Atrasentan, an Endothelin-Receptor Antagonist for Refractory Adenocarcinomas: Safety and Pharmacokinetics

By Michael A. Carducci, Joel B. Nelson, M. Kathy Bowling, Theresa Rogers, Mario A. Eisenberger, Victoria Sinibaldi, Ross Donehower, Terri L. Leahy, Robert A. Carr, Jeffrey D. Isaacson, Todd J. Janus, Amy Andre, Balakrishna S. Hosmane, and Robert J. Padley

Purpose: **Endothelin receptors, particularly the ET_A receptor, have been shown to participate in the pathophysiology of prostate and other cancers. Atrasentan, an endothelin antagonist, binds selectively to the ET_A receptor. This study evaluated the safety, pharmacokinetics, and maximum-tolerated dose of atrasentan in cancer patients.**

Patients and Methods: **Patients who were 18 years or older and had histologically confirmed adenocarcinoma refractory to therapy enrolled in this 28-day, open-label, phase I study. Enrollment was planned for cohorts of three patients at doses escalating from 10 to 140 mg/d. When any patient had dose-limiting toxicity, that cohort was expanded. The primary outcome variable was safety; secondary outcome variables were pharmacokinetics, tumor response, and pain relief.**

Results: **Thirty-one cancer patients (14 prostate) were treated at daily atrasentan doses of 10, 20, 30, 45, 60, and 75 mg (n = 3 to 8 per cohort). The most common adverse events, such as rhinitis, headache, asthenia, and peripheral edema, were reversible on drug discontinuation and responded to symptom-specific treatment. Reversible hemodilution was apparent in laboratory findings and weight gain. Clinically significant headache was the dose-limiting adverse event; the maximum-tolerated dose was 60 mg/d. Pharmacokinetics were dose-proportional across the 10- to 75-mg dose range. Atrasentan was rapidly absorbed; the time to maximum observed concentration was approximately 1.5 hours. The terminal elimination half-life was approximately 24 hours, and steady-state plasma concentrations were achieved within 7 days. Decreases in prostate-specific antigen and pain relief were noted in a patient subset.**

Conclusion: **Adverse events were consistent with atrasentan's pharmacologic vasodilatory effect. Linear, dose-proportional pharmacokinetics suggest that atrasentan can be easily and consistently dosed.**

J Clin Oncol 20:2171-2180. *© 2002 by American Society of Clinical Oncology.*

THE ENDOTHELIN FAMILY is composed of three isopeptides, ET-1, -2, -3, which mediate pleiotropic activities in a wide array of tissues.[1,2] Initially identified as a product of endothelial cells with potent vasoconstrictive and mitogenic properties, ET-1 is the most common circulating form of endothelin and is also found in many epithelial-derived tumors.[3-5]

ET-1 actions are mediated via two G-protein–coupled receptors, ET_A and ET_B, which are distinguished by different binding affinities for the endothelins. The ET_B receptor binds the three isotypes with equal affinity, functioning as a clearance receptor and modulator of ET-1 secretion.[6] In contrast, the caveolae-based ET_A receptor binds ET-1 with a higher affinity than the other isoforms, directly stimulates proliferative responses in neoplastic and normal cells, and potentiates other growth factors commonly implicated in malignant growth.[5-8] ET-1 activation of the ET_A receptor also prevents apoptosis.[9] There are multiple pathways whereby the ET-1/ET_A axis may contribute to the manifestations of cancer, including the modulation of angiogenesis, blood flow, nociception, and bone deposition.[10-15]

A dysregulation of the endothelin axis leading to increased ET-1 production favors tumor growth. This finding was initially described in prostate cancer patients in whom increased plasma ET-1 concentrations were greatest with metastatic, hormone-refractory disease.[16] Furthermore, prostate cancer cell lines, primary tumors, and metastatic prostate cancer lesions express increased amounts of ET-1.[8,16] Concomitant with increased local ET-1 expression in prostate cancer, there is a diminished capacity for endothelin clearance: prostate cancer cells downregulate the expression of neutral endopeptidase, a

From the Division of Medical Oncology, The Johns Hopkins Oncology Center, The Brady Urological Research Institute, The Johns Hopkins University School of Medicine, Baltimore, MD; and Abbott Laboratories, Abbott Park, IL.

