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.

1.4 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 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

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.

2.5 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 is 4.5 mg/m^2 orally once daily until disease progression or unacceptable toxicity *[see Dosage and Administration (2.8)]*.

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

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

  New dose* = current dose x (target concentration divided by current concentration)

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

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

Table 1: Recommended Timing of Therapeutic Drug Monitoring

Event	When to Assess Trough Concentrations After Event
Initiation of everolimus tablets	1 week to 2 weeks
Modification of everolimus tablets dose	1 week 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 months to 6 months
Stable dose with stable BSA	Every 6 months to 12 months

Abbreviation: P-gp, P-glycoprotein.

2.9 Dosage Modifications for Adverse Reactions

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

Table 2: Recommended Dosage Modifications for Everolimus Tablets for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold until improvement to Grade 0 or Grade 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 Grade 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If toxicity recurs at Grade 3, permanently discontinue.
	Grade 4	Permanently discontinue.
Stomatitis *[see Warnings and Precautions (5.5)]*	Grade 2	Withhold until improvement to Grade 0 or Grade 1. Resume at same dose. If recurs at Grade 2, withhold until improvement to Grade 0 or Grade 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 Grade 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.

Adverse Reaction	Severity	Dosage Modification
	Grade 4	Permanently discontinue.
Metabolic events (e.g., hyperglycemia, dyslipidemia) *[see Warnings and Precautions (5.9)]*	Grade 3	Withhold until improvement to Grade 0, Grade 1, or Grade 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 Grade 1. Resume at same dose. If toxicity recurs at Grade 2, withhold until improvement to Grade 0 or Grade 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 Grade 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 Grade 1. Resume at same dose.
	Grade 3 **OR** Grade 4	Withhold until improvement to Grade 0 or Grade 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
Neutropenia *[see Warnings and Precautions (5.10)]*	Grade 3	Withhold until improvement to Grade 0, Grade 1, or Grade 2. Resume at same dose.
	Grade 4	Withhold until improvement to Grade 0, Grade 1, or Grade 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, Grade 1, or Grade 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 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
Breast Cancer and TSC-Associated Renal Angiomyolipoma	• Mild hepatic impairment (Child-Pugh class A) - 7.5 mg orally once daily; decrease the dose to 5 mg orally once daily if a dose of 7.5 mg once daily is not tolerated. • Moderate hepatic impairment (Child-Pugh class B) – 5 mg orally once daily; decrease the dose to 2.5 mg orally once daily if a dose of 5 mg once daily is not tolerated. • Severe hepatic impairment (Child-Pugh class C) – 2.5 mg orally once daily if the desired benefit outweighs the risk; do not exceed a dose of 2.5 mg once daily.
TSC-Associated SEGA	• Severe hepatic impairment (Child-Pugh class C) – 2.5 mg/m^2 orally once daily. • Adjust dose based on everolimus trough concentrations as recommended *[see Dosage and Administration (2.8)]*.

Abbreviations: SEGA, Subependymal Giant Cell Astrocytoma; TSC, Tuberous Sclerosis Complex.

2.11 Dosage Modifications for P-gp and CYP3A4 Inhibitors

- Avoid the concomitant use of P-gp and strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]*.
- Avoid ingesting grapefruit and grapefruit juice.
- Reduce the dose for patients taking everolimus tablets 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 With a P-gp and Moderate CYP3A4 Inhibitor

Indication	Dose Modification for Everolimus Tablets
Breast Cancer and TSC-Associated Renal Angiomyolipoma	• Reduce dose to 2.5 mg once daily. • May increase dose to 5 mg once daily if tolerated. • Resume dose administered prior to inhibitor initiation, once the inhibitor is discontinued for 3 days.
TSC-Associated SEGA	• Reduce the daily dose by 50%. • Change to every other day dosing if the reduced dose is lower than the lowest available strength. • Resume dose administered prior to inhibitor initiation, once the inhibitor is discontinued for 3 days. • Assess trough concentrations when initiating and discontinuing the inhibitor *[see Dosage and Administration (2.8)]*.

