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RESEARCH**

*APPLICATION NUMBER:*

**22-334**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

### INDICATIONS AND USAGE

AFINITOR is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. (1)

### DOSAGE AND ADMINISTRATION

- 10 mg once daily with or without food. (2.1)
- Treatment interruption and/or dose reduction to 5 mg once daily may be needed to manage adverse drug reactions. (2.2)
- For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

### DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg tablets with no score. (3)

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)

- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.4)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.7)
- Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.8, 8.1)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 30\%$ ) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.1)

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

### DRUG INTERACTIONS

- Strong and moderate CYP3A4 or P-gP inhibitors: Avoid concomitant use. (5.5, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2.2, 7.2)

### USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: AFINITOR should not be used in patients with Child-Pugh class C hepatic impairment. For patients with Child-Pugh class B hepatic impairment, reduce dose to 5 mg daily. (2.2, 5.6, 8.7)

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

Revised: 03/2009

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose

The recommended dose of AFINITOR for treatment of advanced renal cell carcinoma is 10 mg, to be taken once daily at the same time every day, either with or without food [see *Clinical Pharmacology* (12.3)]. AFINITOR tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

#### 2.2 Dose Modifications

Management of severe and/or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is 5 mg daily [see *Warnings and Precautions* (5.1)].

**Hepatic impairment:** For patients with moderate hepatic impairment (Child-Pugh class B), reduce the dose to 5 mg daily. AFINITOR has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this patient population [see *Warnings and Precautions* (5.6) and *Use in Specific Populations* (8.7)].

**Strong CYP3A4 inducers:** Avoid the use of concomitant strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). If patients require co-administration of a strong CYP3A4 inducer, consider increasing the AFINITOR dose from 10 mg daily up to 20 mg daily (based on pharmacokinetic data), using 5 mg increments. This dose of AFINITOR is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer [see *Drug Interactions* (7.2)].

### 3 DOSAGE FORMS AND STRENGTHS

5 mg tablet

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

10 mg tablet

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "UHE" on one side and "NVR" on the other.

### 4 CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with AFINITOR. The incidence of Common Toxicity Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was 4% and 0%, 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 such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, discontinue AFINITOR therapy and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with AFINITOR may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

#### 5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens [see *Adverse Reactions* (6.1)]. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR, be vigilant for signs and symptoms of infection and institute appropriate treatment promptly. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

#### 5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR. In the randomized study, approximately 44% of AFINITOR-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 and 2 [see *Adverse Reactions* (6.1)]. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed [see *Drug Interactions* (7.1)].

#### 5.4 Laboratory Tests and Monitoring

*Renal Function*

Elevations of serum creatinine, usually mild, have been reported in clinical trials [see *Adverse Reactions (6.1)*]. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

#### Blood Glucose and Lipids

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

#### Hematological Parameters

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

### 5.5 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong or moderate inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, voriconazole, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil or diltazem) or P-glycoprotein (PgP) should be avoided [see *Drug Interactions (7.1)*].

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) [see *Dosage and Administration (2.2)* and *Drug Interactions (7.2)*].

### 5.6 Hepatic Impairment

The safety and pharmacokinetics of AFINITOR were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.

AFINITOR has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.7)*].

### 5.7 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

### 5.8 Use in Pregnancy

#### Pregnancy Category D

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment [see *Use in Specific Populations (8.1)*].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Non-infectious pneumonitis [see *Warnings and Precautions (5.1)*].
- Infections [see *Warnings and Precautions (5.2)*].

### 6.1 Clinical Studies 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.

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence  $\geq 30\%$ ) 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 AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

**Table 1 Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm**

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any Adverse Reaction	97	52	13	93	23	5

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Gastrointestinal Disorders</b>						
Stomatitis <sup>a</sup>	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
<b>Infections and Infestations<sup>b</sup></b>	37	7	3	18	1	0
<b>General Disorders and Administration Site Conditions</b>						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis <sup>c</sup>	14	4	0	0	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
<b>Metabolism and Nutrition Disorders</b>						
Anorexia	25	1	0	14	<1	0
<b>Nervous System Disorders</b>						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Pain in extremity	10	1	0	7	0	0
<b>Median Duration of Treatment (d)</b>		<b>141</b>			<b>60</b>	

CTCAE Version 3.0

<sup>a</sup> Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

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

<sup>c</sup> Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

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

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

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%)

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

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

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

Nervous system disorders: Insomnia (9%), dizziness (7%), paresthesia (5%)

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

Vascular disorders: Hypertension (4%)

Renal and urinary disorders: Renal failure (3%)

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

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

Hematologic disorders: Hemorrhage (3%)

Key treatment-emergent laboratory abnormalities are presented in Table 2.

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