Submitted October 4, 2001; accepted January 17, 2002.

Supported in part by National Institutes of Heath (NIH)/National Center for Research Resources grant no. M01-RR00052 to the Johns Hopkins University School of Medicine, CaPCure, and NIH grant nos. CA65525, CA74090-01, and SPORE CA58236. Also supported by Abbott Laboratories, Abbott Park, IL. M.A.C. and J.B.N. are consultants to Abbott Laboratories. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Address reprint requests to Michael A. Carducci, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1M89 Bunting-Blaustein, 1650 Orleans St, Baltimore, MD 21231-1000; email: carducci@jhmi.edu.

0732-183X/02/2008-2171/$20.00

key endothelin degradation enzyme, and also the ET_B clearance receptor.[8,17]

ET-1 overexpression is accompanied by increased ET_A receptor expression in prostate tumor cells, which correlates with increasing stage and grade of prostate cancer lesions.[8,18] Similar observations about derangement of the ET-1/ET_A receptor system have been made in ovarian cancer as well as in tumors of the cervix and brain.[19-23] Additional evidence from breast, colon, hepatic, endometrial, and pancreatic neoplastic and stromal tissues suggests a wider participation of the endothelin axis in human cancers.[24,25] Taken together, activation of the endothelin axis in prostate and other cancers may favor autonomous tumor growth and progression via an ET-1 paracrine/autocrine loop.

Selective blockade of endothelin receptors represents a rational, targeted approach to abrogating the pathophysiologic effects of endothelin in cancer.[16] Atrasentan is an orally bioavailable endothelin antagonist that potently (K_i = 34 pM) and selectively (1862 × ET_A > ET_B) binds to the ET_A receptor.[2] Atrasentan reverses or blocks the effects of ET-1, including its proliferative, angiogenic, bone-remodeling, and blood-flow effects.[8,26-29]

On the basis of the potential of a selective ET_A receptor antagonist to block the ET-1/ET_A receptor pathway activity in multiple tumor types, a phase I dose-escalation trial of atrasentan, administered as a once-daily dose for 4 weeks, was performed in patients with refractory adenocarcinomas. Phase I trials in healthy volunteers have demonstrated that the side effects of atrasentan are limited and only mild to moderate in severity in doses up to 40 mg/d,[29,30] with headache and rhinitis being the most common. The objectives of the present trial were to evaluate further the safety, pharmacokinetics, and maximum-tolerated dose of atrasentan in cancer patients. Initial evidence of the antitumor activity of atrasentan was also examined in these patients. This phase I, open-label, dose-escalation trial was performed at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and the General Clinical Research Center in the Johns Hopkins Hospital. Safety monitoring was continued in a separate extension trial.

PATIENTS AND METHODS

Patients

Patients were eligible for enrollment if they had a histologically confirmed diagnosis of an adenocarcinoma that was refractory to standard therapy or for which no standard therapy was available. Patients had to be at least 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and have a life expectancy of at least 3 months.

Additional eligibility criteria included the following: WBC count > 2.0×10^9/L ($2000/mm^3$), absolute neutrophil count > 1.0×10^9/L ($1,000/mm^3$), platelet count > 100×10^9/L ($100,000\ mm^3$), hemoglobin concentration > 1.395 nmol/L (9 g/dL), total serum bilirubin < 25.62 μmol/L (1.5 mg/dL), serum AST and ALT no more than 1.5 times the upper limit of normal, and a calculated creatinine clearance of at least 0.48 mL/sec/m^2 (50 mL/min).

Patients who had surgery, radiotherapy, or chemotherapy in the 28 days before study initiation must have had full recovery from treatment toxicity. Patients who had received corticosteroids within 4 weeks before the trial initiation or had a history of migraine headaches, CNS metastases, or active infection were excluded. Patients had to be able to take oral medication.

Because the potential blood pressure response to antihypertensive drugs combined with atrasentan is unknown, patients had to be discontinued from antihypertensive therapies other than a diuretic at least 7 days before the first dose of atrasentan. Adequate cardiac function was required as assessed by an echocardiogram or multigated acquisition scan showing no signs of severe left ventricular dysfunction.