2.12 Dosage Modifications for P-gp and CYP3A4 Inducers

- Avoid concomitant use of St. John's Wort *(Hypericum perforatum)*.
- Increase the dose for patients taking everolimus tablets 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 With P-gp and Strong CYP3A4 Inducers

Indication	Dose Modification for Everolimus Tablets
Breast Cancer and TSC-Associated Renal Angiomyolipoma	• Avoid co-administration where alternatives exist. • If co-administration 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	• Double the daily dose using increments of 5 mg or less. Multiple increments may be required. • Addition of another strong CYP3A4 inducer in a patient already receiving treatment with a strong CYP3A4 inducer may not require additional dosage modification. • Assess trough concentrations when initiating and discontinuing the inducer *[see Dosage and Administration (2.8)]*. • Resume the dose administered before starting any inducer, once all inducers are discontinued for 5 days.

2.13 Administration and Preparation

- Administer everolimus tablets at the same time each day.
- Administer everolimus tablets consistently either with or without food *[see Clinical Pharmacology (12.3)]*.
- If a dose of everolimus tablets 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 should be administered at its usual time. Double doses should not be administered to make up for the dose that was missed.
- Everolimus tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

3 DOSAGE FORMS AND STRENGTHS

Everolimus tablets:

- 2.5 mg tablets: White to slightly yellow, elongated tablets with a bevelled edge and debossed with "EVE" on one side and "2.5" on the other.
- 5 mg tablets: White to slightly yellow, elongated tablets with bevelled edge and debossed with "EVE" on one side and "5" on the other.

- 7.5 mg tablets: White to slightly yellow, elongated tablets with bevelled edge and debossed with “EVE” on one side and “7.5” on the other.
- 10 mg tablets: White to slightly yellow, elongated tablets with bevelled edge and debossed with “EVE” on one side and “10” on the other.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Non-infectious pneumonitis was reported in up to 19% of patients treated with everolimus in clinical trials, some cases were reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. The incidence of Grade 3 and Grade 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 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 Grade 4 non-infectious pneumonitis, withhold or permanently discontinue everolimus 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 has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1)]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections (e.g., aspergillosis, candidiasis, or PJP), and viral infections (e.g., reactivation of hepatitis B virus) have occurred. Some of these infections have been severe (e.g., sepsis, septic shock, or resulting in multisystem organ failure) or fatal. The incidence of Grade 3 and Grade 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 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 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 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 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 with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor. Permanently discontinue everolimus for angioedema.

5.5 Stomatitis

Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with everolimus at an incidence ranging from 44% to 78% across clinical trials. Grades 3 to 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, 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. Elevations of serum creatinine and proteinuria have been reported in patients taking everolimus *[see Adverse Reactions (6.1)]*. The incidence of Grade 3 and Grade 4 elevations of serum creatinine was up to 2% and up to 1%, respectively. The incidence of Grade 3 and Grade 4 proteinuria was up to 1% and up to 0.5%, respectively. Monitor renal function prior to starting everolimus 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 have the potential to adversely affect wound healing.

Withhold everolimus 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 dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended *[see Dosage and Administration (2.9), Use in Specific Populations (8.5)]*.

5.9 Metabolic Disorders

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

5.10 Myelosuppression

Anemia, lymphopenia, neutropenia, and thrombocytopenia have been reported in patients taking everolimus. The incidence of these Grade 3 and Grade 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 every 6 months for the first year of treatment and annually thereafter. Withhold or permanently discontinue everolimus 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 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. 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 treatment *[see Adverse Reactions (6.2)]*.

Monitor patients closely when everolimus is administered during or sequentially with radiation treatment.

5.13 Embryo-Fetal Toxicity

Based on animal studies and the mechanism of action, everolimus 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 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 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 (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 years to 93 years), and 75% were white. The median follow-up was approximately 13 months.

