

Ulcer Prevention in Long-term Users of Nonsteroidal Anti-inflammatory Drugs

Results of a Double-blind, Randomized, Multicenter, Active- and Placebo-Controlled Study of Misoprostol vs Lansoprazole

David Y. Graham, MD; Naurang M. Agrawal, MD; Donald R. Campbell, MD; Marian M. Haber, MD; Cyndy Collis, BS; Nancy L. Lukasik, BSN; Bidan Huang, PhD

Background: Studies that report prevention of ulcer recurrence among long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs) that do not stratify for *Helicobacter pylori* status may not be generalizable to the large population of individuals without *H pylori*.

Methods: This was a prospective, double-blind, multicenter, active- and placebo-controlled study among 537 patients without *H pylori* who were long-term users of NSAIDs and who had a history of endoscopically documented gastric ulcer. Patients were randomized to receive placebo, 200 µg of misoprostol 4 times a day, or 15 or 30 mg of lansoprazole once daily for 12 weeks. Ulcer status was determined by endoscopy at 4, 8, and 12 weeks.

Results: Patients receiving lansoprazole (15 or 30 mg) remained free from gastric ulcer longer than those who received placebo ($P < .001$) but for a shorter time than those who received misoprostol. By week 12, the percentages of gastric ulcer-free patients were as follows: placebo, 51%

(95% confidence interval [CI], 41.1%-61.3%); misoprostol, 93% (95% CI, 87.2%-97.9%); 15-mg lansoprazole, 80% (95% CI, 72.5%-87.3%); and 30-mg lansoprazole, 82% (95% CI, 75.0%-89.6%). A significantly higher proportion of patients in the misoprostol group reported treatment-related adverse events and early withdrawal from the study. When the impact of withdrawals on ulcer development was considered (as failures), therapy was successful for 69% for each of the active treatment groups and 35% for the placebo group.

Conclusions: Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers but not superior to misoprostol, 800 µg/d. When the poor compliance and potential adverse effects associated with misoprostol are considered, proton pump inhibitors and full-dose misoprostol are clinically equivalent.

Arch Intern Med. 2002;162:169-175

NONSTEROIDAL anti-inflammatory drugs (NSAIDs) are widely used for the relief of pain and inflammation associated with arthritis and other musculoskeletal disorders. The benefit in terms of relief from pain and stiffness is accompanied by the risk of developing a peptic ulcer and a serious, life-threatening ulcer complication.¹ Several studies^{2,3} have been performed in search of cotherapies that might prevent NSAID-induced ulcers and ulcer complications. The use of the synthetic prostaglandin, misoprostol (Cytotec; Pharmacia, Bridgewater, NJ), as a form of replacement therapy repeatedly has been shown to prevent NSAID-induced gastroduodenal ulcers and reduce the incidence of life-threatening ulcer complications.⁴⁻¹⁴ In contrast, neither the topical agent sucralfate nor usual doses of histamine₂ (H₂)-receptor antagonists have been

shown to be effective.^{6,11,15-18} Increased doses of H₂-receptor antagonists were more effective than lower doses, but overall, the success rate was modest.^{17,19-23}

Recently, more profound acid suppression with proton pump inhibitors has been reported as being associated with acceleration of ulcer healing and prevention of ulcer relapse among long-term users of NSAIDs.^{10,18} Neither of the 2 large multicenter studies comparing the proton pump inhibitor omeprazole with misoprostol (Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management [OMNIUM])¹⁰ or ranitidine (Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment [ASTRONAUT])¹⁸ for the prevention of ulcer recurrence among long-term users of NSAIDs presented analyses regarding the association between *Helicobacter pylori* status and prevention of ulcer relapse. Subsequent analyses showed that *H pylori* status had a marked effect on outcome and the development of

Author affiliations are listed at the end of this article. Members of the NSAID-Associated Gastric Ulcer Prevention Study Group are listed in a box on page 174.

PATIENTS AND METHODS

Entry criteria included being 18 years or older, history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or gastrointestinal bleeding, and treatment with stable, full therapeutic doses of an NSAID (with the exception of nabumetone or aspirin [≥ 1300 mg/d; low-dose aspirin for cardiovascular protection was permitted]) for at least the previous month. Two thirds of patients enrolled in this study had previously completed participation in a healing trial for NSAID-associated gastric ulcer. Pretreatment *H pylori* status was determined by a rapid urease test (CLOtest; Tri-Med Specialties Inc, Draper, Utah) or histologic analysis, which was graded according to the updated Sydney System.³² Those patients positive for *H pylori* were excluded, as were those with gastric or duodenal ulcer crater (≥ 5 mm in diameter) or severe erosions (defined as >25 erosions) or erosive reflux esophagitis. Use of a proton pump inhibitor, H_2 -receptor antagonist, or misoprostol within 24 hours before study entry was not permitted. Approval for the study was obtained from the institutional review board of each of the 63 participating centers in North America, and written informed consent was obtained before patient enrollment.

