'NAT' on the other side.

Everolimus Tablets for Oral Suspension

Tablets for oral suspension, white to off white colored, round, flat tablets:

- 2 mg: debossed with "2" on one side and "E" on other side.
- 3 mg: debossed with "3" on one side and "E" on other side.
- 5 mg: debossed with "5" on one side and "E" on other side.

4. CONTRAINDICATIONS

Everolimus tablets/everolimus tablets for oral suspension are 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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

Everolimus tablets/everolimus tablets for oral suspension have 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor. Permanently discontinue everolimus tablets/everolimus tablets for oral suspension for angioedema.

5.5 Stomatitis

Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral

suspension, 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 everolimus tablets. Elevations of serum creatinine and proteinuria have been reported in patients taking everolimus tablets/everolimus tablets for oral suspension [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 everolimus tablets/everolimus tablets for oral suspension 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, everolimus tablets/everolimus tablets for oral suspension have the potential to adversely affect wound healing.

Withhold everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets dose was 6% in patients \geq 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients \geq 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension and annually thereafter. In diabetic patients, monitor fasting serum glucose more frequently as clinically indicated. Monitor lipid profile prior to starting everolimus tablets/everolimus tablets for oral suspension and annually thereafter. When possible, achieve optimal

glucose and lipid control prior to starting everolimus tablets/everolimus tablets for oral suspension. For Grade 3 to 4 metabolic events, withhold or permanently discontinue everolimus tablets/everolimus tablets for oral suspension based on severity [see *Dosage and Administration (2.9)*].

5.10 Myelosuppression

Anemia, lymphopenia, neutropenia, and thrombocytopenia have been reported in patients taking everolimus tablets/everolimus tablets for oral suspension. 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 everolimus tablets/everolimus tablets for oral suspension every 6 months for the first year of treatment and annually thereafter. Withhold or permanently discontinue everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension. 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 everolimus tablets/everolimus tablets for oral suspension treatment [see *Adverse Reactions (6.2)*].

Monitor patients closely when everolimus tablets/everolimus tablets for oral suspension are administered during or sequentially with radiation treatment.

5.13 Embryo-Fetal Toxicity

Based on animal studies and the mechanism of action, everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension and for 8 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with everolimus tablets/everolimus tablets for oral suspension 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 (5.12)]

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 everolimus tablets (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 everolimus tablets. The rate of adverse reactions resulting in permanent discontinuation was 24% for the everolimus tablets arm. Dose adjustments (interruptions or reductions) occurred in 63% of patients in the everolimus tablets arm.

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

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

| | Everolimus Tablets with Exemestane N = 482 | | Placebo with Exemestane N = 238 | |
|--|--|--------------------|---------------------------------------|--------------------|
| | All Grades % | Grade 3- 4 % | All Grades % | Grade 3- 4 % |
| Gastrointestinal | | | | |
| Stomatitis* | 67 | 8 [†] | 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 [†] | 13 | 0.4 |
| Dry mouth | 11 | 0 | 7 | 0 |
| General | | | | |
| Fatigue | 36 | 4 | 27 | 1 [†] |
| Edema peripheral | 19 | 1 [†] | 6 | 0.4 [†] |
| Pyrexia | 15 | 0.2 [†] | 7 | 0.4 [†] |
| Asthenia | 13 | 2 | 4 | 0 |
| Infections | | | | |
| Infections [‡] | 50 | 6 | 25 | 2 [†] |
| Investigations | | | | |
| Weight loss | 25 | 1 [†] | 6 | 0 |
| Metabolism and nutrition | | | | |
| Decreased appetite | 30 | 1 [†] | 12 | 0.4 [†] |
| Hyperglycemia | 14 | 5 | 2 | 0.4 [†] |
| Musculoskeletal and connective tissue | | | | |
| Arthralgia | 20 | 0.8 [†] | 17 | 0 |
| Back pain | 14 | 0.2 [†] | 10 | 0.8 [†] |
| Pain in extremity | 9 | 0.4 [†] | 11 | 2 [†] |
| Nervous system | | | | |
| Dysgeusia | 22 | 0.2 [†] | 6 | 0 |
| Headache | 21 | 0.4 [†] | 14 | 0 |
| Psychiatric | | | | |
| Insomnia | 13 | 0.2 [†] | 8 | 0 |
| Respiratory, thoracic and mediastinal | | | | |
| Cough | 24 | 0.6 [†] | 12 | 0 |
| Dyspnea | 21 | 4 | 11 | 1 |
| Epistaxis | 17 | 0 | 1 | 0 |
| Pneumonitis [§] | 19 | 4 | 0.4 | 0 |
| Skin and subcutaneous tissue | | | | |
| Rash | 39 | 1 [†] | 6 | 0 |
| Pruritus | 13 | 0.2 [†] | 5 | 0 |
| Alopecia | 10 | 0 | 5 | 0 |

| | | | | |
|-----------------|---|---|----|---|
| Vascular | | | | |
| Hot flush | 6 | 0 | 14 | 0 |

Grading according to NCI CTCAE Version 3.0.

* Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis, and lip ulceration.

† No Grade 4 adverse reactions were reported.

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

§ Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

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

| Laboratory Parameter | Everolimus Tablets with Exemestane N = 482 | | Placebo with Exemestane N = 238 | |
|----------------------|---|------------------|------------------------------------|------------------|
| | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| Hematology* | | | | |
| Anemia | 68 | 6 | 40 | 1 |
| Leukopenia | 58 | 2 [†] | 28 | 6 |
| Thrombocytopenia | 54 | 3 | 5 | 0.4 |
| Lymphopenia | 54 | 12 | 37 | 6 |
| Neutropenia | 31 | 2 [†] | 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 [†] |
| Hypertriglyceridemia | 50 | 0.8 [†] | 26 | 0 |
| Hypoalbuminemia | 33 | 0.8 [†] | 16 | 0.8 [†] |
| Hypokalemia | 29 | 4 | 7 | 1 [†] |
| Increased creatinine | 24 | 2 | 13 | 0 |

Grading according to NCI CTCAE Version 3.0.

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

† 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 everolimus tablets (10 mg orally once daily) in combination with exemestane (25 mg orally once daily), patients started dexamethasone 0.5 mg/5 mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with everolimus tablets 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets (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 everolimus tablets upon disease progression.

The most common adverse reactions (incidence \geq 30%) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common Grade 3-4 adverse reactions (incidence \geq 5%) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence \geq 50%) were anemia, hyperglycemia, increased alkaline phosphatase, hypercholesterolemia, decreased bicarbonate, and increased AST. The most common Grade 3-4 laboratory abnormalities (incidence \geq 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 everolimus tablets. Causes of death on the everolimus tablets 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 everolimus tablets, 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 everolimus tablets group. Dose delay or reduction was necessary in 61% of everolimus tablets patients. Grade 3-4 renal failure occurred in six patients in the everolimus tablets arm. Thrombotic events included five patients with pulmonary embolus in the everolimus tablets arm as well as three patients with thrombosis in the everolimus tablets arm.

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

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

Table 8: Adverse Reactions Reported in \geq 10% of Patients With PNET in RADIANT-3

| | Everolimus Tablets | Placebo |
|--|--------------------|---------|
|--|--------------------|---------|

| | N = 204 | | N = 203 | |
|--|--------------|------------------|--------------|------------------|
| | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| Gastrointestinal | | | | |
| Stomatitis* | 70 | 7 [†] | 20 | 0 |
| Diarrhea [‡] | 50 | 6 | 25 | 3 [†] |
| Abdominal pain | 36 | 4 [†] | 32 | 7 |
| Nausea | 32 | 2 [†] | 33 | 2 [†] |
| Vomiting | 29 | 1 [†] | 21 | 2 [†] |
| Constipation | 14 | 0 | 13 | 0.5 [†] |
| Dry mouth | 11 | 0 | 4 | 0 |
| General | | | | |
| Fatigue/malaise | 45 | 4 | 27 | 3 |
| Edema (general and peripheral) | 39 | 2 | 12 | 1 [†] |
| Fever | 31 | 1 | 13 | 0.5 [†] |
| Asthenia | 19 | 3 [†] | 20 | 3 [†] |
| Infections | | | | |
| Nasopharyngitis/rhinitis/URI | 25 | 0 | 13 | 0 |
| Urinary tract infection | 16 | 0 | 6 | 0.5 [†] |
| Investigations | | | | |
| Weight loss | 28 | 0.5 [†] | 11 | 0 |
| Metabolism and nutrition | | | | |
| Decreased appetite | 30 | 1 [†] | 18 | 1 [†] |
| Diabetes mellitus | 10 | 2 [†] | 0.5 | 0 |
| Musculoskeletal and connective tissue | | | | |
| Arthralgia | 15 | 1 | 7 | 0.5 [†] |
| Back pain | 15 | 1 [†] | 11 | 1 [†] |
| Pain in extremity | 14 | 0.5 [†] | 6 | 1 [†] |
| Muscle spasms | 10 | 0 | 4 | 0 |
| Nervous system | | | | |
| Headache/migraine | 30 | 0.5 [†] | 15 | 1 [†] |
| Dysgeusia | 19 | 0 | 5 | 0 |
| Dizziness | 12 | 0.5 [†] | 7 | 0 |
| Psychiatric | | | | |
| Insomnia | 14 | 0 | 8 | 0 |
| Respiratory, thoracic and mediastinal | | | | |
| Cough/productive cough | 25 | 0.5 [†] | 13 | 0 |
| Epistaxis | 22 | 0 | 1 | 0 |
| Dyspnea/dyspnea exertional | 20 | 3 | 7 | 0.5 [†] |
| Pneumonitis [§] | 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 [†] |

Grading according to NCI CTCAE Version 3.0.

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

† No Grade 4 adverse reactions were reported.

‡ Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

§ Includes pneumonitis, interstitial lung disease, pulmonary fibrosis, and restrictive pulmonary disease.

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

| Laboratory parameter | Everolimus Tablets 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 |
| 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 everolimus tablets (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 everolimus tablets was 9.3 months; 64% of patients were treated for ≥ 6 months and 39% were treated for ≥ 12 months. Everolimus tablets was discontinued for adverse reactions in 29% of patients, dose reduction or delay was required in 70% of everolimus tablets-treated patients.

Serious adverse reactions occurred in 42% of everolimus tablets-treated patients and included 3 fatal events (cardiac failure, respiratory failure, and septic shock). Adverse reactions occurring at an incidence of $\geq 10\%$ and at $\geq 5\%$ absolute incidence over placebo (all Grades) or $\geq 2\%$ 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 $\geq 10\%$ of Everolimus Tablets-Treated Patients With Non-Functional NET of GI or Lung Origin in RADIANT-4

| | Everolimus Tablets N = 202 | | Placebo N = 98 | |
|--|-------------------------------|--------------------|--------------------|--------------------|
| | All Grades % | Grade 3- 4 % | All Grades % | Grade 3- 4 % |
| Gastrointestinal | | | | |
| Stomatitis* | 63 | 9 [†] | 22 | 0 |
| Diarrhea | 41 | 9 | 31 | 2 [†] |
| Nausea | 26 | 3 | 17 | 1 [†] |
| Vomiting | 15 | 4 [†] | 12 | 2 [†] |
| General | | | | |
| Peripheral edema | 39 | 3 [†] | 6 | 1 [†] |
| Fatigue | 37 | 5 | 36 | 1 [†] |
| Asthenia | 23 | 3 | 8 | 0 |
| Pyrexia | 23 | 2 | 8 | 0 |
| Infections | | | | |
| Infections [‡] | 58 | 11 | 29 | 2 |
| Investigations | | | | |
| Weight loss | 22 | 2 [†] | 11 | 1 [†] |
| Metabolism and nutrition | | | | |
| Decreased appetite | 22 | 1 [†] | 17 | 1 [†] |
| Nervous system | | | | |
| Dysgeusia | 18 | 1 [†] | 4 | 0 |
| Respiratory, thoracic and mediastinal | | | | |
| Cough | 27 | 0 | 20 | 0 |
| Dyspnea | 20 | 3 [†] | 11 | 2 |
| Pneumonitis [§] | 16 | 2 [†] | 2 | 0 |

| | | | | |
|------------------------------|----|----------------|---|---|
| Epistaxis | 13 | 1 [†] | 3 | 0 |
| Skin and subcutaneous | | | | |
| Rash | 30 | 1 [†] | 9 | 0 |
| Pruritus | 17 | 1 [†] | 9 | 0 |

Grading according to NCI CTCAE Version 4.03.

* Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration, and mucosal inflammation.

† No Grade 4 adverse reactions were reported.

‡ Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock and viral myocarditis.

§ Includes pneumonitis and interstitial lung disease.

Table 11: Selected Laboratory Abnormalities in $\geq 10\%$ of Everolimus Tablets-Treated Patients With Non-Functional NET of GI or Lung Origin in RADIANT-4

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

Grading according to NCI CTCAE Version 4.03.

* No Grade 4 laboratory abnormalities were reported.

Renal Cell Carcinoma (RCC)

The data described below reflect exposure to everolimus tablets (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 everolimus tablets.

The most common adverse reactions (incidence $\geq 30\%$) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence $\geq 3\%$) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence $\geq 50\%$) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence $\geq 3\%$) 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 everolimus tablets arm. The rate of adverse reactions resulting in permanent discontinuation was 14% for the everolimus tablets 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 everolimus tablets treatment were for infections, anemia, and stomatitis.

Adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving everolimus tablets vs. placebo are presented in Table 12. Laboratory abnormalities are presented in Table 13.

Table 12: Adverse Reactions Reported in $\geq 10\%$ of Patients With RCC and at a Higher Rate in the Everolimus Tablets Arm than in the Placebo Arm in RECORD-1

| | Everolimus Tablets N = 274 | | Placebo N = 137 | |
|--|-------------------------------|--------------------|--------------------|--------------------|
| | All Grades % | Grade 3- 4 % | All Grades % | Grade 3- 4 % |
| Gastrointestinal | | | | |
| Stomatitis* | 44 | 4 | 8 | 0 |
| Diarrhea | 30 | 2 [†] | 7 | 0 |
| Nausea | 26 | 2 [†] | 19 | 0 |
| Vomiting | 20 | 2 [†] | 12 | 0 |
| Infections[‡] | 37 | 10 | 18 | 2 |
| General | | | | |
| Asthenia | 33 | 4 | 23 | 4 |
| Fatigue | 31 | 6 [†] | 27 | 4 |
| Edema peripheral | 25 | <1 [†] | 8 | <1 [†] |
| Pyrexia | 20 | <1 [†] | 9 | 0 |
| Mucosal inflammation | 19 | 2 [†] | 1 | 0 |
| Respiratory, thoracic and mediastinal | | | | |
| Cough | 30 | <1 [†] | 16 | 0 |
| Dyspnea | 24 | 8 | 15 | 3 [†] |
| Epistaxis | 18 | 0 | 0 | 0 |
| Pneumonitis [§] | 14 | 4 [†] | 0 | 0 |
| Skin and subcutaneous | | | | |

| | | | | |
|--|----|-----------------|----|-----------------|
| tissue | | | | |
| Rash | 29 | 1 [†] | 7 | 0 |
| Pruritus | 14 | <1 [†] | 7 | 0 |
| Dry skin | 13 | <1 [†] | 5 | 0 |
| Metabolism and nutrition | | | | |
| Anorexia | 25 | 2 [†] | 14 | <1 [†] |
| Nervous system | | | | |
| Headache | 19 | 1 | 9 | <1 [†] |
| Dysgeusia | 10 | 0 | 2 | 0 |
| Musculoskeletal and connective tissue | | | | |
| Pain in extremity | 10 | 1 [†] | 7 | 0 |

Grading according to NCI CTCAE Version 3.0.

* Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

† No Grade 4 adverse reactions were reported.

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

§ Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with everolimus tablets 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 Everolimus Tablets Arm than the Placebo Arm in RECORD-1

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

Grading according to NCI CTCAE Version 3.0.

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

† 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 everolimus tablets 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 everolimus tablets.

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

Adverse reactions reported with an incidence of \geq 10% for patients receiving everolimus tablets and occurring more frequently with everolimus tablets than with placebo are

presented in Table 14. Laboratory abnormalities are presented in Table 15.

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

| | Everolimus Tablets N = 79 | | Placebo N = 39 | |
|--|------------------------------|----------------|-------------------|----------------|
| | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| Gastrointestinal | | | | |
| Stomatitis* | 78 | 6† | 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.

* Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.

† No Grade 4 adverse reactions were reported.

Amenorrhea occurred in 15% of everolimus tablets-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 everolimus tablets-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 Everolimus Tablets-Treated Patients With TSC-Associated Renal Angiomyolipoma in EXIST-2

| | Everolimus Tablets | Placebo |
|--|--------------------|---------|
|--|--------------------|---------|

| | N = 79 | | 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* | 8 | 0 |
| Thrombocytopenia | 19 | 0 | 3 | 0 |
| Chemistry | | | | |
| Hypercholesterolemia | 85 | 1* | 46 | 0 |
| Hypertriglyceridemia | 52 | 0 | 10 | 0 |
| Hypophosphatemia | 49 | 5* | 15 | 0 |
| Increased alkaline phosphatase | 32 | 1* | 10 | 0 |
| Increased AST | 23 | 1* | 8 | 0 |
| Increased ALT | 20 | 1* | 15 | 0 |
| Hyperglycemia (fasting) | 14 | 0 | 8 | 0 |

Grading according to NCI CTCAE Version 3.0.

* No Grade 4 laboratory abnormalities were reported.

Updated safety information from 112 patients treated with everolimus tablets 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 everolimus tablets 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 everolimus tablets.

The most common adverse reactions reported for everolimus tablets (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 everolimus tablets-treated patients. The most common adverse reaction leading to everolimus tablets dose adjustment was stomatitis.

Adverse reactions reported with an incidence of \geq 10% for patients receiving everolimus

tablets and occurring more frequently with everolimus tablets than with placebo are reported in Table 16. Laboratory abnormalities are presented in Table 17.

Table 16: Adverse Reactions Reported in $\geq 10\%$ of Everolimus Tablets-Treated Patients With TSC-Associated SEGA in EXIST-1

| | Everolimus Tablets N = 78 | | Placebo N = 39 | |
|--|------------------------------|----------------|-------------------|----------------|
| | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| Gastrointestinal | | | | |
| Stomatitis* | 62 | 9 [†] | 26 | 3 [†] |
| Vomiting | 22 | 1 [†] | 13 | 0 |
| Diarrhea | 17 | 0 | 5 | 0 |
| Constipation | 10 | 0 | 3 | 0 |
| Infections | | | | |
| Respiratory tract infection [‡] | 31 | 3 | 23 | 0 |
| Gastroenteritis [§] | 10 | 5 | 3 | 0 |
| Pharyngitis streptococcal | 10 | 0 | 3 | 0 |
| General | | | | |
| Pyrexia | 23 | 6 [†] | 18 | 3 [†] |
| Fatigue | 14 | 0 | 3 | 0 |
| Psychiatric | | | | |
| Anxiety, aggression or other behavioral disturbance [¶] | 21 | 5 [†] | 3 | 0 |
| Skin and subcutaneous tissue | | | | |
| Rash [#] | 21 | 0 | 8 | 0 |
| Acne | 10 | 0 | 5 | 0 |

Grading according to NCI CTCAE Version 3.0.

* Includes mouth ulceration, stomatitis, and lip ulceration.

† No Grade 4 adverse reactions were reported.

‡ Includes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral.

§ Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection.

¶ Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

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

Amenorrhea occurred in 17% of everolimus tablets-treated females aged 10 to 55 years (3 of 18). For this same group of everolimus tablets-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 everolimus tablets-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 Everolimus Tablets-Treated Patients With TSC-Associated SEGA in EXIST-1

| | Everolimus Tablets N = 78 | | Placebo N = 39 | |
|--------------------------------------|------------------------------|----------------|-------------------|----------------|
| | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| Hematology | | | | |
| Elevated partial thromboplastin time | 72 | 3* | 44 | 5* |
| Neutropenia | 46 | 9* | 41 | 3* |
| 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* | 3 | 0 |

Grading according to NCI CTCAE Version 3.0.

* No Grade 4 laboratory abnormalities were reported.

Updated safety information from 111 patients treated with everolimus tablets 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 everolimus tablets for oral suspension low trough (LT) (n = 117), everolimus tablets for oral suspension 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 everolimus tablets for oral suspension 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 $\geq 1\%$) 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 $\geq 3\%$) leading to dose adjustments in the everolimus tablets for oral suspension arms were stomatitis, pneumonia, and pyrexia.

Adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving everolimus tablets for oral suspension are presented in Table 18. Laboratory abnormalities are presented in Table 19.

Table 18: Adverse Reactions Reported in $\geq 10\%$ of Everolimus Tablets For Oral Suspension -Treated Patients With TSC-Associated Partial-Onset Seizures in EXIST-3

| | Everolimus tablets for oral suspension | | | | 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* | 55 | 3 [†] | 64 | 4 [†] | 9 | 0 |
| Diarrhea | 17 | 0 | 22 | 0 | 5 | 0 |
| Vomiting | 12 | 0 | 10 | 2 [†] | 9 | 0 |
| Infections | | | | | | |
| Nasopharyngitis | 14 | 0 | 16 | 0 | 16 | 0 |
| Upper respiratory tract infection | 13 | 0 | 15 | 0 | 13 | 0.8 [†] |
| General | | | | | | |
| Pyrexia | 20 | 0 | 14 | 0.8 [†] | 5 | 0 |
| Respiratory, thoracic and mediastinal | | | | | | |
| Cough | 11 | 0 | 10 | 0 | 3 | 0 |
| Skin and subcutaneous tissue | | | | | | |
| Rash | 6 | 0 | 10 | 0 | 3 | 0 |

Grading according to NCI CTCAE Version 4.03.

* Includes stomatitis, mouth ulceration, aphthous ulcer, lip ulceration, tongue ulceration, mucosal inflammation, gingival pain.

† No Grade 4 adverse reactions were reported.

The following additional adverse reactions occurred in $< 10\%$ of everolimus tablets for

oral suspension treated patients (% everolimus tablets for oral suspension LT, % everolimus tablets for oral suspension 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 $\geq 10\%$ Everolimus Tablets For Oral Suspension -Treated Patients With TSC-Associated Partial-Onset Seizures

| | Everolimus tablets for oral suspension | | | | Placebo | |
|--------------------------------|--|-------------|----------------------|-------------|--------------|-------------|
| | Target of 3-7 ng/mL | | Target of 9-15 ng/mL | | | |
| | N = 117 | | N = 130 | | N = 119 | |
| | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % | All Grades % | Grade 3-4 % |
| Hematology | | | | | | |
| Neutropenia | 25 | 4* | 37 | 6 | 23 | 7* |
| Anemia | 27 | 0.9* | 30 | 0 | 21 | 0.8* |
| Thrombocytopenia | 12 | 0 | 15 | 0 | 6 | 0 |
| Chemistry | | | | | | |
| Hypercholesterolemia | 86 | 0 | 85 | 0.8* | 58 | 0 |
| Hypertriglyceridemia | 43 | 2* | 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* | 16 | 2 | 3 | 0 |

Grading according to NCI CTCAE version 4.03.

* No Grade 4 laboratory abnormalities were reported.

Updated safety information from 357 patients treated with everolimus tablets for oral suspension 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 postapproval use of everolimus tablets/everolimus tablets for oral suspension. 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, lymphedema
- *Injury, poisoning and procedural complications*: Radiation Sensitization and Radiation Recall

7. DRUG INTERACTIONS

7.1 Effect of Other Drugs on Everolimus Tablets/Everolimus Tablets for Oral Suspension

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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension may be at increased risk for angioedema. Avoid the concomitant use of ACE inhibitors with everolimus tablets/everolimus tablets for oral suspension [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)*], everolimus tablets/everolimus tablets for oral suspension can cause fetal harm when administered to a pregnant woman. There are limited case reports of everolimus tablets 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension [see *Use in Specific Populations (8.1)*].

Contraception

Everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension. Based on these findings, everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets. In male rats, sperm motility, sperm count, plasma testosterone levels and fertility were diminished at AUC similar to those of the clinical dose of everolimus tablets 10 mg orally once daily. Based on these findings, everolimus tablets/everolimus tablets for oral suspension may impair fertility in male patients [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

TSC-Associated SEGA

The safety and effectiveness of everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets-treated patients < 6 years had at least one infection compared to 67% of 55 everolimus tablets-treated patients ≥ 6 years. Thirty-five percent of 23 everolimus tablets-treated patients < 6 years of age had at least 1 serious infection compared to 7% of 55 everolimus tablets-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, everolimus tablets did not appear to adversely impact growth and pubertal development in the 115 pediatric patients treated with everolimus tablets for a median duration of 4.1 years.

TSC-Associated Partial-Onset Seizures

The safety and effectiveness of everolimus tablets for oral suspension has been established for the adjunctive treatment of pediatric patients aged 2 years and older with

TSC-associated partial-onset seizures. Use of everolimus tablets for oral suspension 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 everolimus tablets for oral suspension and everolimus tablets 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 everolimus tablets for oral suspension-treated patients < 6 years had at least one infection, compared to 53% of 177 everolimus tablets for oral suspension-treated patients ≥ 6 years. Sixteen percent of 70 everolimus tablets for oral suspension-treated patients < 6 years of age had at least 1 serious infection, compared to 4% of 177 everolimus tablets for oral suspension-treated patients ≥ 6 years of age. Two fatal cases due to infections were reported in pediatric patients.

Other Indications

The safety and effectiveness of everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets were ≥ 65 years of age, while 7% were ≥ 75 years of age. In RADIANT-3, 30% of patients with PNET treated with everolimus tablets 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

Everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets 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

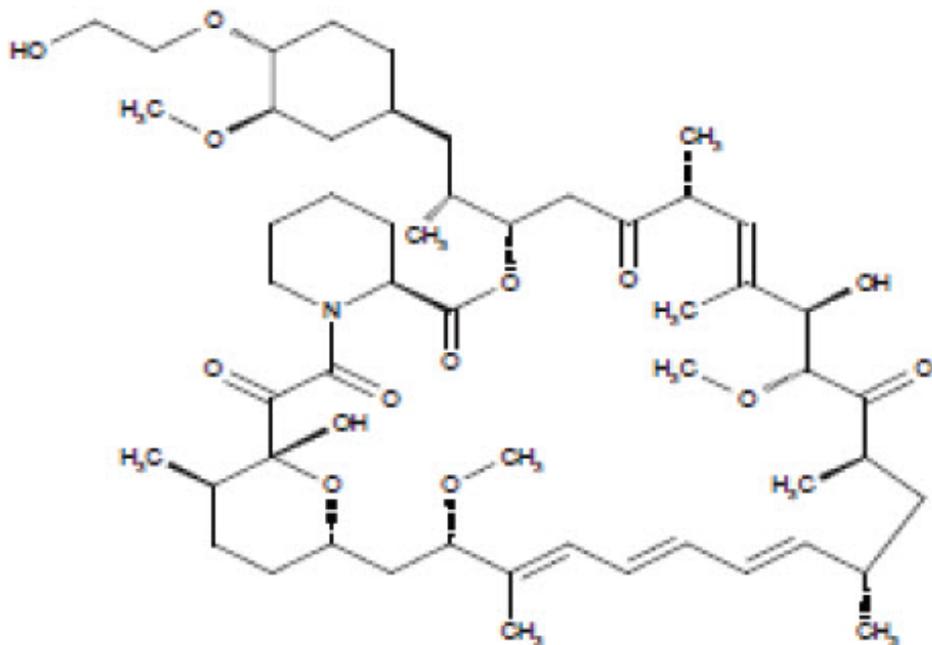
everolimus tablets/everolimus tablets for oral suspension as recommended and adjust the dose based on everolimus trough concentrations [see *Dosage and Administration* (2.8, 2.10)].

11. DESCRIPTION

Everolimus Tablets and 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-azatricyclo[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:



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

Everolimus tablets for oral suspension 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, anhydrous lactose, 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 everolimus tablets (20 mg and 50 mg) and placebo. Everolimus tablets at single doses up to 50 mg did not prolong the QT/QTc interval.

12.3 Pharmacokinetics

Absorption

After administration of everolimus tablets 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 everolimus tablets 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 everolimus tablets for oral suspension, 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 everolimus tablets for oral suspension and everolimus tablets; the C_{max} of everolimus in the everolimus tablets for oral suspension dosage form was 20% to 36% lower than that of everolimus tablets. The predicted trough concentrations at steady-state were similar after daily administration.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus tablets 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/m^2 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 everolimus tablets were 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 everolimus tablets with rifampin, a P-gp and strong inducer of CYP3A4, decreased everolimus AUC by 63% and C_{\max} by 58% compared to everolimus tablets alone [see *Dosage and Administration (2.12)*].

Effect of Everolimus on CYP3A4 Substrates: No clinically significant pharmacokinetic interactions were observed between everolimus tablets 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 everolimus tablets resulted in a 25% increase in midazolam C_{\max} and a 30% increase in midazolam $\text{AUC}_{0-\text{inf}}$.