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

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

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

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

	Everolimus with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Gastrointestinal				
Stomatitis[a]	67	8[d]	11	0.8
Diarrhea	33	2	18	0.8
Nausea	29	0.4	28	1
Vomiting	17	1	12	0.8
Constipation	14	0.4[d]	13	0.4
Dry mouth	11	0	7	0
General				
Fatigue	36	4	27	1[d]
Edema peripheral	19	1[d]	6	0.4[d]
Pyrexia	15	0.2[d]	7	0.4[d]
Asthenia	13	2	4	0
Infections				
Infections[b]	50	6	25	2[d]
Investigations				
Weight loss	25	1[d]	6	0
Metabolism and nutrition				
Decreased appetite	30	1[d]	12	0.4[d]
Hyperglycemia	14	5	2	0.4[d]
Musculoskeletal and connective tissue				
Arthralgia	20	0.8[d]	17	0
Back pain	14	0.2[d]	10	0.8[d]
Pain in extremity	9	0.4[d]	11	2[d]
Nervous system				
Dysgeusia	22	0.2[d]	6	0
Headache	21	0.4[d]	14	0
Psychiatric				
Insomnia	13	0.2[d]	8	0
Respiratory, thoracic and mediastinal				
Cough	24	0.6[d]	12	0
Dyspnea	21	4	11	1
Epistaxis	17	0	1	0

	Everolimus with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Pneumonitis[c]	19	4	0.4	0
Skin and subcutaneous tissue				
Rash	39	1[d]	6	0
Pruritus	13	0.2[d]	5	0
Alopecia	10	0	5	0
Vascular				
Hot flush	6	0	14	0

Grading according to NCI CTCAE Version 3.0.
[a]Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis, and lip ulceration.
[b]Includes all reported infections, including but not limited to, urinary tract infections, respiratory tract (upper and lower) infections, skin infections, and gastrointestinal tract infections.
[c]Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.
[d]No Grade 4 adverse reactions were reported.

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

Laboratory Parameter	Everolimus with Exemestane N = 482		Placebo with Exemestane N = 238	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Hematology[a]				
Anemia	68	6	40	1
Leukopenia	58	2[b]	28	6
Thrombocytopenia	54	3	5	0.4
Lymphopenia	54	12	37	6
Neutropenia	31	2[b]	11	2
Chemistry				
Hypercholesterolemia	70	1	38	2
Hyperglycemia	69	9	44	1
Increased AST	69	4	45	3
Increased ALT	51	4	29	5[b]
Hypertriglyceridemia	50	0.8[b]	26	0
Hypoalbuminemia	33	0.8[b]	16	0.8[b]
Hypokalemia	29	4	7	1[b]
Increased creatinine	24	2	13	0

Grading according to NCI CTCAE Version 3.0.
[a]Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.
[b]No Grade 4 laboratory abnormalities were reported.

Topical Prophylaxis for Stomatitis

In a single arm study (SWISH; N = 92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning everolimus (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 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 Grade 4 stomatitis within 8 weeks. The incidence of Grade 2 to Grade 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 Grade 4 stomatitis were reported. Oral candidiasis was reported in 2% of patients in this study compared to 0.2% in the BOLERO-2 trial.

Co-administration of everolimus and dexamethasone alcohol-free oral solution has not been studied in pediatric patients.

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 in 118 patients with renal angiomyolipoma as a feature of TSC (n = 113) or sporadic lymphangioleiomyomatosis (n = 5). The median age of patients was 31 years (18 years to 61 years), 89% were white, and 34% were male. The median duration of blinded study treatment was 48 weeks (2 weeks to 115 weeks) for patients receiving everolimus.

The most common adverse reaction reported for everolimus (incidence ≥ 30%) was stomatitis. The most common Grade 3 to Grade 4 adverse reactions (incidence ≥ 2%) were stomatitis and amenorrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3 to Grade 4 laboratory abnormality (incidence ≥ 3%) was hypophosphatemia.