Patients who had prostate cancer and had not undergone bilateral orchiectomy were maintained on therapy with a luteinizing hormone–releasing hormone agonist. Withdrawal of antiandrogen therapy with a subsequent rise in prostate-specific antigen was required, with a minimum withdrawal period of 4 weeks for flutamide and 8 weeks for bicalutamide or nilutamide. Additional concomitant therapy for the management of prostate cancer was not permitted.

The institutional review board at The Johns Hopkins Hospital approved the study. The protocol was in accordance with an assurance filed with and approved by the Department of Health and Human Services. All patients gave written informed consent before any study-related procedures were initiated.

Study Protocol

For this open-label, dose-escalation study, atrasentan was supplied as 2.5-, 5-, 10-, and 25-mg capsules. The drug was administered orally once daily on day 1 and from days 3 through 28 at a fixed dose. It was withheld on day 2 to permit pharmacokinetic analyses during a 48-hour period. Patients were required to fast for 8 hours before dosing; food consumption was also prohibited for at least 2 hours after dosing on days 1, 7, 14, and 28.

Successive cohorts of patients (three per group) were started on fixed doses of atrasentan at an initial dose of 10 mg/d. Subsequent planned dose levels were 20, 30, 45, 60, 75, 95, 115, and 140 mg/d, although the protocol stipulated that dose escalation would be halted when a maximum-tolerated dose was reached. The maximum-tolerated dose was defined as one dose level below that at which dose-limiting toxicity (DLT) was observed in one third or more of the patients. When DLT occurred in any single patient, drug administration was stopped in that patient until the toxicity resolved or the patient's baseline status was restored. If desired, the patient could continue therapy at the next lower dose, remaining there for the 28-day duration of the study unless DLT recurred, in which case the patient was discontinued from the study. (Participation of any patient in a cohort at a higher dose level was prohibited.) When one of three patients in a cohort experienced a DLT, three more patients were added to the cohort. Then, when no additional DLTs were observed in the group after 28 days, an additional cohort of three patients were enrolled at the next higher dose. For studying the relationship of pharmacokinetic parameters and safety, the trial included an additional schedule for administering the total daily dose of atrasentan. Once the maximum-tolerated dose was defined, an additional cohort of three patients were enrolled at the equivalent daily maximum-tolerated dose administered as a divided dose (twice daily).

In general, adverse events were graded as mild, moderate, or severe. DLTs and laboratory abnormalities were graded using the National Cancer Institute common toxicity criteria (NCI-CTC), version 1. DLT was defined as any drug-related adverse event that qualified as severe or as NCI grade 3 or 4.

Blood samples were drawn for pharmacokinetic analysis of atrasentan and immunoreactive ET concentrations before the initial dose on days 1 and 28 and at the following intervals thereafter: 15, 30, and 45 minutes and 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, 36, and 48 hours. Predose samples were also drawn on days 7, 14, and 21.

An extension trial was planned to assess the longer-term safety of atrasentan. To be eligible, patients were required to complete the 28-day study, demonstrate tumor regression or stable disease, and have no worsening of pain during the 28-day period. Patients who elected to enter the extension trial continued at their previous dose on a once-daily schedule of administration.

Clinical Assessments

Before enrollment, patients underwent a complete examination, including medical history, physical examination, and radiographic assessment. Subsequent weekly evaluations included physical examination and laboratory studies. A final radiographic assessment was performed within 1 week of the final study day.

Changes in cancer-related pain were evaluated using the Brief Pain Inventory–Short Form,[31] which was administered at baseline and weekly thereafter. For establishing valid baseline data, patients who required opioid analgesics had their medications stabilized for 4 weeks before the initiation of treatment. Patients had to have adequate pain control to be enrolled in the study, defined as 2 of 3 consecutive days with a pain score of 4 or less, tolerable side effects from analgesics, and the use of no more than four rescue doses of analgesic per day. During the study, each patient rated the average level of pain for every 24-hour period using integers on the Numeric Rating Scale;[32] analgesic use was recorded in a diary at bedtime. A positive pain response to treatment was defined as either a reduction of $\geq$ 25% from baseline score for at least 2 consecutive weeks without a concomitant increase in opioid analgesic use or a reduction from baseline score of $\geq$ 25% in opioid analgesic use for at least 2 consecutive weeks without an increase in pain score.