The coadministration of everolimus tablets with exemestane increased exemestane C_{\min} by 45% and $C_{2\text{h}}$ 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets 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, everolimus tablets/everolimus tablets for oral suspension 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 everolimus tablets 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 everolimus tablets 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 \geq 0.1 mg/kg (approximately 4% the human exposure based on AUC at the recommended dose of everolimus tablets 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 everolimus tablets 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 \geq 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets 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 everolimus tablets 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 | Everolimus Tablets 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* (0.38, 0.54) | < 0.0001 [†] |
| Independent radiological review | 11.0 (9.7, 15.0) | 4.1 (2.9, 5.6) | 0.38* (0.3, 0.5) | < 0.0001 [†] |
| Best overall response (% , 95% CI) | | | | |

| | | | |
|--|----------------------|--------------------|------------------|
| Objective response rate (ORR) [‡] | 12.6% (9.8, 15.9) | 1.7% (0.5, 4.2) | n/a [§] |
|--|----------------------|--------------------|------------------|

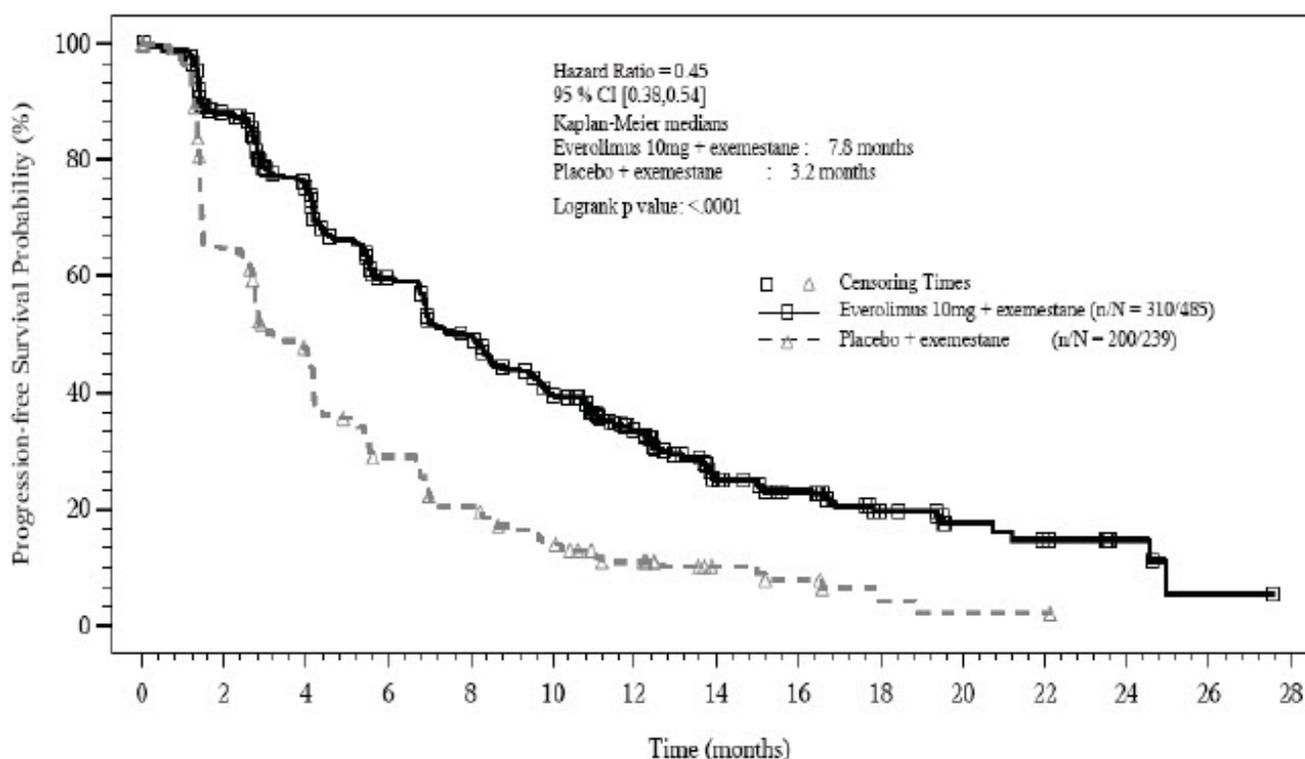
* Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis.

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

‡ Objective response rate = proportion of patients with CR or PR.

§ Not applicable.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival by Investigator Radiological Review in Hormone Receptor-Positive, HER-2 Negative Breast Cancer in BOLERO-2



14.2 Neuroendocrine Tumors (NET)

Pancreatic Neuroendocrine Tumors (PNET)

A randomized, double-blind, multi-center trial (RADIANT-3, NCT00510068) of everolimus tablets in combination with best supportive care (BSC) compared to placebo in combination with BSC was conducted in patients with locally advanced or metastatic advanced PNET and disease progression within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes vs. no) and WHO performance status (0 vs. 1 and 2). Treatment with somatostatin analogs was allowed as part of BSC. The major efficacy outcome was PFS evaluated by RECIST. After documented radiological progression, patients randomized to placebo could receive open-label everolimus tablets. Other outcome measures included ORR, response duration, and OS.

Patients were randomized 1:1 to receive either everolimus tablets 10 mg once daily (n = 207) or placebo (n = 203). Demographics were well balanced (median age 58 years, 55% male, 79% White). Of the 203 patients randomized to BSC, 172 patients (85%) received

everolimus tablets following documented radiologic progression.

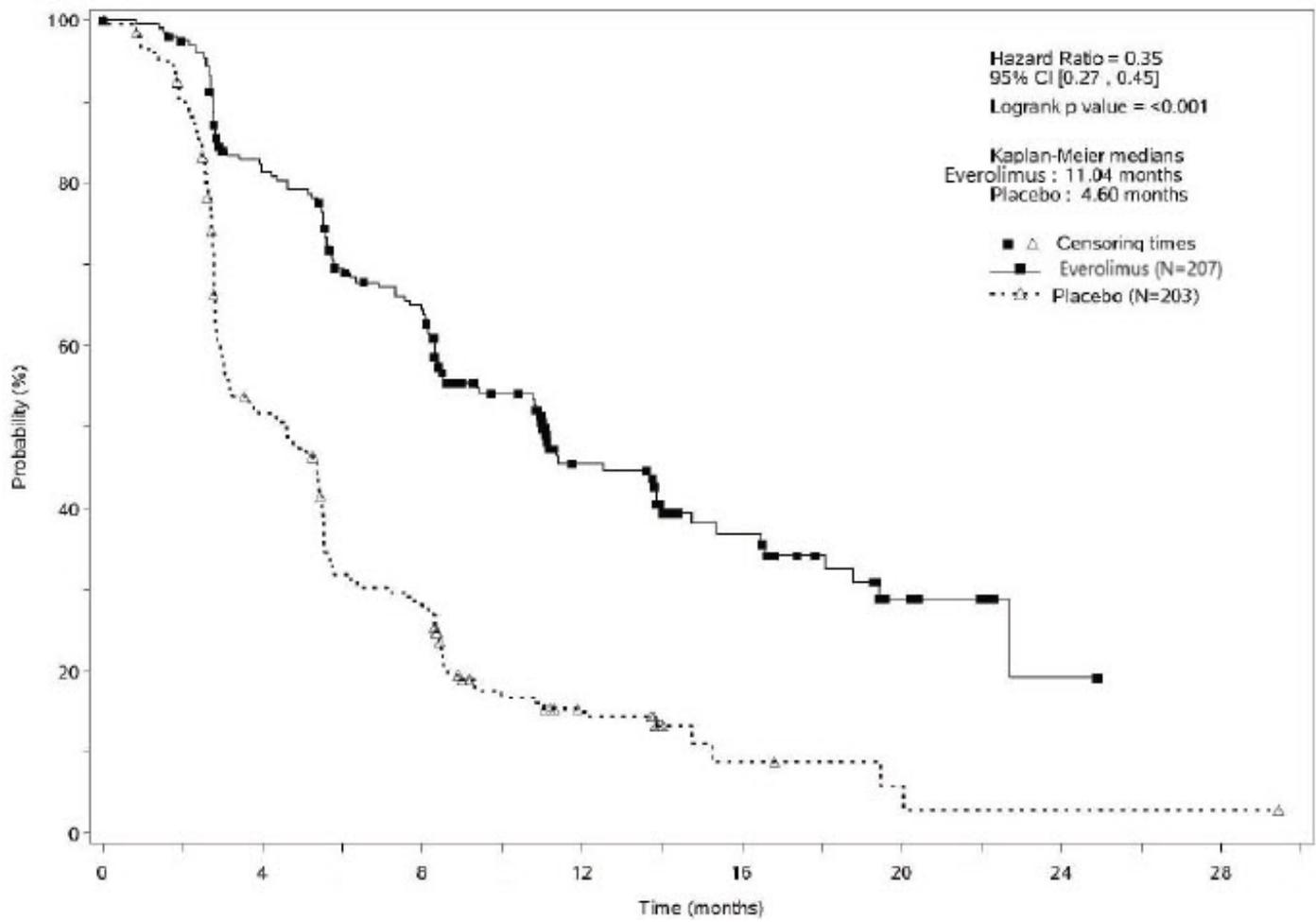
The trial demonstrated a statistically significant improvement in PFS (Table 21 and Figure 2). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analog use. The PFS results by investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 21.

Table 21: Progression-Free Survival Results in PNET in RADIANT-3

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

* Includes adjudication for discrepant assessments between investigator radiological review and central radiological review.

Figure 2: Kaplan-Meier Curves for Progression-Free Survival by Investigator Radiological Review in PNET in RADIANT-3



Investigator-determined response rate was 4.8% in the everolimus tablets arm and there were no complete responses. Overall Survival (OS) was not statistically significantly different between arms [HR = 0.94 (95% CI 0.73, 1.20); p = 0.30].

NET of Gastrointestinal (GI) or Lung Origin

A randomized, double-blind, multicenter study (RADIANT-4, NCT01524783) of everolimus tablets in combination with BSC compared to placebo in combination with BSC was conducted in patients with unresectable, locally advanced or metastatic, well differentiated, non-functional NET of GI (excluding pancreatic) or lung origin. The study required that patients had well-differentiated (low or intermediate grade) histology, no prior or current history of carcinoid symptoms, and evidence of disease progression within 6 months prior to randomization. Patients were randomized 2:1 to receive either everolimus tablets 10 mg once daily or placebo, and stratified by prior somatostatin analog use (yes vs. no), tumor origin and WHO performance status (0 vs. 1). The major efficacy outcome measure was PFS based on independent radiological assessment evaluated by RECIST. Additional efficacy outcome measures were OS and ORR.

A total of 302 patients were randomized, 205 to the everolimus tablets arm and 97 to the placebo arm. The median age was 63 years (22 to 86 years); 47% were male; 76% were White; 74% had WHO performance status of 0 and 26% had WHO performance status of 1. The most common primary sites of tumor were lung (30%), ileum (24%), and rectum (13%).

The study demonstrated a statistically significant improvement in PFS per independent

radiological review (Table 22 and Figure 3). The final OS analysis did not show a statistically significant difference between those patients who received everolimus tablets or placebo (HR = 0.90 [95% CI: 0.66, 1.24]).

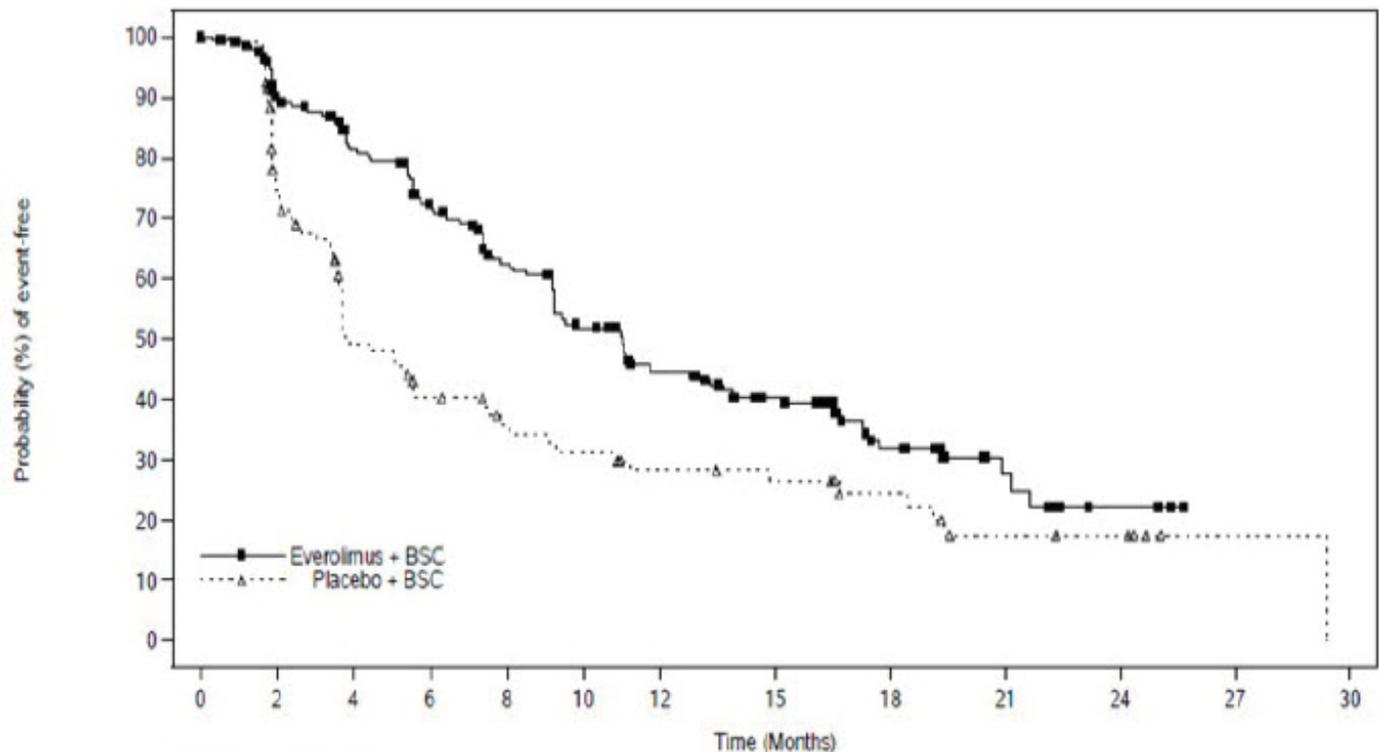
Table 22: Progression-Free Survival in Neuroendocrine Tumors of Gastrointestinal or Lung Origin in RADIANT-4

| | Everolimus Tablets N = 205 | Placebo N = 97 |
|----------------------------------|---------------------------------------|---------------------------|
| Progression-Free Survival | | |
| Number of Events | 113 (55%) | 65 (67%) |
| Progressive Disease | 104 (51%) | 60 (62%) |
| Death | 9 (4%) | 5 (5%) |
| Median PFS in months (95% CI) | 11.0 (9.2, 13.3) | 3.9 (3.6, 7.4) |
| Hazard Ratio (95% CI)* | 0.48 (0.35, 0.67) | |
| p-value† | < 0.001 | |
| Overall Response Rate | 2% | 1% |

* Hazard ratio is obtained from the stratified Cox model.

† p-value is obtained from the stratified log-rank test.

Figure 3: Kaplan-Meier Curves for Progression-Free Survival in NET of GI or Lung Origin in RADIANT-4



| | No. of patients still at risk | | | | | | | | | | | | |
|------------------|-------------------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|
| Time (Months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 15 | 18 | 21 | 24 | 27 | 30 |
| Everolimus + BSC | 205 | 168 | 145 | 124 | 101 | 81 | 65 | 52 | 26 | 10 | 3 | 0 | 0 |
| Placebo + BSC | 97 | 65 | 39 | 30 | 24 | 21 | 17 | 15 | 11 | 6 | 5 | 1 | 0 |

Lack of Efficacy in Locally Advanced or Metastatic Functional Carcinoid Tumors

The safety and effectiveness of everolimus tablets in patients with locally advanced or metastatic functional carcinoid tumors have not been demonstrated. In a randomized (1:1), double-blind, multi-center trial (RADIANT-2, NCT00412061) in 429 patients with carcinoid tumors, everolimus tablets in combination with long-acting octreotide (Sandostatin LAR[®]) was compared to placebo in combination with long-acting octreotide. After documented radiological progression, patients on the placebo arm could receive everolimus tablets; of those randomized to placebo, 67% received open-label everolimus tablets in combination with long-acting octreotide. The study did not meet its major efficacy outcome measure of a statistically significant improvement in PFS and the final analysis of OS favored the placebo in combination with long-acting octreotide arm.