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

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

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

	Everolimus N = 79		Placebo N = 39	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Gastrointestinal				
Stomatitis[a]	78	6[b]	23	0
Vomiting	15	0	5	0

	Everolimus N = 79		Placebo N = 39	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Diarrhea	14	0	5	0
General				
Peripheral edema	13	0	8	0
Infections				
Upper respiratory tract infection	11	0	5	0
Musculoskeletal and connective tissue				
Arthralgia	13	0	5	0
Respiratory, thoracic and mediastinal				
Cough	20	0	13	0
Skin and subcutaneous tissue				
Acne	22	0	5	0

Grading according to NCI CTCAE Version 3.0.
[a]Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.
[b]No Grade 4 adverse reactions were reported.

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

	Everolimus N = 79		Placebo N = 39	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Hematology				
Anemia	61	0	49	0
Leukopenia	37	0	21	0
Neutropenia	25	1	26	0
Lymphopenia	20	1[a]	8	0
Thrombocytopenia	19	0	3	0
Chemistry				
Hypercholesterolemia	85	1[a]	46	0

	Everolimus N = 79		Placebo N = 39	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Hypertriglyceridemia	52	0	10	0
Hypophosphatemia	49	5[a]	15	0
Increased alkaline phosphatase	32	1[a]	10	0
Increased AST	23	1[a]	8	0
Increased ALT	20	1[a]	15	0
Hyperglycemia (fasting)	14	0	8	0

Grading according to NCI CTCAE Version 3.0.
[a]No Grade 4 laboratory abnormalities were reported.

Updated safety information from 112 patients treated with everolimus 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 in 117 patients with SEGA and TSC. The median age of patients was 9.5 years (0.8 years to 26 years), 93% were white, and 57% were male. The median duration of blinded study treatment was 52 weeks (24 weeks to 89 weeks) for patients receiving everolimus.

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

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

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

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

	Everolimus N = 78		Placebo N = 39	
	All Grades %	Grade 3 to Grade 4 %	All Grades %	Grade 3 to Grade 4 %
Gastrointestinal				
Stomatitis[a]	62	9[f]	26	3[f]
Vomiting	22	1[f]	13	0
Diarrhea	17	0	5	0
Constipation	10	0	3	0
Infections				
Respiratory tract infection[b]	31	3	23	0
Gastroenteritis[c]	10	5	3	0
Pharyngitis streptococcal	10	0	3	0
General				
Pyrexia	23	6[f]	18	3[f]
Fatigue	14	0	3	0
Psychiatric				
Anxiety, aggression or other behavioral disturbance[d]	21	5[f]	3	0
Skin and subcutaneous tissue				
Rash[e]	21	0	8	0
Acne	10	0	5	0

Grading according to NCI CTCAE Version 3.0.
[a]Includes mouth ulceration, stomatitis, and lip ulceration.
[b]Includes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral.
[c]Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection.
[d]Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.
[e]Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria.
[f]No Grade 4 adverse reactions were reported.

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

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

Grading according to NCI CTCAE Version 3.0.
[a]No Grade 4 laboratory abnormalities were reported.

Updated safety information from 111 patients treated with everolimus 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%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of everolimus. 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

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 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 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 may be at increased risk for angioedema. Avoid the concomitant use of ACE inhibitors with everolimus *[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 can cause fetal harm when administered to a pregnant woman. There are limited case reports of everolimus 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 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/m^2) with resulting exposures of approximately 4% of the human exposure at the recommended dose of everolimus 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/m^2), approximately 1.6 times the recommended dose of everolimus 10 mg orally once daily or the median dose administered to patients with tuberous sclerosis complex (TSC)-associated subependymal giant cell astrocytoma (SEGA). The effect in rabbits occurred in the presence of maternal toxicities.