A complete tumor response was defined as the disappearance of all known disease; a partial response was defined as a decrease of 50% or more in bidimensionally measurable lesions without an increase in any other lesions. Progressive disease was defined as an increase in the size of existing lesions, the appearance of new lesions on imaging studies (computed topography or magnetic resonance imaging), the appearance of new cancer-related symptoms, or the worsening of existing symptoms. In patients with documented elevations in a tumor marker (prostate-specific antigen, CA-125, CA 19-9, CA 15-3, or CEA), biologic response was evaluated by measurement of serum concentrations 1 to 3 days before initiation of treatment and weekly thereafter.

Pharmacokinetic Procedures

Atrasentan plasma concentrations were determined using a validated liquid chromatography assay method with fluorescence detection.[33] The immunoreactive ET plasma concentrations were determined using a validated enzyme-linked immunoassay method.[29]

With the use of standard noncompartmental methods, the maximum and minimum observed concentrations (C_{max} and C_{min}), time to maximum observed concentration (T_{max}), and area under the plasma concentration-time curve (AUC) were determined for atrasentan and immunoreactive ET. For atrasentan, the AUC was calculated from time 0 to infinity (AUC∞) after dosing on day 1 and during the interval after dosing on day 28 ($AUC_{0\ to\ 24}$). The terminal phase elimination rate constant (β) was obtained using a least-squares linear regression analysis of the terminal log-linear portion of the plasma concentration-time profile. A minimum of three concentration-time data points was used to determine β. The terminal elimination half-life (t1/2) was calculated as $\ln(2)/\beta$. Oral clearance (CL/F) was obtained by dividing the dose by the AUC value. For immunoreactive ET, the AUC values were determined during 24 hours on days 1 and 28.

To test for the dose proportionality of pharmacokinetic parameters, we performed analyses of covariance on atrasentan pharmacokinetic values with body weight as the covariate. In these analyses, the primary test was designed to have good power for a trend with dose and was performed on a linear contrast orthogonal to the dose. To test for time independence, analyses of variance with dose as the only factor were performed on the difference between day 1 and day 28 pharmacokinetic measures. To assess the time when steady state occurs, we used repeated measures analyses with body weight as the covariate to compare the dose-normalized atrasentan predose concentrations on days 7, 14, 21, and 28. In the framework of these analyses, the change from day 7 to day 28 was also tested. The same analyses were performed for the immunoreactive ET parameters. All analyses used the procedures GLM of SAS/STAT (SAS Institute Inc, Gary, NC) version 6.12. $P < .05$ was considered to be statistically significant. All calculations were performed before rounding.

Table 1. Characteristics of 31 Cancer Patients Treated With Atrasentan

Characteristic		No. Patients (N = 31)
Age, years		
Median	57	
Range	42-76	
Sex		
Male		23
Female		8
Type of cancer		
Prostate		14
Other*		17
Previous therapies		
Surgery		30
Chemotherapy		28
Radiotherapy		20
Hormone treatment		16

*Includes cancer of the colon (n = 6), breast (n = 2), renal cell (n = 3), lung (n = 4), pancreas (n = 1), and unknown primary site (n = 1).

RESULTS

Patient Characteristics

Thirty-one patients were enrolled onto this trial between July 1997 and April 1999. Table 1 lists the patients' characteristics. Overall, patients had good performance status; eight patients had an ECOG performance status of 0, and 23 patients had an ECOG performance status of 1. All patients had previously received a combination of therapies.

Table 2. Treat-Emergent Adverse Events Reported by ≥10% of 31 Cancer Patients Receiving Atrasentan