14.3 Renal Cell Carcinoma (RCC)

An international, multi-center, randomized, double-blind trial (RECORD-1, NCT00410124) comparing everolimus tablets 10 mg once daily and placebo, both in conjunction with BSC, was conducted in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon- α was also permitted. Randomization was stratified according to prognostic score and prior anticancer therapy. The major efficacy outcome measure for the trial was PFS evaluated by RECIST, based on a blinded, independent, central radiologic review. After documented radiological progression, patients randomized to placebo could receive open-label everolimus tablets. Other outcome measures included OS.

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

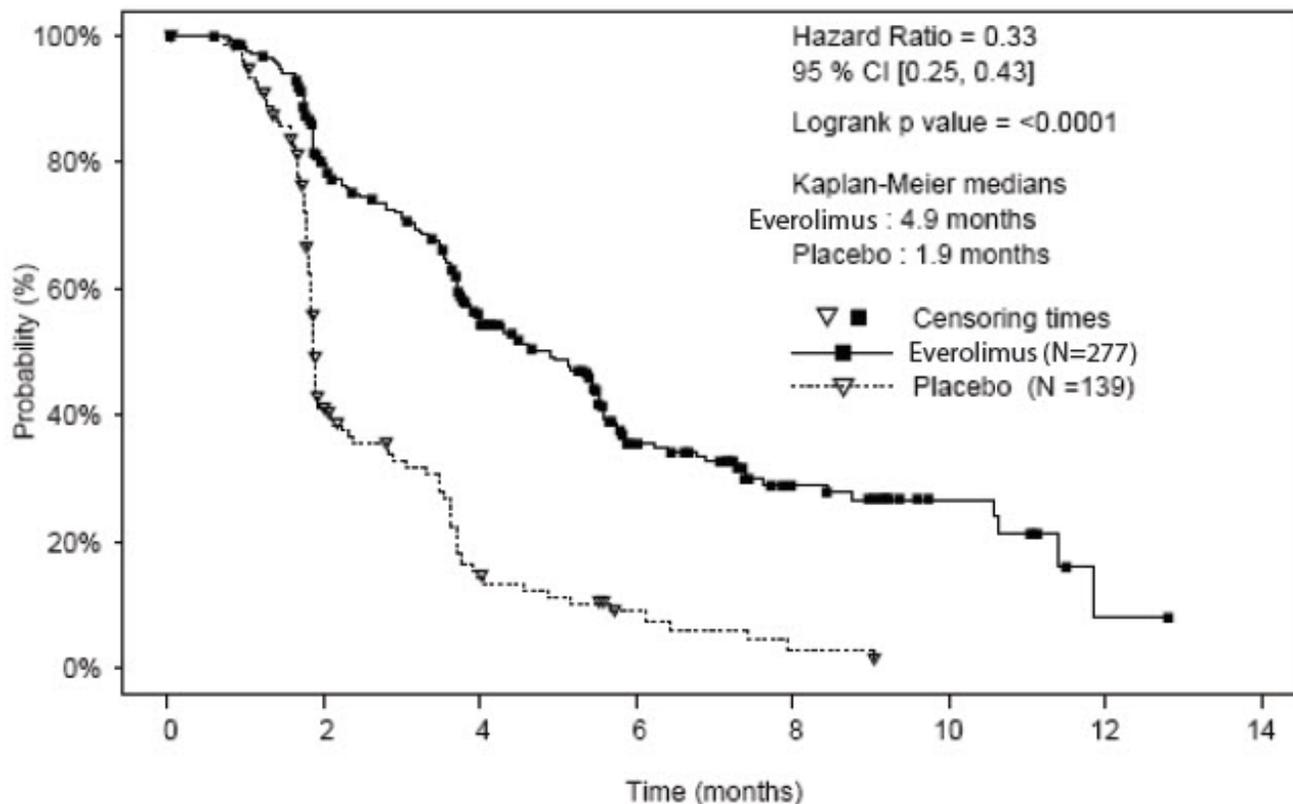
Everolimus tablets were superior to placebo for PFS (Table 23 and Figure 4). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. Final OS results yield a hazard ratio of 0.90 (95% CI: 0.71, 1.14), with no statistically significant difference between the arms. Planned cross-over from placebo due to disease progression to open-label everolimus tablets occurred in 80% of the 139 patients and may have confounded the OS benefit.

Table 23: Progression-Free Survival and Objective Response Rate by Central Radiologic Review in RCC in RECORD-1

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

* Log-rank test stratified by prognostic score.
† Not applicable.

Figure 4: Kaplan-Meier Curves for Progression-Free Survival in RCC in RECORD-1



14.4 Tuberos Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-2, NCT00790400) of everolimus tablets was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n = 113) or sporadic lymphangiomyomatosis (n = 5). The key eligibility requirements for this trial were at least one angiomyolipoma of ≥ 3 cm in longest diameter on CT/MRI based on local radiology assessment, no immediate indication for surgery, and age ≥ 18 years. Patients received everolimus tablets 10 mg or matching placebo orally once daily until disease progression or unacceptable toxicity. CT or MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks and annually thereafter. Clinical and photographic assessment of skin lesions were conducted at baseline and every 12 weeks thereafter until treatment discontinuation. The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review, which was defined as a $\geq 50\%$ reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of kidney volume increase $\geq 20\%$, and no angiomyolipoma related bleeding of \geq Grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. The primary analyses of efficacy outcome measures were limited to the blinded treatment period and conducted 6 months after the last patient was randomized. The comparative angiomyolipoma response rate analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at

randomization (yes vs. no).

Of the 118 patients enrolled, 79 were randomized to everolimus tablets and 39 to placebo. The median age was 31 years (18 to 61 years), 34% were male, and 89% were White. At baseline, 17% of patients were receiving EIAEDs. On central radiology review at baseline, 92% of patients had at least 1 angiomyolipoma of ≥ 3 cm in longest diameter, 29% had angiomyolipomas ≥ 8 cm, 78% had bilateral angiomyolipomas, and 97% had skin lesions. The median values for the sum of all target renal angiomyolipoma lesions at baseline were 85 cm³ (9 to 1612 cm³) and 120 cm³ (3 to 4520 cm³) in the everolimus tablets and placebo arms, respectively. Forty-six (39%) patients had prior renal embolization or nephrectomy. The median duration of follow-up was 8.3 months (0.7 to 24.8 months) at the time of the primary analysis.

The renal angiomyolipoma response rate was statistically significantly higher in everolimus tablets-treated patients (Table 24). The median response duration was 5.3+ months (2.3+ to 19.6+ months).

There were 3 patients in the everolimus tablets arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review (defined as a $\geq 25\%$ increase from nadir in the sum of angiomyolipoma target lesion volumes to a value greater than baseline, appearance of a new angiomyolipoma ≥ 1 cm in longest diameter, an increase in renal volume $\geq 20\%$ from nadir for either kidney and to a value greater than baseline, or Grade ≥ 2 angiomyolipoma-related bleeding). The time to angiomyolipoma progression was statistically significantly longer in the everolimus tablets arm (HR 0.08 [95% CI: 0.02, 0.37]; $p < 0.0001$).

Table 24: Angiomyolipoma Response Rate in TSC-Associated Renal Angiomyolipoma in EXIST-2

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

* Per independent central radiology review.

Skin lesion response rates were assessed by local investigators for 77 patients in the everolimus tablets arm and 37 patients in the placebo arm who presented with skin lesions at study entry. The skin lesion response rate was statistically significantly higher in the everolimus tablets arm (26% vs. 0, $p = 0.0011$); all skin lesion responses were partial responses, defined as visual improvement in 50% to 99% of all skin lesions durable for at least 8 weeks (Physician's Global Assessment of Clinical Condition).

Patients randomized to placebo were permitted to receive everolimus tablets at the time of angiomyolipoma progression or after the time of the primary analysis. After the primary analysis, patients treated with everolimus tablets underwent additional follow-up CT or MRI scans to assess tumor status until discontinuation of treatment or completion of 4 years of follow-up after the last patient was randomized. A total of 112 patients (79 randomized to everolimus tablets and 33 randomized to placebo) received at least one

dose of everolimus tablets. The median duration of everolimus tablets treatment was 3.9 years (0.5 months to 5.3 years) and the median duration of follow-up was 3.9 years (0.9 months to 5.4 years). During the follow-up period after the primary analysis, 32 patients (in addition to the 33 patients identified at the time of the primary analysis) had an angiomyolipoma response based upon independent central radiology review. Among the 65 responders out of 112 patients, the median time to angiomyolipoma response was 2.9 months (2.6 to 33.8 months). Fourteen percent of the 112 patients treated with everolimus tablets had angiomyolipoma progression by the end of the follow-up period. No patient underwent a nephrectomy for angiomyolipoma progression and one patient underwent renal embolization while treated with everolimus tablets.

14.5 Tuberos Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA)

EXIST-1

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-1, NCT00789828) of everolimus tablets was conducted in 117 pediatric and adult patients with SEGA and TSC. Eligible patients had at least one SEGA lesion ≥ 1 cm in longest diameter on MRI based on local radiology assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received everolimus tablets at a starting dose of 4.5 mg/m² daily, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL as tolerated. Everolimus tablets or matched placebo continued until disease progression or unacceptable toxicity. MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter.

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

Of the 117 patients enrolled, 78 were randomized to everolimus tablets and 39 to placebo. The median age was 9.5 years (0.8 to 26 years); a total of 20 patients were < 3 years, 54 patients were 3 to < 12 years, 27 patients were 12 to < 18 years, and 16 patients were ≥ 18 years; 57% were male, and 93% were White. At baseline, 18% of patients were receiving EIAEDs. Based on central radiology review at baseline, 98% of patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter, 79% had bilateral SEGAs, 43% had ≥ 2 target SEGA lesions, 26% had growth in or into the inferior surface of the ventricle, 9% had evidence of growth beyond the subependymal tissue adjacent to the ventricle, and 7% had radiographic evidence of hydrocephalus. The median values for the sum of all target SEGA lesions at baseline were 1.63 cm³ (0.18 to 25.15 cm³) and 1.30 cm³ (0.32 to 9.75 cm³) in the everolimus tablets and placebo arms, respectively. Eight (7%) patients had prior SEGA-related surgery. The median duration of follow-up was 8.4 months (4.6 to 17.2 months) at the time of primary analysis.

The SEGA response rate was statistically significantly higher in everolimus tablets-treated

patients (Table 25). At the time of the primary analysis, all SEGA responses were ongoing and the median duration of response was 5.3 months (2.1 to 8.4 months).

With a median follow-up of 8.4 months, SEGA progression was detected in 15.4% of the 39 patients randomized to receive placebo and none of the 78 patients randomized to receive everolimus tablets. No patient in either treatment arm required surgical intervention.

Table 25: Subependymal Giant Cell Astrocytoma Response Rate in TSC-Associated SEGA in EXIST-1

| | Everolimus Tablets N=78 | Placebo N=39 | p-value |
|---|--|-------------------------|------------------------|
| Primary analysis SEGA response rate* - (%) | 35 | 0 | < 0.0001 |
| 95% CI | 24, 46 | 0, 9 | |

* Per independent central radiology review.

Patients randomized to placebo were permitted to receive everolimus tablets at the time of SEGA progression or after the primary analysis, whichever occurred first. After the primary analysis, patients treated with everolimus tablets underwent additional follow-up MRI scans to assess tumor status until discontinuation of treatment or completion of 4 years of follow-up after the last patient was randomized. A total of 111 patients (78 patients randomized to everolimus tablets and 33 patients randomized to placebo) received at least one dose of everolimus tablets. Median duration of everolimus tablets treatment and follow-up was 3.9 years (0.2 to 4.9 years).

By four years after the last patient was enrolled, 58% of the 111 patients treated with everolimus tablets had a $\geq 50\%$ reduction in SEGA volume relative to baseline, including 27 patients identified at the time of the primary analysis and 37 patients with a SEGA response after the primary analysis. The median time to SEGA response was 5.3 months (2.5 to 33.1 months). Twelve percent of the 111 patients treated with everolimus tablets had documented disease progression by the end of the follow-up period and no patient required surgical intervention for SEGA during the study.

Study 2485

Study 2485 (NCT00411619) was an open-label, single-arm trial conducted to evaluate the antitumor activity of everolimus tablets 3 mg/m²/orally once daily in patients with SEGA and TSC. Serial radiological evidence of SEGA growth was required for entry. Tumor assessments were performed every 6 months for 60 months after the last patient was enrolled or disease progression, whichever occurred earlier. The major efficacy outcome measure was the reduction in volume of the largest SEGA lesion with 6 months of treatment, as assessed via independent central radiology review. Progression was defined as an increase in volume of the largest SEGA lesion over baseline that was $\geq 25\%$ over the nadir observed on study.

A total of 28 patients received everolimus tablets for a median duration of 5.7 years (5 months to 6.9 years); 82% of the 28 patients remained on everolimus tablets for at least 5 years. The median age was 11 years (3 to 34 years), 61% male, 86% White.

At the primary analysis, 32% of the 28 patients (95% CI: 16%, 52%) had an objective response at 6 months, defined as at least a 50% decrease in volume of the largest SEGA lesion. At the completion of the study, the median duration of durable response was 12 months (3 months to 6.3 years).

By 60 months after the last patient was enrolled, 11% of the 28 patients had documented disease progression. No patient developed a new SEGA lesion while on everolimus tablets. Nine additional patients were identified as having a $\geq 50\%$ volumetric reduction in their largest SEGA lesion between 1 to 4 years after initiating everolimus tablets, including 3 patients who had surgical resection with subsequent regrowth prior to receiving everolimus tablets.

14.6 Tuberos Sclerosis Complex (TSC)-Associated Partial-Onset Seizures

The efficacy of everolimus tablets for oral suspension as an adjunctive anti-epileptic drug (AED) was evaluated in a randomized, double-blind, multicenter, placebo-controlled study conducted in patients with TSC-associated partial-onset seizures (EXIST-3, NCT01713946). Patients with a history of inadequate control of partial-onset seizures despite treatment with ≥ 2 sequential AED regimens were randomized to receive placebo or everolimus tablets for oral suspension once daily at a dose to achieve a low trough (LT) level (3-7 ng/mL) or a high trough (HT) level (9-15 ng/mL). Randomization was stratified by age group (1 to <6, 6 to < 12, 12 to <18, ≥ 18 years). The study consisted of 3 phases: an 8-week Baseline observation phase; an 18-week double-blind, placebo-controlled Core phase (6-week titration period and a 12-week maintenance period), and an Extension phase of ≥ 48 weeks. Patients were required to have a diagnosis of TSC per the modified Gomez criteria, and ≥ 16 partial-onset seizures during the Baseline phase while receiving a stable dose of 1 to 3 concomitant AEDs. The starting doses for everolimus tablets for oral suspension in the Core phase ranged from 3 to 6 mg/m² orally once daily, depending on age, in patients not receiving concomitant CYP3A4/P-gp inducers and from 5 to 9 mg/m² orally once daily, depending on age, in patients receiving concomitant CYP3A4/P-gp inducers. During the 6-week titration period, everolimus trough levels were assessed every 2 weeks and up to 3 dose adjustments were allowed to attempt to reach the targeted everolimus trough concentration range.