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

8.2 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 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 *[see Use in Specific Populations (8.1)]*.

Contraception

Everolimus 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 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 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. Based on these findings, everolimus 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. 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 10 mg orally once daily. Based on these findings, everolimus may impair fertility in male patients *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

TSC-Associated SEGA

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

Other Indications

The safety and effectiveness of everolimus in pediatric patients have not been established in:

- Hormone receptor-positive, HER2-negative breast cancer
- TSC-associated renal angiomyolipoma

8.5 Geriatric Use

In BOLERO-2, 40% of patients with breast cancer treated with everolimus 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 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.

8.6 Hepatic Impairment

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

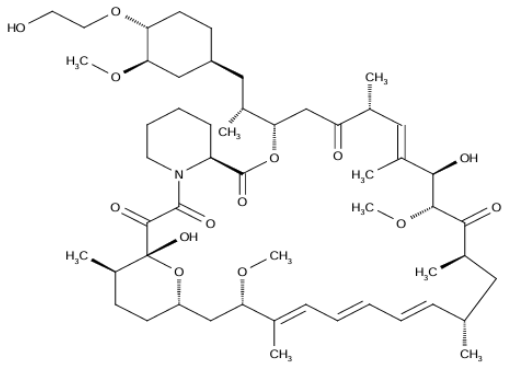
For patients with breast cancer and TSC-associated renal angiomyolipoma who have hepatic impairment, reduce the everolimus dose as recommended *[see Dosage and Administration (2.10)]*.

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

11 DESCRIPTION

Everolimus tablets 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-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone. The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.22 g/mol. The structural formula is:



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

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.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Absorption

After administration of everolimus in patients with advanced solid tumors, peak everolimus concentrations are reached 1 hour 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/m^2 to 14.4 mg/m^2.

Effect of Food: In healthy subjects, a high-fat meal (containing approximately 1,000 calories and 55 grams of fat) reduced systemic exposure to everolimus 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%.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 ng/mL to 5,000 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 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 mL/min 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, 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 was co-administered with:

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

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

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

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

The co-administration of everolimus with exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%; however, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

The co-administration of everolimus 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 times and 0.2 times the estimated human exposure based on AUC at the recommended dose of everolimus 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 (1,500 mg/m^2/day, approximately 255-fold the recommended dose of everolimus 10 mg orally once daily, and approximately 200-fold the median dose administered to patients with TSC-associated SEGA, based on the BSA), administered as 2 doses, 24 hours apart.

Based on non-clinical findings, everolimus 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 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 $AUC_{0\text{-}24h}$ values 10% to 81% lower than human exposure at the recommended dose of everolimus 10 mg orally once daily. After a 10 week to 13 week non-treatment period, the fertility index increased from zero (infertility) to 60%.

Oral doses of everolimus in female rats at doses ≥ 0.1 mg/kg (approximately 4% the human exposure based on AUC at the recommended dose of everolimus 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 in combination with exemestane vs. placebo in combination with exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Patients were

permitted to have received 0 to 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 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 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 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 arm. There were no complete responses and 4 partial responses (1.7%) in the placebo in combination with exemestane arm.