	Atrasentan Total Daily Dose													
	10 mg (n = 3)		20 mg (n = 3)		30 mg (n = 4)		45 mg (n = 8)		60 mg (n = 7)		75 mg (n = 6)		Total (n = 31)	
Adverse Event*	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Rhinitis	2	67	3	100	4	100	7	88	7	100	6	100	29	94
Headache	0		3	100	4	100	4	50	7	100	6	100	24	77
Asthenia	1	33	1	33	3	75	3	38	4	57	2	33	14	45
Peripheral edema	1	33	1	33	0		5	63	4	57	2	33	12	39
Anorexia	1	33	0		2	50	2	25	1	14	4	67	10	32
Nausea	1	33	1	33	0		1	13	2	29	4	67	9	29
Vomiting	1	33	2	67	0		0		1	14	3	50	7	23
Nausea and vomiting	0		0		1	25	1	13	2	29	2	33	6	19
Constipation	1	33	0		0		0		4	57	1	17	6	19
Dyspnea	0		0		0		3	38	3	43	0		6	19
Pain	0		1	33	0		0		1	14	2	33	4	13
Chills	0		0		1	25	0		1	14	2	33	4	13
Accidental injury	1	33	0		0		2	25	0		0		3	10
Back pain	0		2	67	0		0		1	14	0		3	10
Facial edema	0		0		0		2	25	1	14	0		3	10
Dyspepsia	0		0		0		1	13	2	29	0		3	10
Anxiety	0		0		0		1	13	2	29	0		3	10
Insomnia	0		0		0		0		2	29	1	17	3	10
Lung disorder	0		0		0		1	13	1	14	1	17	3	10
Pneumonia	0		0		0		0		2	29	1	17	3	10
Rash	0		0		1	25	1	13	0		1	17	3	10
Any event	3	100	3	100	4	100	7	88	7	100	6	100	30	97

*Adverse events were coded using COSTART terms. Each patient was counted only once for each event regardless of the number of times the event was experienced.

The 31 patients were treated daily with oral atrasentan at six different doses: 10, 20, 30, 45, 60, and 75 mg. Cohorts consisted of three, three, four, eight, seven, and six patients, respectively. Of the 31 patients, 24 completed the study. Seven patients were withdrawn prematurely, six because of disease progression and one because of the adverse events of dyspnea and peripheral edema. No deaths occurred during the study.

Safety

The most common adverse effects were rhinitis (94%), headache (77%), asthenia (45%), and peripheral edema (39%) (Table 2). The severity of clinical events was collected using a mild, moderate, or severe grading system, and laboratory abnormalities were graded using the NCI-CTC version 1. The majority of adverse events, 73%, were rated as mild or as NCI grade 2 or lower in intensity and were reversible within 7 days after discontinuation of the study drug. Seven patients experienced clinical adverse events rated as severe by the investigator; only one of these events, peripheral edema, was thought to be possibly related to atrasentan therapy. The other events were determined not to be related or probably not related to atrasentan therapy by the investigator. These events included hemoptysis and dyspnea in a lung cancer patient; nausea, vomiting, and a gastrointestinal obstruction in a patient with colon cancer; renal failure in a prostate cancer patient; nausea and vomiting in a prostate cancer patient; back pain in a patient with renal cell cancer; and a pleural effusion in a patient with metastatic breast cancer. Five grade 3 laboratory toxicities were observed, consisting of one case each of hyperglycemia, hypernatremia, hyperkalemia, elevated active partial prothrombin time, and decreased hemoglobin. There were no grade 4 laboratory toxicities.

Rhinitis, manifesting as rhinorrhea and upper airway congestion, was the most common toxicity and often led to subjective complaints of dyspnea. Rated as mild in 24 patients and moderate in 5 patients, it resulted in no study withdrawals. Rhinitis worsened when patients were recumbent. When necessary, symptoms were managed with over-the-counter medications such as topical decongestants or antihistamines. The rhinitis was not dose related, occurring across all dose levels.

Headache was considered mild in 16 patients and moderate in 8 patients and caused no patients to discontinue treatment. Symptoms were described as having the features of a vascular headache. Although the headaches were of mild to moderate intensity and similar to a migraine, nausea

and photophobia were absent. Typically, the headache began with the initiation of therapy and resolved after several days of atrasentan treatment. Onset and duration were not dose related. These headaches were controlled, as necessary, with standard analgesic therapy.

Mild asthenia was reported in 10 patients, and moderate asthenia was reported in 4 patients. It resulted in no study discontinuations, and no specific therapy was required.