The major efficacy outcome measure was the percentage reduction in seizure frequency from the Baseline phase, during the maintenance period of the Core phase. Additional efficacy outcome measures included response rate, defined as at least a 50% reduction in seizure frequency from the Baseline phase during the maintenance period of the Core phase, and seizure freedom rate during the maintenance period of the Core phase.

A total of 366 patients were randomized to everolimus tablets for oral suspension LT (n = 117), everolimus tablets for oral suspension HT (n = 130) or placebo (n = 119). Median age was 10.1 years (2.2 to 56 years); 28% of patients were < 6 years, 31% were 6 to < 12 years, 22% were 12 to < 18 years, and 18% were ≥ 18 years). The majority were white (65%) and male (52%). The most common major features of TSC were cortical tubers (92%), hypomelanotic macules (84%), and subependymal nodules (83%). While 17% of the patients had SEGA, 42% had renal angiomyolipoma, and 9% had both SEGA and renal angiomyolipoma; no patients were receiving treatment with everolimus tablets or everolimus tablets for oral suspension for these manifestations of TSC. During the Baseline phase, 65% of patients had complex partial seizures, 52% had secondarily generalized seizures, 19% had simple partial seizures, and 2% had

generalized onset seizures. The median seizure frequency per week during the Baseline phase was 9.4 for all patients and 47% of patients were receiving 3 AEDs during the Baseline phase. The efficacy results are summarized in Table 26.

Table 26: Percentage Reduction in Seizure Frequency and Response Rate in TSC-Associated Partial-Onset Seizures in EXIST-3

| | Everolimus tablets for oral suspension | | Placebo N=119 |
|--|--|----------------------------------|-------------------|
| | Target of 3-7 ng/mL N=117 | Target of 9-15 ng/mL N=130 | |
| Seizures per week | | | |
| Median at Baseline (Min, Max) | 8.6 (1.4, 192.9) | 9.5 (0.3, 218.4) | 10.5 (1.3, 231.7) |
| Median at Core phase* (Min, Max) | 6.8 (0.0, 193.5) | 4.9 (0.0, 133.7) | 8.5 (0.0, 217.7) |
| Percentage reduction from Baseline to Core phase (Maintenance*) | | | |
| Median | 29.3 | 39.6 | 14.9 |
| 95% CI [†] | 18.8, 41.9 | 35.0, 48.7 | 0.1, 21.7 |
| p-value [‡] | 0.003 | < 0.001 | |
| Response rate | | | |
| Responders, n (%) | 28.2 | 40 | 15.1 |
| 95% CI [§] | 20.3, 37.3 | 31.5, 49.0 | 9.2, 22.8 |

* If patient discontinued before starting the Maintenance period, then the Titration period is used.

† 95% CI of the median based on bootstrap percentiles.

‡ p-values were for superiority vs. placebo, and obtained from rank ANCOVA with Baseline seizure frequency as covariate, stratified by age subgroup.

§ Exact 95% CI obtained using Clopper-Pearson method.

15. REFERENCES

1. OSHA Hazardous Drugs. *OSHA*.
<http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

16. HOW SUPPLIED/STORAGE AND HANDLING

Everolimus Tablets

2.5 mg tablets

White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and '2.5' on the other side; available in:

Bottles of 30 tablets NDC 51991-821-33

Blisters of 28 tablets NDC 51991-821-28

Each carton contains 4 blister cards of 7 tablets each

5 mg tablets

White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and '5' on the other side; available in:

Bottles of 30 tablets NDC 51991-822-33

Blisters of 28 tablets NDC 51991-822-28

Each carton contains 4 blister cards of 7 tablets each

7.5 mg tablets

White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and '7.5' on the other side; available in:

Bottles of 30 tablets NDC 51991-823-33

Blisters of 28 tablets NDC 51991-823-28

Each carton contains 4 blister cards of 7 tablets each

10 mg tablets

White to off-white coloured, oval, flat shaped tablets and no score, debossed with 'EVR' on one side and 'NAT' on the other side; available in:

Bottles of 30 tablets NDC 51991-824-33

Blisters of 28 tablets NDC 51991-824-28

Each carton contains 4 blister cards of 7 tablets each

Everolimus Tablets for Oral Suspension

2 mg tablets for oral suspension: White to off white colored, round, flat tablets, debossed with "2" on one side and "E" on other side; available in:

| | |
|------------------------|------------------|
| Blisters of 28 tablets | NDC 51991-990-28 |
| Bottles of 28 tablets | NDC 51991-990-77 |

Each carton contains 4 blister cards of 7 tablets each

3 mg tablets for oral suspension: White to off white colored, round, flat tablets, debossed with "3" on one side and "E" on other side; available in:

| | |
|------------------------|------------------|
| Blisters of 28 tablets | NDC 51991-991-28 |
| Bottles of 28 tablets | NDC 51991-991-77 |

Each carton contains 4 blister cards of 7 tablets each

5 mg tablets for oral suspension: White to off white colored, round, flat tablets, debossed with "5" on one side and "E" on other side; available in:

| | |
|------------------------|------------------|
| Blisters of 28 tablets | NDC 51991-992-28 |
| Bottles of 28 tablets | NDC 51991-992-77 |

Each carton contains 4 blister cards of 7 tablets each

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). See USP Controlled Room Temperature.

Store in the original container, protect from light and moisture.

Follow special handling and disposal procedures for anti-cancer pharmaceuticals.¹

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Non-infectious Pneumonitis

Advise patients of the risk of developing non-infectious pneumonitis and to immediately report any new or worsening respiratory symptoms to their healthcare provider [see *Warnings and Precautions (5.1)*].

Infections

Advise patients that they are more susceptible to infections and that they should

immediately report any signs or symptoms of infections to their healthcare provider [see *Warnings and Precautions (5.2)*].

Hypersensitivity Reactions

Advise patients of the risk of clinically significant hypersensitivity reactions and to promptly contact their healthcare provider or seek emergency care for signs of hypersensitivity reaction, including rash, itching, hives, difficulty breathing or swallowing, flushing, chest pain, or dizziness [see *Contraindications (4), Warnings and Precautions (5.3)*].

Angioedema with Concomitant Use of ACE Inhibitors

Advise patients to avoid ACE inhibitors and to promptly contact their healthcare provider or seek emergency care for signs or symptoms of angioedema [see *Warnings and Precautions (5.4)*].

Stomatitis

Advise patients of the risk of stomatitis and to use alcohol-free mouthwashes during treatment [see *Warnings and Precautions (5.5)*].

Renal Impairment

Advise patients of the risk of developing kidney failure and the need to monitor their kidney function periodically during treatment [see *Warnings and Precautions (5.6)*].

Risk of Impaired Wound Healing

Advise patients that everolimus tablets/everolimus tablets for oral suspension may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [see *Warnings and Precautions (5.7)*].

Geriatric Patients

Inform patients that in a study conducted in patients with breast cancer, the incidence of deaths and adverse reactions leading to permanent discontinuation was higher in patients ≥ 65 years compared to patients < 65 years [see *Warnings and Precautions (5.8), Use in Specific Populations (8.5)*].

Metabolic Disorders

Advise patients of the risk of metabolic disorders and the need to monitor glucose and lipids periodically during therapy [see *Warnings and Precautions (5.9)*].

Myelosuppression

Advise patients of the risk of myelosuppression and the need to monitor CBCs periodically during therapy [see *Warnings and Precautions (5.10)*].

Risk of Infection or Reduced Immune Response With Vaccination

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines [see *Warnings and Precautions (5.11)*].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 8 weeks after the last dose. Advise patients to inform their healthcare provider of a known

or suspected pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 weeks after the last dose [see *Warnings and Precautions (5.13), Use in Specific Populations (8.1, 8.3)*].

Radiation Sensitization and Radiation Recall

Radiation sensitization and recall can occur in patients treated with radiation prior to, during, or subsequent to everolimus tablets/everolimus tablets for oral suspension treatment. Advise patients to inform their healthcare provider if they have had or are planning to receive radiation therapy [see *Warnings and Precautions (5.12)*].

Lactation

Advise women not to breastfeed during treatment with everolimus tablets/everolimus tablets for oral suspension and for 2 weeks after the last dose [see *Use in Specific Populations (8.2)*].

Infertility

Advise males and females of reproductive potential of the potential risk for impaired fertility [see *Use in Specific Populations (8.3)*].

Manufactured by:

NATCO PHARMA LIMITED

Visakhapatnam - 531019

AP, India

Distributed by:

Breckenridge Pharmaceutical, Inc.

Berkeley Heights, NJ 07922

PATIENT INFORMATION

| EVEROLIMUS (E-ver-OH-li-mus) TABLETS | EVEROLIMUS (E-ver-OH-li-mus) TABLETS FOR ORAL SUSPENSION |
|--|---|
| Read this Patient Information leaflet that comes with everolimus tablets or everolimus tablets for oral suspension 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 everolimus tablets and everolimus tablets for oral suspension? Everolimus tablets and everolimus tablets for oral suspension 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: <ul style="list-style-type: none">• 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 everolimus tablets or everolimus tablets for oral suspension. Talk with your healthcare provider before taking everolimus tablets or everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension.

5. Mouth ulcers and sores. Mouth ulcers and sores are common during treatment with everolimus tablets or everolimus tablets for oral suspension but can also be severe. When you start treatment with everolimus tablets or everolimus tablets for oral suspension, 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 restart 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 everolimus tablets or everolimus tablets for oral suspension.

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

What are everolimus tablets?

Everolimus tablets are 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.

Everolimus tablets are 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 are everolimus tablets for oral suspension?

Everolimus tablets for oral suspension 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 everolimus tablets and everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension if you have had a severe allergic reaction to everolimus.

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

- a medicine that contains sirolimus
- a medicine that contains temsirolimus

Ask your healthcare provider if you do not know.

Before taking everolimus tablets or everolimus tablets for oral suspension, 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 everolimus tablets or everolimus tablets for oral suspension. 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 everolimus tablets or everolimus tablets for oral suspension.

- Are pregnant, can become pregnant, or have a partner who can become pregnant. Everolimus tablets or everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension.
- You should use effective birth control during treatment and for 8 weeks after your last dose of everolimus tablets or everolimus tablets for oral suspension.

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

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 everolimus passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of everolimus tablets or everolimus tablets for oral suspension.
- Are planning to have surgery or if you have had a recent surgery. You should stop taking everolimus tablets or everolimus tablets for oral suspension at least 1 week before planned surgery. See "**What are the possible side effects of everolimus tablets and everolimus tablets for oral suspension?**"
- Have received radiation therapy or are planning to receive radiation therapy in the future. See "**What are the possible side effects of everolimus tablets and everolimus tablets for oral suspension?**"

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

Everolimus tablets or everolimus tablets for oral suspension may affect the way other medicines work, and other medicines can affect how everolimus tablets or everolimus tablets for oral suspension tablets work. Taking everolimus tablets or everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension may need to be changed. You should also tell your healthcare provider before you start taking any new medicine.

How should I take everolimus tablets or everolimus tablets for oral suspension?

- Your healthcare provider will prescribe the dose of everolimus tablets or everolimus tablets for oral suspension that is right for you.
- Take everolimus tablets or everolimus tablets for oral suspension exactly as your healthcare provider tells you to.
- Your healthcare provider may change your dose of everolimus tablets or everolimus tablets for oral suspension or tell you to temporarily interrupt dosing, if needed.
- **Take only everolimus tablets or everolimus tablets for oral suspension. Do not mix everolimus tablets and everolimus tablets for oral suspension together.**
- See instructions at the end of this patient information sheet to open blister pack.
- Take everolimus tablets or everolimus tablets for oral suspension 1 time each day at about the same time.
- Take everolimus tablets or everolimus tablets for oral suspension the same way each time, either with food or without food.
- If you take too much everolimus tablets or everolimus tablets for oral suspension, contact your healthcare provider or go to the nearest hospital emergency room right away. Take the pack of everolimus tablets or everolimus tablets for oral suspension with you.
- If you miss a dose of everolimus tablets or everolimus tablets for oral suspension, 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 everolimus tablets or everolimus tablets for oral suspension, skip the dose for that day. The next day, take everolimus tablets or everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension to treat SEGA or everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension you need to take.

EVEROLIMUS TABLETS:

- Swallow everolimus tablets whole with a glass of water. Do not take any tablet that is

broken or crushed.

EVEROLIMUS TABLETS FOR ORAL SUSPENSION:

- If your healthcare provider prescribes everolimus tablets for oral suspension 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 everolimus tablets for oral suspension must be prepared as a suspension before it is given.
- Everolimus tablets for oral suspension 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 everolimus tablets for oral suspension for another person.

What should I avoid while taking everolimus tablets or everolimus tablets for oral suspension?

You should not drink grapefruit juice or eat grapefruit during your treatment with everolimus tablets or everolimus tablets for oral suspension. It may make the amount of everolimus tablets or everolimus tablets for oral suspension in your blood increase to a harmful level.

What are the possible side effects of everolimus tablets or everolimus tablets for oral suspension?

Everolimus tablets and everolimus tablets for oral suspension can cause serious side effects, including:

- **See "What is the most important information I should know about everolimus tablets and everolimus tablets for oral suspension?" for more information.**
- **Risk of wound healing problems.** Wounds may not heal properly during everolimus tablets and everolimus tablets for oral suspension treatment. Tell your healthcare provider if you plan to have any surgery before starting or during treatment with everolimus tablets and everolimus tablets for oral suspension.
 - You should stop taking everolimus tablets and everolimus tablets for oral suspension at least 1 week before planned surgery.
 - Your healthcare provider should tell you when you may start taking everolimus tablets and everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension.
- **Decreased blood cell counts.** Everolimus tablets and everolimus tablets for oral suspension 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 everolimus tablets or everolimus tablets for oral suspension.
- **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 everolimus tablets 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 everolimus tablets and everolimus tablets for oral suspension 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 everolimus tablets and everolimus tablets for oral suspension:

- Absence of menstrual periods (menstruation). You may miss 1 or more menstrual periods. Tell your healthcare provider if this happens.
- Everolimus tablets and everolimus tablets for oral suspension 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.
- Everolimus tablets and everolimus tablets for oral suspension 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 everolimus tablets and everolimus tablets for oral suspension. 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 everolimus tablets or everolimus tablets for oral suspension?

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

Keep everolimus tablets or everolimus tablets for oral suspension and all medicines out of the reach of children.

General information about the safe and effective use of everolimus tablets and everolimus tablets for oral suspension.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use everolimus tablets or everolimus tablets for oral

suspension for a condition for which it was not prescribed. Do not give everolimus tablets or everolimus tablets for oral suspension to other people, even if they have the same problem you have. It may harm them. This leaflet summarizes the most important information about everolimus tablets and everolimus tablets for oral suspension. 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 1-800-367-3395 or go to www.breckenridgepharma.com.

What are the ingredients in everolimus tablets?

Active ingredient: everolimus.

Inactive ingredients: anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, and magnesium stearate.

What are the ingredients in everolimus tablets for oral suspension?

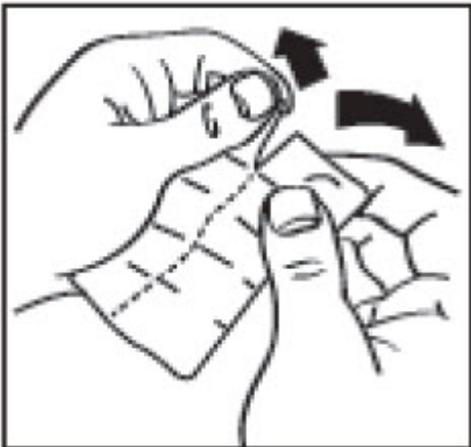
Active ingredient: everolimus.

Inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, crospovidone, hypromellose, anhydrous lactose, magnesium stearate, mannitol, and microcrystalline cellulose.

How should I open everolimus tablets or everolimus tablets for oral suspension child-resistant blister?

EVEROLIMUS TABLETS

- Separate each unit of the blister individually through perforation and peel the lidding foil from "PEEL HERE" portion.



- Pull apart 1 of the blister units from the blister pack by tearing along the dotted lines (Perforations) until it is fully separated



- Peel the lidding foil from "PEEL HERE" portion.

EVEROLIMUS TABLETS FOR ORAL SUSPENSION

This tablet is for oral suspension only.

TABLET MUST BE DISPERSED IN WATER.

TABLET MUST NOT BE SWALLOWED WHOLE, CHEWED OR CRUSHED.

REFER TO THE INSTRUCTIONS FOR USE FOR COMPLETE INSTRUCTIONS ON THE PREPARATION AND ADMINISTRATION OF EVEROLIMUS TABLETS FOR ORAL SUSPENSION.



- Use scissors to open the blister card along the dotted line and remove the prescribed number of everolimus tablets for oral suspension from the blister card.

Manufactured by:

NATCO PHARMA LIMITED

Visakhapatnam - 531019

AP, India

Distributed by:

Breckenridge Pharmaceutical, Inc.

Berkeley Heights, NJ 07922

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

Revised: 09/2025

Instructions For Use

Everolimus (E-ver-OH-li-mus) Tablets for Oral Suspension

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

Important Information:

- **Take everolimus tablets for oral suspension as a suspension only.**
Everolimus tablets for oral suspension is prepared as a suspension of undissolved medicine that is mixed with water, and then it is taken by mouth. Do not chew, crush, or swallow everolimus tablets for oral suspension whole.
- **Everolimus tablets for oral suspension can cause harm to an unborn baby.**
When possible, the suspension should be prepared by an adult who is not pregnant or planning to become pregnant.
- Keep everolimus tablets for oral suspension and the prepared suspension out of the reach of children.
- Anyone who prepares suspensions of everolimus tablets for oral suspension for

another person should wear gloves to avoid possible contact with the drug.

- Only use water with everolimus tablets for oral suspension to prepare the suspension. Do not prepare the suspension with juice or any other liquids.
- The suspension must be given right away. If you do not give the dose within 60 minutes after it has been prepared, throw away the dose and prepare a new dose of everolimus tablets for oral suspension.
- Before starting to prepare the suspension, collect all of the supplies that you will need to prepare and take the suspension. Do not use any of these supplies for purposes other than preparing and taking the everolimus tablets for oral suspension.

Supplies needed to prepare the suspension in an oral syringe:

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

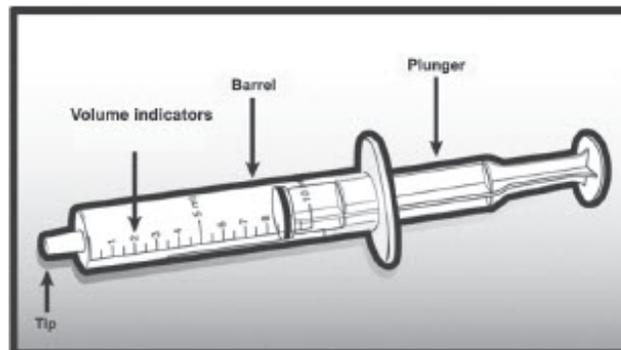


Figure A

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

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

Preparing a dose of everolimus tablets for oral suspension using an oral syringe:

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

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

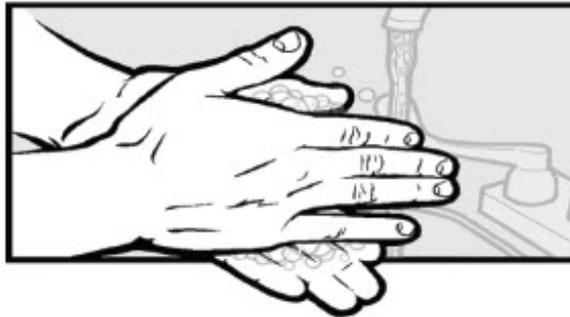


Figure B

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



Figure C

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

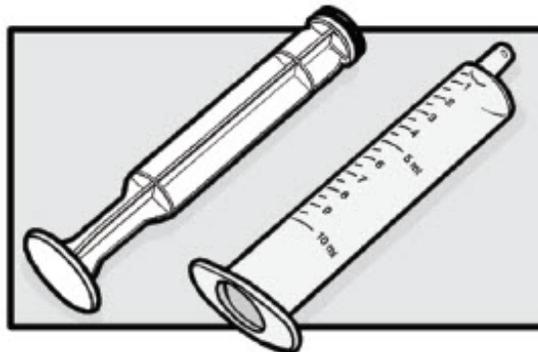


Figure D

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

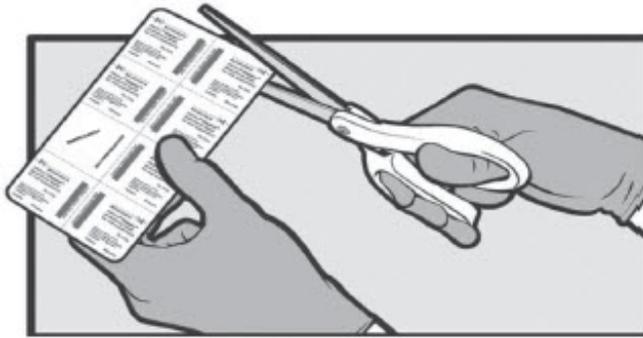


Figure E

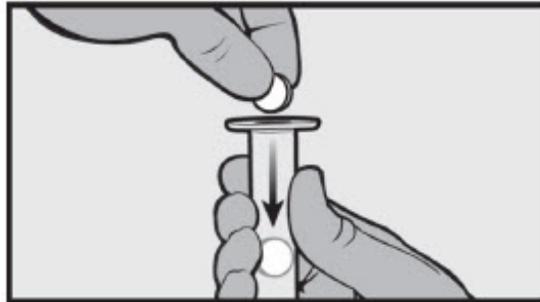


Figure F

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

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

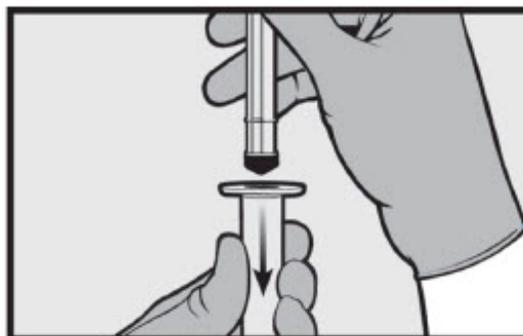


Figure G

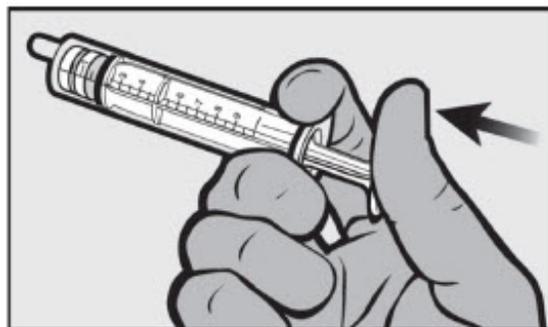


Figure H

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

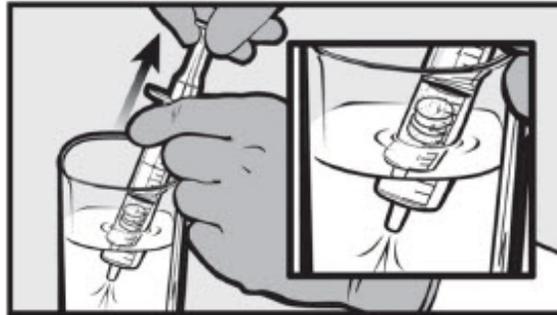


Figure I

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



Figure J

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



Figure K

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

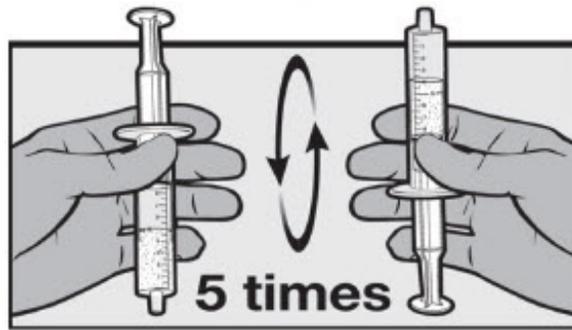


Figure L

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

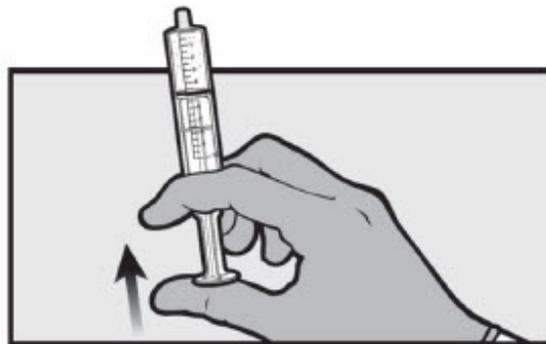


Figure M

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

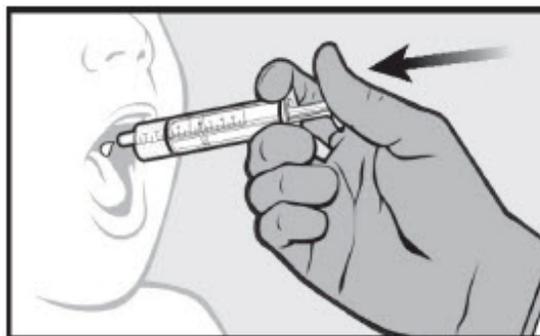


Figure N

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



Figure O

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

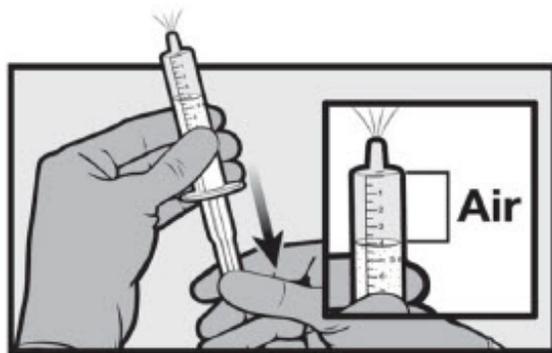


Figure P

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



Figure Q

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

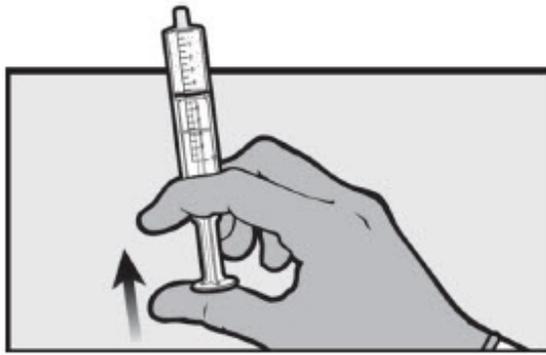


Figure R

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



Figure S

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

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

Step 19: Wash your hands.

Preparing a dose of everolimus tablets for oral suspension using a small drinking glass:

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

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



Figure T

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

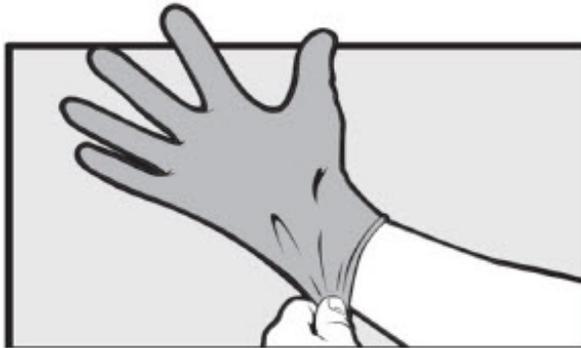


Figure U

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

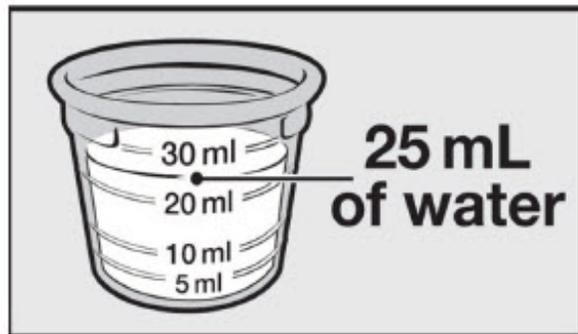


Figure V

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



Figure W

Doses up to 10 mg can be prepared in the small drinking glass. **If your total prescribed dose is more than 10 mg, you will need to split the dose.**

Follow steps 4 through 10 for the first half of the dose. Then repeat steps 4 through 10 for the second half of the dose. Ask your pharmacist or healthcare provider if you are not sure what to do.