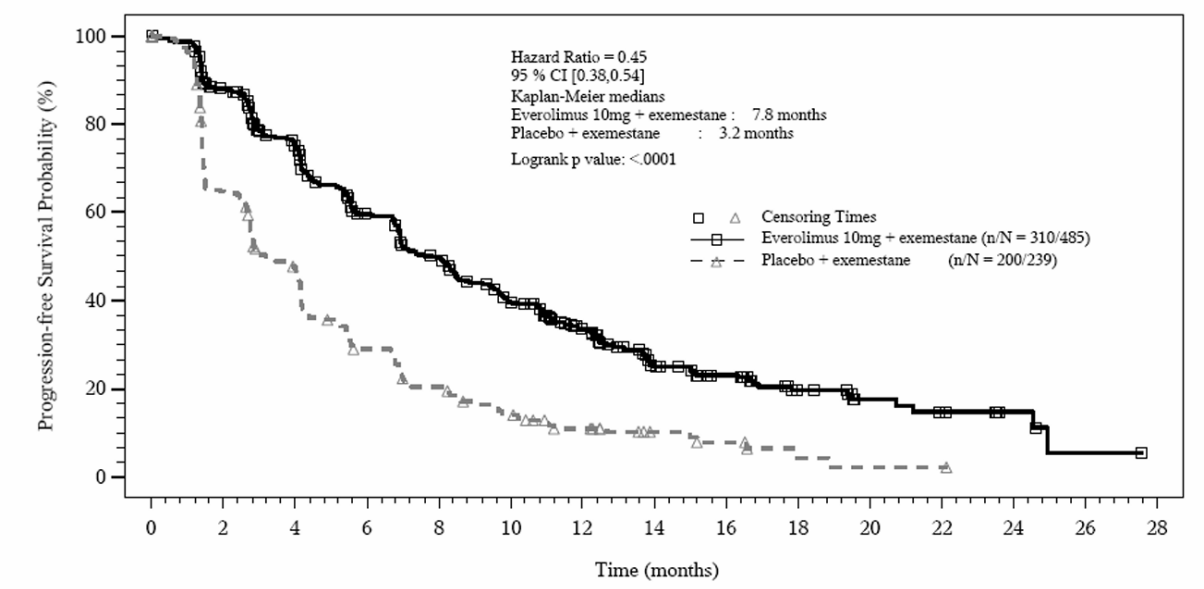
After a median follow-up of 39.3 months, there was no statistically significant difference in OS between the everolimus in combination with exemestane arm and the placebo in combination with exemestane arm [HR 0.89 (95% CI: 0.73, 1.10)].

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

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

[a]Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis.
[b]p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis.
[c]Objective response rate = proportion of patients with CR or PR.
[d]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



14.4 Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-2, NCT00790400) of everolimus was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n = 113) or sporadic lymphangioleiomyomatosis (n = 5). The key eligibility requirements for this trial were at least one angiomyolipoma of ≥ 3 cm in longest diameter on CT/MRI based on local radiology assessment, no immediate indication for surgery, and age ≥ 18 years. Patients received everolimus 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 ≥ 50% reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of kidney volume increase ≥ 20%, and no angiomyolipoma related bleeding of ≥ Grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. 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 and 39 to placebo. The median age was 31 years (18 years 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 cm^3 (9 cm^3 to 1,612 cm^3) and 120 cm^3 (3 cm^3 to 4,520 cm^3) in the everolimus 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 month to 24.8 months) at the time of the primary analysis.

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

There were 3 patients in the everolimus arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review (defined as a ≥ 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 ≥ 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 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 N = 79	**Placebo N = 39**	**p-value**
Primary analysis			
Angiomyolipoma response rate[a] – (%)	**41.8**	**0**	**< 0.0001**
95% CI	(30.8, 53.4)	(0.0, 9.0)	

[a]Per independent central radiology review.

Skin lesion response rates were assessed by local investigators for 77 patients in the everolimus 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 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 at the time of angiomyolipoma progression or after the time of the primary analysis. After the primary analysis, patients treated with everolimus 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 and 33 randomized to placebo) received at least one dose of everolimus. The median duration of everolimus 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 months to 33.8 months). Fourteen percent of the 112 patients treated with everolimus 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.

14.5 Tuberous 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 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 at a starting dose of 4.5 mg/m^2 daily, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 ng/mL to 15 ng/mL as tolerated. Everolimus or matched placebo continued until disease progression or unacceptable toxicity. MRI scans for disease assessment were obtained at baseline, 12 weeks, 24 weeks, and 48 weeks, and annually thereafter.

