

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

AFINITOR<sup>®</sup> 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 diltiazem) 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.

	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>	<b>37</b>	<b>7</b>	<b>3</b>	<b>18</b>	<b>1</b>	<b>0</b>
<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.

Table 2 Key Laboratory Abnormalities Reported at a Higher rate in the AFINITOR Arm than the Placebo Arm

Laboratory Parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
<b>Hematology*</b>						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
<b>Clinical Chemistry</b>						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0

\* Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

## 7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump Pgp. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

### 7.1 Agents that may Increase Everolimus Blood Concentrations

**CYP3A4 Inhibitors and Pgp Inhibitors:** In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a Pgp inhibitor) - C<sub>max</sub> and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a Pgp inhibitor) - C<sub>max</sub> and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a Pgp inhibitor) - C<sub>max</sub> and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong or moderate inhibitors of CYP3A4 and Pgp inhibitors should not be used [see *Warnings and Precautions (5.5)*].

### 7.2 Agents that may Decrease Everolimus Blood Concentrations

**CYP3A4 Inducers:** In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C<sub>max</sub> by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong inducers of CYP3A4 or Pgp if alternative treatment cannot be administered [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.5)*].

### 7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.8)*].

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 receiving AFINITOR and for up to 8 weeks after ending treatment.

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 occurred at approximately 4% the exposure (AUC<sub>0-24h</sub>) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. 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 approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced

body weight (up to 9% reduction from the control) and slight reduction in survival in 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.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were  $\geq 0.1$  mg/kg (0.6 mg/m<sup>2</sup>) and 0.8 mg/kg (9.6 mg/m<sup>2</sup>), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m<sup>2</sup>).

### 8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

In the randomized study, 41% of AFINITOR-treated patients were  $\geq 65$  years in age, while 7% percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out [see *Clinical Pharmacology* (12.3)].

No dosage adjustment is required in elderly patients [see *Clinical Pharmacology* (12.3)].

### 8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

### 8.7 Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily [see *Dosage and Administration* (2.2), *Warnings and Precautions* (3.6) and *Clinical Pharmacology* (12.3)].

The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed and use in this patient population is not recommended [see *Warnings and Precautions* (3.6)].

## 10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

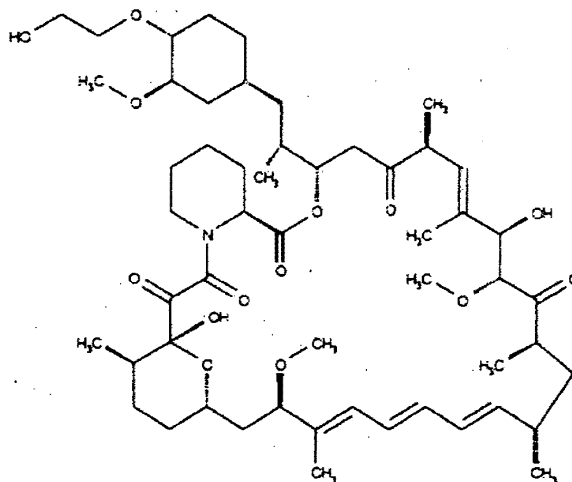
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

## 11 DESCRIPTION

AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-((1R)-2-((1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl)-1-methylethyl)-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza-tricyclo[30.3.1.0<sup>6,9</sup>]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is C<sub>51</sub>H<sub>83</sub>NO<sub>14</sub> and the molecular weight is 958.2. The structural formula is



# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.