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



Figure X

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

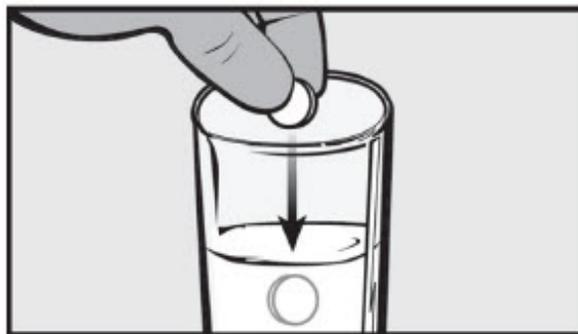


Figure Y

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

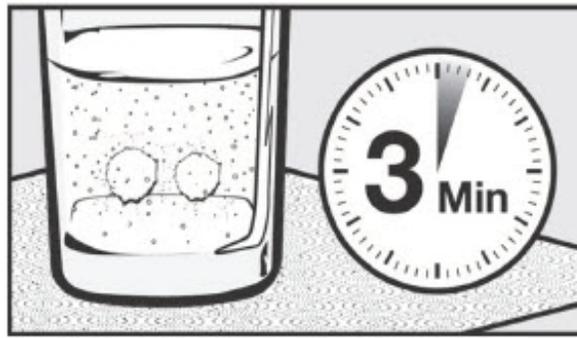


Figure Z

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

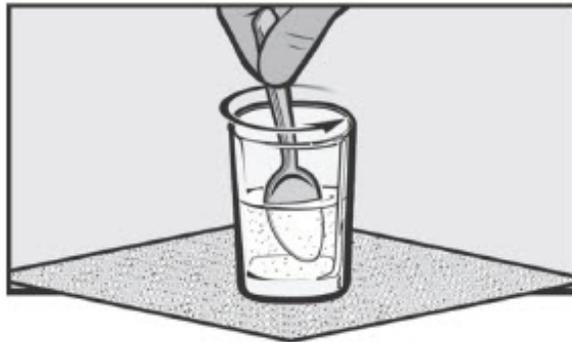


Figure AA

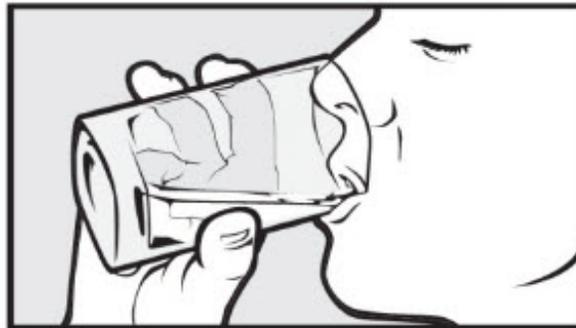


Figure BB

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

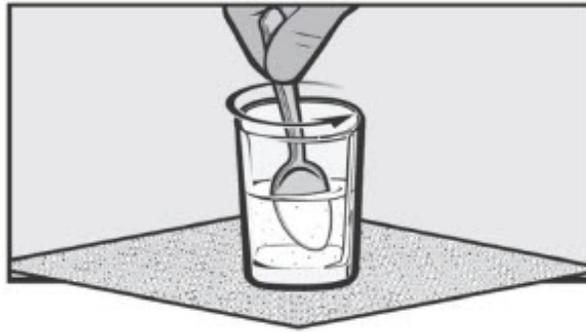


Figure CC

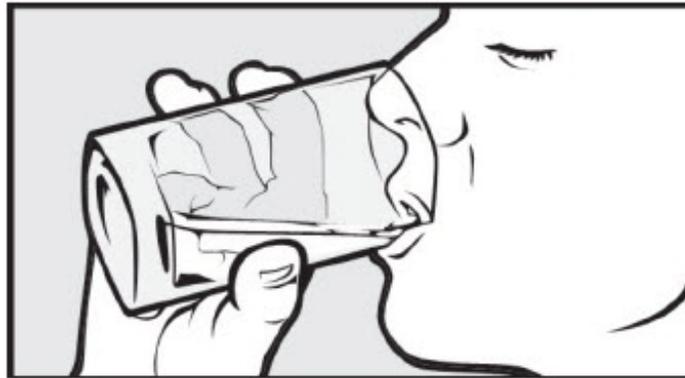


Figure DD

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

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

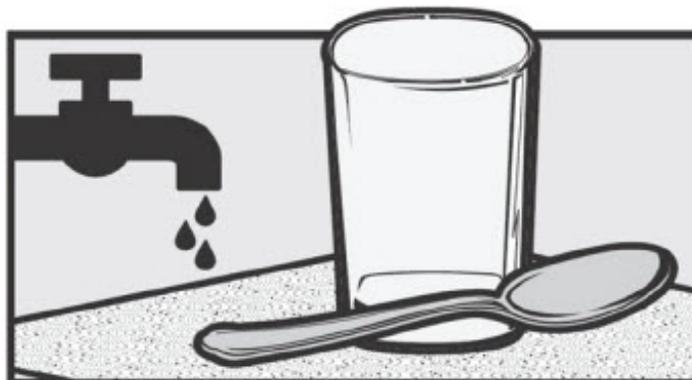


Figure EE

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

Step 13: Wash your hands.

How should I store everolimus tablets for oral suspension?

- Store everolimus tablets for oral suspension at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep everolimus tablets for oral suspension in the pack it comes in.
- Open the blister pack just before taking everolimus tablets for oral suspension.

- Keep everolimus tablets for oral suspension dry and away from light.
- Do not use everolimus tablets for oral suspension that is out of date or no longer needed.

Keep everolimus tablets for oral suspension and all medicines out of the reach of children.

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

Manufactured by:
 Natco Pharma Limited
 Visakhapatnam - 531019, India

Distributed by:
 Breckenridge Pharmaceutical, Inc.
 Berkeley Heights, NJ 07922

Revised: 02/2025

PRINCIPAL DISPLAY PANEL - 2.5 mg Tablet Bottle Label

NDC 51991-821-33

Everolimus Tablets

2.5 mg

Rx Only

30 Tablets

breckenridge
 A Towa
 Company

Each tablet contains 2.5 mg everolimus
For oral use.
Dosage: See package insert.
 Store at 20°C to 25°C (68°F to 77°F);
 excursions permitted between
 15°C and 30°C (59°F and 86°F).
 See USP Controlled Room
 Temperature. Store in the original
 container; protect from light and
 moisture.
**Keep this and all drugs out of the
 reach of children.**
 For more information, visit
www.breckenridgepharma.com or
 call 1-800-367-3395.

NDC 51991-821-33

Everolimus Tablets

2.5 mg

Rx Only 30 Tablets



M.L.: 18/VSP/AP/2018/F/G
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 Berkeley Heights, NJ 07922
 Manufactured by:
 Natco Pharma Limited
 Visakhapatnam - 531019
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40100805
Iss 09/2024

Unvarnished area

2D Barcode

NDC 51991-821-33
 GTIN 00351991821335
 S/N 1234567890
 LOT 123456789
 EXP YYYY-MMM-DD



3 5 1 9 9 1 1 8 2 1 3 3 5

PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

NDC 51991-822-33

Everolimus Tablets

5 mg

Rx Only

30 Tablets

breckenridge

A Towa

Company

Each tablet contains 5 mg everolimus
For oral use.
Dosage: See package insert.
Store at 20°C to 25°C (68°F to 77°F);
excursions permitted between
15°C and 30°C (59°F and 86°F).
See USP Controlled Room
Temperature. Store in the original
container; protect from light and
moisture.
**Keep this and all drugs out of the
reach of children.**
For more information, visit
www.breckenridgepharma.com or
call 1-800-367-3395.

5 mg

Rx Only 30 Tablets

breckenridge | A Towa
Company

NDC 51991-822-33

M.L.: 18/VSP/AP/2018/F/G

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GTIN 00351991822332
S/N 1234567890
LOT 123456789
EXP YYYY-MMM-DD

3 5 1 9 9 1 8 2 2 3 3 2

PRINCIPAL DISPLAY PANEL - 7.5 mg Tablet Bottle Label

NDC 51991-823-33

Everolimus Tablets

7.5 mg

Rx Only

30 Tablets

breckenridge

A Towa

Company

Each tablet contains 7.5 mg everolimus
For oral use.
Dosage: See package insert.
 Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). See USP Controlled Room Temperature. Store in the original container; protect from light and moisture.
Keep this and all drugs out of the reach of children.
 For more information, visit www.breckenridgepharma.com or call 1-800-367-3395.

NDC 51991-823-33

Everolimus Tablets

7.5 mg

Rx Only 30 Tablets

breckenridge | A Towa Company

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Manufactured by:
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 Visakhapatnam - 531019
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2D Barcode

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 GTIN 00351991823339
 S/N 1234567890
 LOT 123456789
 EXP YYYY-MMM-DD



PRINCIPAL DISPLAY PANEL - 10 mg Tablet Bottle Label

NDC 51991-824-33

Everolimus Tablets

10 mg

Rx Only

30 Tablets

breckenridge

A Towa

Company

Each tablet contains 10 mg everolimus
For oral use.
Dosage: See package insert.
 Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). See USP Controlled Room Temperature. Store in the original container; protect from light and moisture.
Keep this and all drugs out of the reach of children.
 For more information, visit www.breckenridgepharma.com or call 1-800-367-3395.

NDC 51991-824-33

Everolimus Tablets

10 mg

Rx Only 30 Tablets

breckenridge | A Towa Company

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2D Barcode

NDC 51991-824-33
 GTIN 00351991824336
 S/N 1234567890
 LOT 123456789
 EXP YYYY-MMM-DD



PRINCIPAL DISPLAY PANEL - 2 mg Tablet Bottle Label

NDC 51991-990-77

Everolimus Tablets

for Oral Suspension

2 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED
WHOLE, CHEWED OR CRUSHED

Rx Only

28 Tablets for Oral Suspension

breckenridge

A Towa

Company

Each tablet contains 2 mg everolimus

For oral use.
See package insert for dosage information.
See enclosed Everolimus Tablets for Oral Suspension Instructions for use.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). See USP Controlled Room Temperature.
Store in the original container. Protect from light and moisture.
Keep this and all drugs out of the reach of children.
For more information, visit www.breckenridgepharma.com or call 1-800-367-3395.

NDC 51991-990-77

**Everolimus Tablets
for Oral Suspension**

2 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED
WHOLE, CHEWED OR CRUSHED

Rx Only 28 Tablets for Oral Suspension

breckenridge | A Towa Company

Manufactured by:
Natco Pharma Limited
Visakapatnam – 531 019,
AP, India



3 5 1 9 9 1 1 9 9 0 7 7 2

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M.L.: 18/VSP/AP/2018/F/G

Iss 09/2025
40100966

Unvarnished area
42 x 18 mm

2D Barcode

NDC 51991-990-77
GTIN 00351991990772
S/N 1234567890
LOT 123456789
EXP YYYY-MMM-DD

PRINCIPAL DISPLAY PANEL - 2 mg Tablet Blister Card Carton

NDC 51991-990-28

Rx Only

Everolimus Tablets for
Oral Suspension

2 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED WHOLE, CHEWED OR CRUSHED.

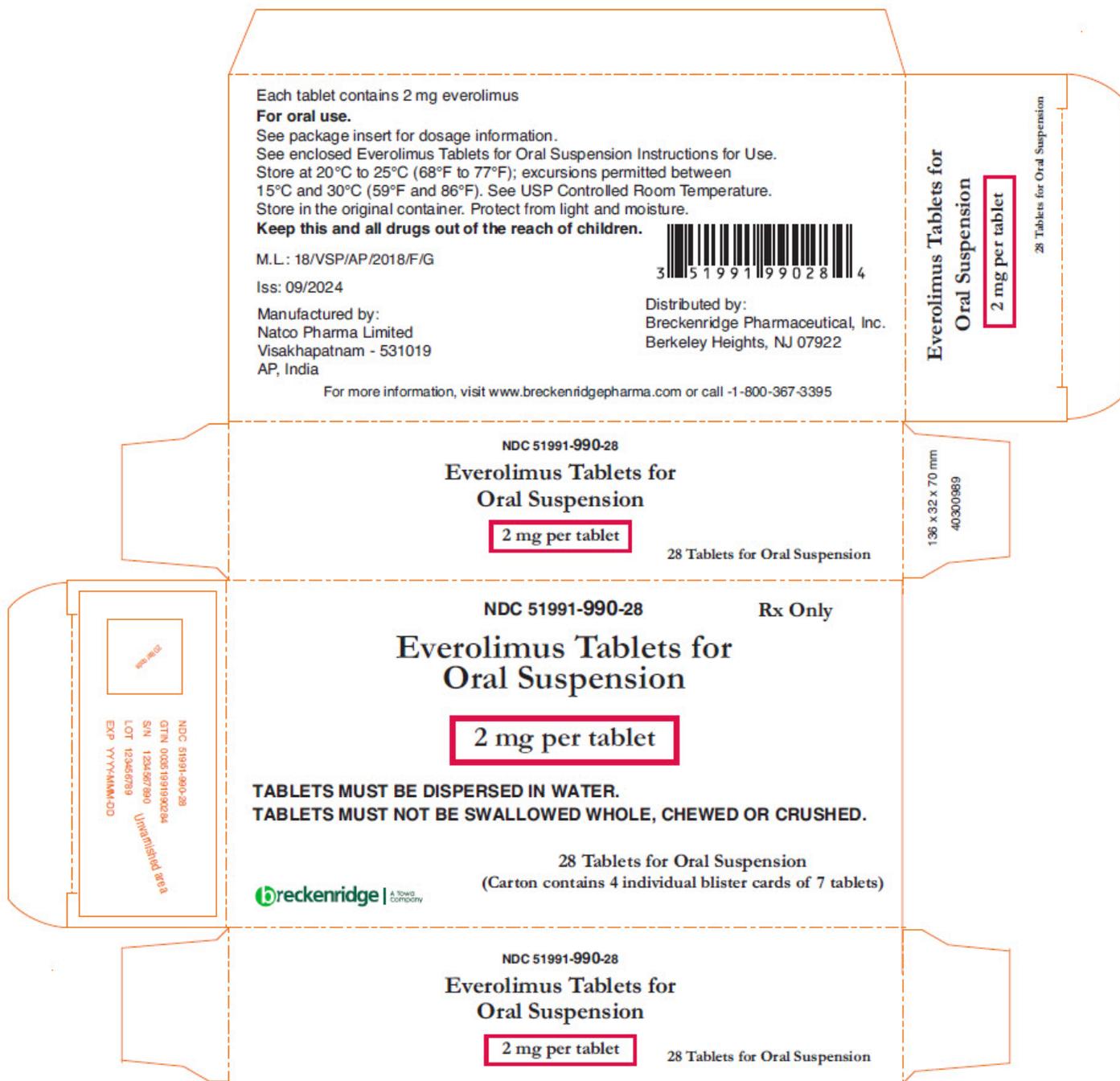
breckenridge

A Towa

Company

28 Tablets for Oral Suspension

(Carton contains 4 individual blister cards of 7 tablets)



PRINCIPAL DISPLAY PANEL - 3 mg Tablet Bottle Label

NDC 51991-991-77

Everolimus Tablets
 for Oral Suspension

3 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
 TABLETS MUST NOT BE SWALLOWED
 WHOLE, CHEWED OR CRUSHED

Rx Only
 28 Tablets for Oral Suspension

breckenridge
A Towa
Company

Each tablet contains 3 mg everolimus

For oral use.
See package insert for dosage information.
See enclosed Everolimus Tablets for Oral Suspension Instructions for use.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). See USP Controlled Room Temperature.
Store in the original container. Protect from light and moisture.
Keep this and all drugs out of the reach of children.
For more information, visit www.breckenridgepharma.com or call 1-800-367-3395.