Mild peripheral edema was experienced by 10 patients, moderate edema was experienced by two patients, and severe edema was experienced by one patient. The edema occurred principally at the 45-mg dose and above. Typically, the edema was cosmetic in nature and responded to diuretic therapy (furosemide and hydrochlorothiazide), when used. No relationship was found between the occurrence of peripheral edema and patients' medical history, cardiopulmonary status, concomitant medications, or site of metastatic disease.

One of seven patients who received 60 mg/d atrasentan experienced an episode of severe peripheral edema and moderate dyspnea. This 52-year-old man with metastatic lung cancer developed bilateral leg edema and worsening dyspnea after 14 days of atrasentan. Although the patient responded to diuretics and withdrawal of the drug, a similar episode occurred on rechallenge with 45 mg of atrasentan. The patient subsequently withdrew from the study with spontaneous resolution of his symptoms. Review of the patient's medical records revealed a history of cardiomyopathy, hypertension, and dyspnea on exertion. A previous echocardiogram had shown moderate left ventricular hypertrophy and moderate to severe left ventricular dysfunction.

Dose-Limiting Toxicity

Dose escalation was halted at 75 mg because of a change in the character of the headaches that occurred in the six patients in this group. The headache experienced by these patients was more intense and of longer duration (in some cases occurring throughout the 28-day period) than that described in patients who were on lower doses; it necessitated chronic analgesic therapy, ranging from nonsteroidal anti-inflammatory drugs to opioid medications. This occurred whether patients received 75 mg of atrasentan as a single daily dose or as 37.5 mg twice daily. The study investigators judged that these headaches were consistent with DLT. Therefore, additional patients were enrolled in the 45-mg and 60-mg dose groups for further assessment of safety and pharmacokinetics. Two patients from the 75-mg group elected to continue atrasentan into the extension trial with chronic analgesic use.

Laboratory Evaluation

After 1 week of atrasentan initiation, a mean hemoglobin decrease of 1.3 ± 0.1 g/dL (mean ± SE) was observed, with a corresponding decrease in hematocrit. By day 28, hemoglobin values stabilized across all dose groups, with a mean decrease of 1.9 ± 0.2 g/dL from baseline. Hemoglobin changes were unrelated to dose levels. There was no evidence of hemolysis as reflected by stable serum bilirubin, serum lactate dehydrogenase, mean RBC volume, and mean cell hemoglobin concentration. Peripheral blood smears and urinalyses were also unchanged. Although two patients experienced worsening anemia that required blood transfusion, the cause was judged to be disease related in both cases.

Serum albumin and total protein concentrations decreased in parallel with the changes in hemoglobin. At week 4, albumin and total protein concentrations had declined by 0.27 ± 0.06 g/dL and 0.48 ± 0.09 g/dL, respectively. The changes in hemoglobin and serum proteins were unrelated to dose levels.

When atrasentan was stopped for 1 week before the extension trial, the acute decreases in chemistry and hematology values returned toward baseline values. Rechallenge with atrasentan in the extension trial reproduced the initial responses in laboratory values observed on first exposure, with subsequent stabilization after 2 weeks. Serum hepatic transaminase and creatinine values did not increase significantly over baseline. No grade 4 toxicities were observed.

Vital Signs

Atrasentan produced within the first week of the study declines in diastolic blood pressure that were maintained through day 28. At day 7 and day 28, overall mean diastolic pressure was decreased from baseline by − 7.9 ± 1.8 mmHg ($P < .001$) and − 4.8 ± 1.8 mmHg ($P = .01$), respectively, with the most pronounced changes occurring in patients who were hypertensive at baseline (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg). At day 28, the mean change in diastolic pressure from baseline in hypertensive patients was − 7.4 ± 2.5 mmHg (n = 11), compared with − 3.4 ± 2.3 mmHg for normotensive patients (n = 20). Mean systolic blood pressure did not change significantly from baseline: − 4.4 ± 3.1 mmHg at day 7 and − 1.5 ± 2.7 mmHg at day 28. Although the average pulse rate increased significantly at day 7 (10.4 ± 2.2 bpm; $P < .001$), the difference from baseline was no longer apparent by day 28 (+3.8 ± 2.5 bpm). No dose-response relationships were observed for these changes at day 7 and day 28.

There were no study discontinuations as a result of the blood pressure responses. One patient, who received 45 mg

DOCKET ALARM

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.