The main efficacy outcome measure was SEGA response rate based on independent central radiology review. SEGA response was defined as a ≥ 50% reduction in the sum of SEGA volume relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, and new or worsening hydrocephalus. 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 and 39 to placebo. The median age was 9.5 years (0.8 years to 26 years); a total of 20 patients were < 3 years, 54 patients were 3 years to < 12 years, 27 patients were 12 years 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 cm^3 (0.18 cm^3 to 25.15 cm^3) and 1.30 cm^3 (0.32 cm^3 to 9.75 cm^3) in the everolimus and placebo arms, respectively. Eight (7%) patients had prior SEGA-related surgery. The median duration of follow-up was 8.4 months (4.6 months to 17.2 months) at the time of primary analysis.

The SEGA response rate was statistically significantly higher in everolimus-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 months 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. 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 N = 78	**Placebo N = 39**	**p-value**
Primary analysis			
SEGA response rate[a] - (%)	**35**	**0**	**< 0.0001**
95% CI	24, 46	0, 9	

[a]Per independent central radiology review.

Patients randomized to placebo were permitted to receive everolimus at the time of SEGA progression or after the primary analysis, whichever occurred first. After the primary analysis, patients treated with everolimus 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 and 33 patients randomized to placebo) received at least one dose of everolimus. Median duration of everolimus treatment and follow-up was 3.9 years (0.2 year to 4.9 years).

By four years after the last patient was enrolled, 58% of the 111 patients treated with everolimus had a ≥ 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 months to 33.1 months). Twelve percent of the 111 patients treated with everolimus 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 3 mg/m^2/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 ≥ 25% over the nadir observed on study.

A total of 28 patients received everolimus for a median duration of 5.7 years (5 months to 6.9 years); 82% of the 28 patients remained on everolimus for at least 5 years. The median age was 11 years (3 years 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. Nine additional patients were identified as having a ≥ 50% volumetric reduction in their largest SEGA lesion between 1 year to 4 years after initiating everolimus, including 3 patients who had surgical resection with subsequent regrowth prior to receiving everolimus.

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 slightly yellow, elongated tablets with a bevelled edge and debossed with “EVE” on one side and “2.5” on the other; available in:

Bottles of 28 tablets……..NDC 82293-030-10

Blister carton of 28 tablets……NDC 82293-030-21
(Each carton contains 4 blister cards of 7 tablets each)

Blister carton of 30 tablets……NDC 82293-030-31
(Each carton contains aluminum pouch of 3 blister cards of 10 tablets each and silica gel)

5 mg tablets: White to slightly yellow, elongated tablets with bevelled edge and debossed with "EVE" on one side and "5" on the other; available in:

Bottles of 28 tablets……..NDC 82293-031-10

Blister carton of 28 tablets……NDC 82293-031-21
(Each carton contains 4 blister cards of 7 tablets each)

Blister carton of 30 tablets……NDC 82293-031-31
(Each carton contains aluminum pouch of 3 blister cards of 10 tablets each and silica gel)

7.5 mg tablets: White to slightly yellow, elongated tablets with bevelled edge and debossed with "EVE" on one side and "7.5" on the other; available in:

Bottles of 28 tablets……NDC 82293-032-10

Blister carton of 28 tablets……..NDC 82293-032-21
(Each carton contains 4 blister cards of 7 tablets each)

Blister carton of 30 tablets……..NDC 82293-032-31
(Each carton contains aluminum pouch of 3 blister cards of 10 tablets each and silica gel)

10 mg tablets: White to slightly yellow, elongated tablets with bevelled edge and debossed with "EVE" on one side and "10" on the other; available in:

Bottles of 28 tablets …….NDC 82293-033-10

Blister carton of 28 tablets ……NDC 82293-033-21
(Each carton contains 4 blister cards of 7 tablets each)

Blister carton of 30 tablets…….NDC 82293-033-31
(Each carton contains aluminum pouch of 3 blister cards of 10 tablets each and silica gel)

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).

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 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 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 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)]*.

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