NDC 51991-991-77

**Everolimus Tablets
for Oral Suspension**

3 mg per tablet

**TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED
WHOLE, CHEWED OR CRUSHED**

Rx Only 28 Tablets for Oral Suspension

breckenridge | A Towa Company

Manufactured by:
Natco Pharma Limited
Visakapatnam – 531 019,
AP, India



Distributed by:
Breckenridge Pharmaceutical, Inc.
Berkeley Heights, NJ 07922

M.L.: 18/VSP/AP/2018/F/G

Iss 09/2025
40100967

Unvarnished area
42 x 18 mm
2D Barcode

NDC 51991-991-77
GTIN 00351991991779
S/N 1234567890
LOT 123456789
EXP YYYY-MMM-DD

PRINCIPAL DISPLAY PANEL - 3 mg Tablet Blister Card Carton

NDC 51991-991-28

Rx Only

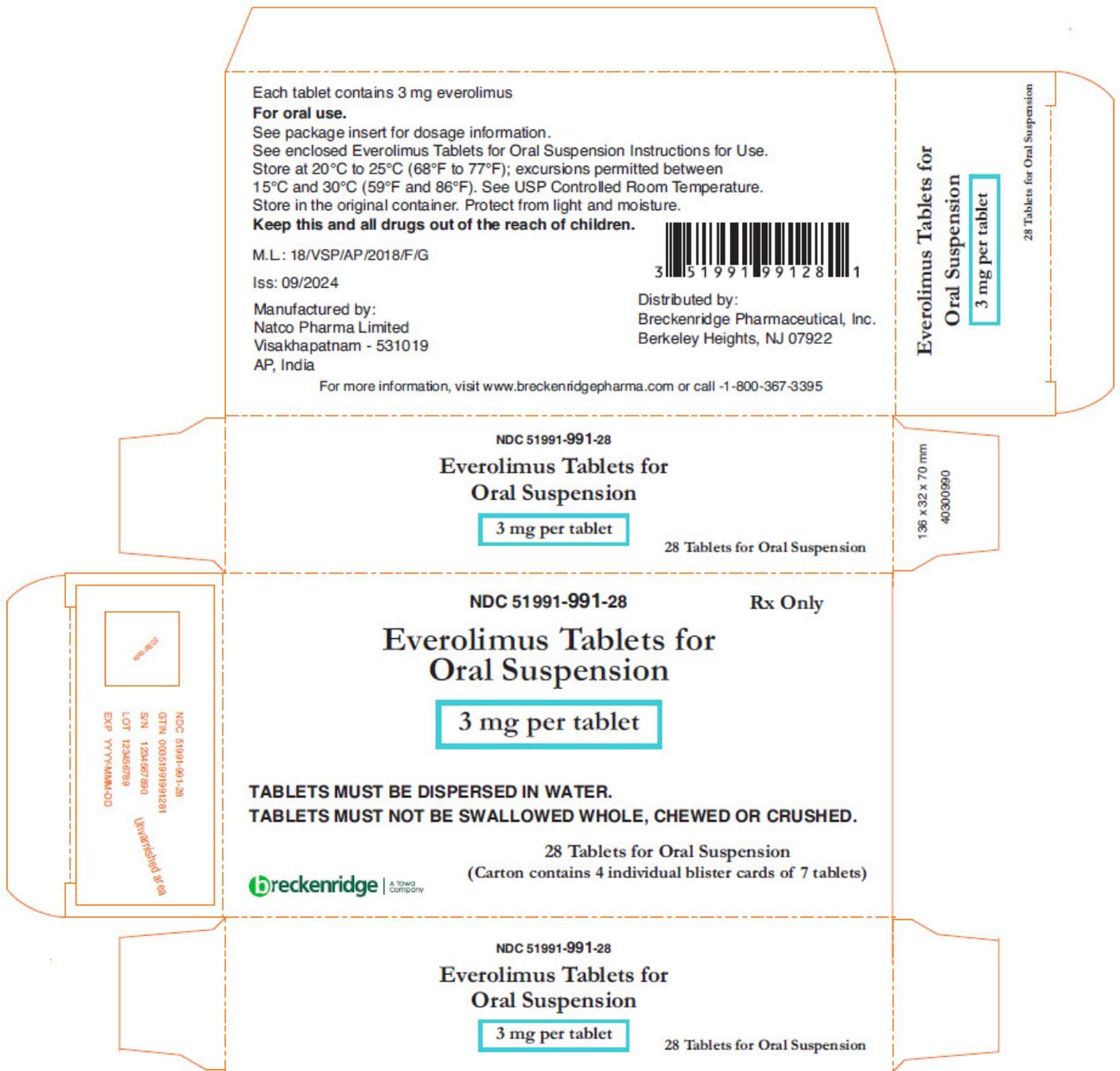
Everolimus Tablets for
Oral Suspension

3 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED WHOLE, CHEWED OR CRUSHED.

breckenridge
A Towa
Company

28 Tablets for Oral Suspension
(Carton contains 4 individual blister cards of 7 tablets)



PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

NDC 51991-992-77

Everolimus Tablets
 for Oral Suspension

5 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
 TABLETS MUST NOT BE SWALLOWED
 WHOLE, CHEWED OR CRUSHED

Rx Only

28 Tablets for Oral Suspension

breckenridge
A Towa
Company

Each tablet contains 5 mg everolimus

For oral use.
See package insert for dosage information.
See enclosed Everolimus Tablets for Oral Suspension Instructions for use.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). See USP Controlled Room Temperature.
Store in the original container. Protect from light and moisture.
Keep this and all drugs out of the reach of children.
For more information, visit www.breckenridgepharma.com or call 1-800-367-3395.

NDC 51991-992-77

**Everolimus Tablets
for Oral Suspension**

5 mg per tablet

**TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED
WHOLE, CHEWED OR CRUSHED**

Rx Only 28 Tablets for Oral Suspension

breckenridge | A Towa Company

Manufactured by:
Natco Pharma Limited
Visakapatnam – 531 019,
AP, India

Distributed by:
Breckenridge Pharmaceutical, Inc.
Berkeley Heights, NJ 07922

M.L.: 18/VSP/AP/2018/F/G

Iss 09/2025
40100968

3 5 1 9 9 1 1 9 9 2 7 7 6

Unvarnished area
42 x 18 mm
2D Barcode

NDC 51991-992-77
GTIN 00351991992776
S/N 1234567890
LOT 123456789
EXP YYYY-MMM-DD

PRINCIPAL DISPLAY PANEL - 5 mg Tablet Blister Card Carton

NDC 51991-992-28

Rx Only

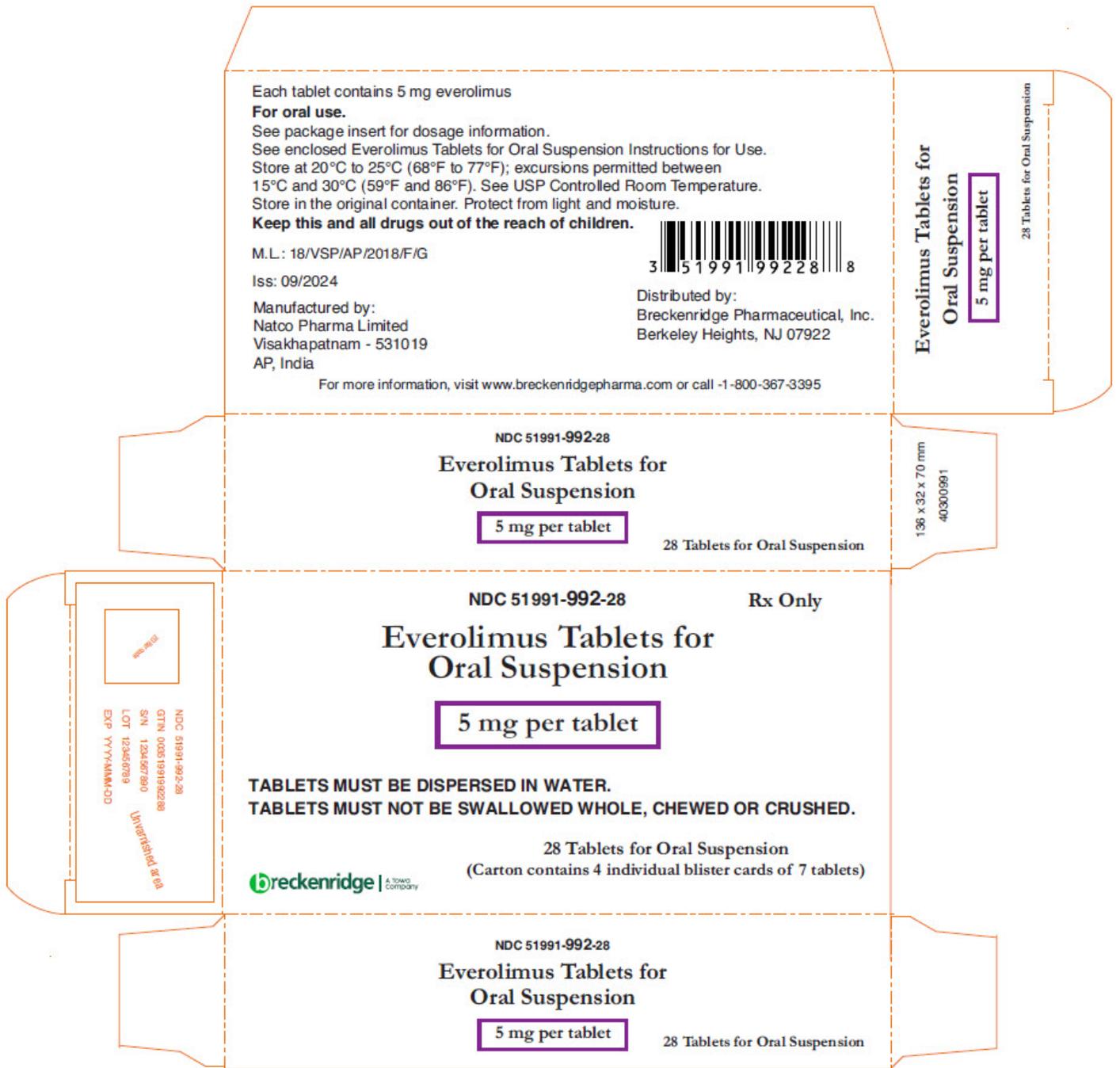
Everolimus Tablets for
Oral Suspension

5 mg per tablet

TABLETS MUST BE DISPERSED IN WATER.
TABLETS MUST NOT BE SWALLOWED WHOLE, CHEWED OR CRUSHED.

breckenridge
A Towa
Company

28 Tablets for Oral Suspension
(Carton contains 4 individual blister cards of 7 tablets)



EVEROLIMUS

everolimus tablet

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-821 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 2.5 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|--|----------|
| Acetone (UNII: 1364PS73AF) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Butylated hydroxytoluene (UNII: 1P9D0Z171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|----------|-------|--------------|----------|
| Color | WHITE | Score | no score |
| Shape | OVAL | Size | 10mm |
| Flavor | | Imprint Code | EVR;2;5 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-821-28 | 4 in 1 CARTON | 03/05/2021 | |
| 1 | NDC:51991-821-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-821-33 | 30 in 1 BOTTLE; Type 0: Not a Combination Product | 06/05/2023 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA205426 | 03/05/2021 | |

EVEROLIMUS

everolimus tablet

Product Information

| | | | |
|-------------------------|-------------------------|--------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-822 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 5 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|--|----------|
| Acetone (UNII: 1364PS73AF) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Butylated hydroxytoluene (UNII: 1P9D0Z171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|----------|-------|--------------|----------|
| Color | WHITE | Score | no score |
| Shape | OVAL | Size | 12mm |
| Flavor | | Imprint Code | EVR;5 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-822-28 | 4 in 1 CARTON | 03/05/2021 | |
| 1 | NDC:51991-822-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-822-33 | 30 in 1 BOTTLE; Type 0: Not a Combination Product | 06/05/2023 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA205426 | 03/05/2021 | |

EVEROLIMUS

everolimus tablet

Product Information

| | | | |
|-------------------------|-------------------------|--------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-823 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 7.5 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|--|----------|
| Acetone (UNII: 1364PS73AF) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Butylated hydroxytoluene (UNII: 1P9D0Z171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|----------|-------|--------------|----------|
| Color | WHITE | Score | no score |
| Shape | OVAL | Size | 14mm |
| Flavor | | Imprint Code | EVR;7;5 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-823-28 | 4 in 1 CARTON | 03/05/2021 | |
| 1 | NDC:51991-823-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-823-33 | 30 in 1 BOTTLE; Type 0: Not a Combination Product | 06/05/2023 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA205426 | 03/05/2021 | |

EVEROLIMUS

everolimus tablet

Product Information

| | | | |
|-------------------------|-------------------------|--------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-824 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 10 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|--|----------|
| Acetone (UNII: 1364PS73AF) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Butylated hydroxytoluene (UNII: 1P9DOZ171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|----------|-------|--------------|----------|
| Color | WHITE | Score | no score |
| Shape | OVAL | Size | 15mm |
| Flavor | | Imprint Code | EVR;NAT |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-824-28 | 4 in 1 CARTON | 10/01/2021 | |
| 1 | NDC:51991-824-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-824-33 | 30 in 1 BOTTLE; Type 0: Not a Combination Product | 06/05/2023 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA205426 | 03/05/2021 | |

EVEROLIMUS

everolimus tablet, for suspension

Product Information

| | | | |
|-------------------------|-------------------------|--------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-990 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 2 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|-----------------|----------|
|-----------------|----------|

| | |
|---|--|
| BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Acetone (UNII: 1364PS73AF) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U) | |
| Mannitol (UNII: 3OWL53L36A) | |
| SILICON DIOXIDE (UNII: ETJ7Z6XBU4) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|-----------------|-------|---------------------|----------|
| Color | WHITE | Score | no score |
| Shape | ROUND | Size | 9mm |
| Flavor | | Imprint Code | E;2 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-990-28 | 4 in 1 CARTON | 01/28/2025 | |
| 1 | NDC:51991-990-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-990-77 | 28 in 1 BOTTLE; Type 0: Not a Combination Product | 07/31/2025 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA217640 | 01/28/2025 | |

EVEROLIMUS

everolimus tablet, for suspension

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-991 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 3 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|---|----------|
| BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Acetone (UNII: 1364PS73AF) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U) | |
| Mannitol (UNII: 3OWL53L36A) | |
| SILICON DIOXIDE (UNII: ETJ7Z6XBU4) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|-----------------|-------|---------------------|----------|
| Color | WHITE | Score | no score |
| Shape | ROUND | Size | 10mm |
| Flavor | | Imprint Code | E;3 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-991-28 | 4 in 1 CARTON | 01/28/2025 | |
| 1 | NDC:51991-991-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-991-77 | 28 in 1 BOTTLE; Type 0: Not a Combination Product | 07/31/2025 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA217640 | 01/28/2025 | |

EVEROLIMUS

everolimus tablet, for suspension

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:51991-992 |
| Route of Administration | ORAL | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|-------------------|----------|
| Everolimus (UNII: 9HW64Q8G6G) (Everolimus - UNII:9HW64Q8G6G) | Everolimus | 5 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|---|----------|
| BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K) | |
| Hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82) | |
| Anhydrous lactose (UNII: 3SY5LH9PMK) | |
| Acetone (UNII: 1364PS73AF) | |
| Crospovidone (120 .MU.M) (UNII: 68401960MK) | |
| MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U) | |
| Mannitol (UNII: 3OWL53L36A) | |
| SILICON DIOXIDE (UNII: ETJ7Z6XBU4) | |
| Magnesium Stearate (UNII: 70097M6I30) | |

Product Characteristics

| | | | |
|-----------------|-------|---------------------|----------|
| Color | WHITE | Score | no score |
| Shape | ROUND | Size | 12mm |
| Flavor | | Imprint Code | E;5 |
| Contains | | | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:51991-992-28 | 4 in 1 CARTON | 01/28/2025 | |
| 1 | NDC:51991-992-99 | 7 in 1 BLISTER PACK; Type 0: Not a Combination Product | | |
| 2 | NDC:51991-992-77 | 28 in 1 BOTTLE; Type 0: Not a Combination Product | 07/31/2025 | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA | ANDA217640 | 01/28/2025 | |

Labeler - Breckenridge Pharmaceutical, Inc. (119102319)

Registrant - Natco Pharma Limited (650224736)

Establishment

| Name | Address | ID/FEI | Business Operations |
|-------------------|---------|-----------|---|
| Natco Pharma Ltd. | | 918588174 | MANUFACTURE(51991-821, 51991-822, 51991-823, 51991-824) |

Establishment

| Name | Address | ID/FEI | Business Operations |
|----------------------|---------|-----------|--|
| Natco Pharma Limited | | 675484209 | MANUFACTURE(51991-821, 51991-822, 51991-823, 51991-824, 51991-990, 51991-991, 51991-992) |

Revised: 9/2025

Breckenridge Pharmaceutical, Inc.