STUDY DESIGN

Patients were randomly assigned in blocks of 4 to receive 12 weeks of placebo, 200 μ g of misoprostol 4 times daily with or after meals and a bedtime snack, or 15 or 30 mg of lansoprazole once daily before breakfast. Both patients and investigators remained masked to treatment group (with the exception of those receiving misoprostol). Patients received antacid tablets (Gelusil; Parke-Davis, Morris Plains, NJ) for use as needed for symptom relief. Patients were instructed to avoid antiulcer medication other than study medication, ulcerogenic medication (except NSAIDs or aspirin as noted herein), and agents that alter hemostasis.

Compliance and adverse events were assessed by returned pill count and direct questioning at each treatment visit. Symptoms were assessed on a daily basis by patient diary, where patients recorded episodes of daytime and nighttime abdominal pain (defined as none, mild, moder-

ate, or severe), study drug and NSAID dosing information, and frequency of antacid consumption. Endoscopy with biopsy was performed each month for 3 consecutive months to determine the presence of a gastric ulcer(s). Esophageal and duodenal mucosa were also evaluated.

STATISTICAL ANALYSIS

Statistical analyses were conducted using statistical software (SAS version 6.12; SAS Institute Inc, Cary, NC). Given a gastric ulcer prevention rate of 92% for one of the active treatment groups at the week 12 evaluation and a lower limit of 10%, a sample size of 120 subjects per treatment group would have 81% power to show noninferiority between active treatment groups.

Per-protocol and intent-to-treat analyses were conducted for ulcer occurrence, abdominal pain, and antacid use, the latter 2 based on patient daily diary data. For all efficacy and safety end points, pairwise comparisons were made between treatment groups.

The comparability of the treatment groups at baseline was assessed with respect to demographic variables using the χ^2 test (F test for age) and medical and social histories by the Fisher exact test. Baseline severity of symptoms, based on an investigator interview, was compared among the treatment groups using the Cochran-Mantel-Haenszel method for ordered response variables.

Life table methods were used to estimate the ulcer incidence rates. The life table analysis of time to ulcer occurrence was performed using the Cochran-Mantel-Haenszel method to test treatment differences between groups. Factors including age; sex; race; treatment for an acute NSAID-associated gastric ulcer immediately before study enrollment; hiatal hernia; investigator; alcohol, tobacco, or caffeine use; and acute baseline gastric ulcer size (measured during a screening endoscopy conducted when the subject participated in a previous healing study) were controlled for in the analysis. The treatment groups were compared with respect to percentage of days with and average severity of daytime and nighttime abdominal pain and amount of antacid use based on diary data using the Wilcoxon 2-sample test. The Fisher exact test was used to compare the incidence of treatment-related adverse events (defined as possibly or probably related) between the treatment groups.

endoscopic ulcers, with *H pylori* infection being associated with an overrepresentation of duodenal ulcers.²⁴ Separation of the prevention of ulcers that are unequivocally related to NSAID use and not to *H pylori* infection is important to the clinician because there are now considerable data to suggest the gastroduodenal outcome in long-term users of NSAIDs differs among those with and without *H pylori* infection.^{24,25} In addition, the presence of an ulcer in an *H pylori*-infected NSAID user is an indication for eradication of the infection because it is impossible to ascertain which was the actual cause of the ulcer. There is also increasing evidence that the use of antisecretory therapy with H_2 -receptor antagonists or proton pump inhibitors is associated with acceleration of corpus gastritis in those with *H pylori* infection,²⁶⁻³¹ which may make it prudent to eradicate *H pylori* in those for whom long-term NSAID and antisecretory cotherapy is contemplated.

This study attempted to overcome some of the shortcomings of the OMNIUM and ASTRONAUT studies.^{10,18} Although the OMNIUM study evaluated 2 doses of the proton pump inhibitor for ulcer healing, this comparison was not extended to the ulcer prevention portion of the study, in which only the lower dose, 20 mg, was used.¹⁰ Those studies also used a dose of misoprostol essentially devoid of antisecretory activity and a dose of ranitidine that had been proven to be subtherapeutic for this indication (ie, 400 μ g/d and 300 mg/d, respectively).^{11,12,15,16} In addition, they did not separate unequivocal NSAID ulcers from those complicated by *H pylori* infection. We report the results of a large, double-blind, multicenter, randomized, active- and placebo-controlled study designed to identify the optimal therapy for preventing unequivocal NSAID-induced gastric or duodenal ulcers. This study compared 2 doses of lansopra-

Table 1. Patient Disposition by Treatment Group

Variable	No. of Patients			
	Placebo	Misoprostol, 200 µg 4 Times Daily	Lansoprazole, 15 mg/d	Lansoprazole, 30 mg/d
Enrolled	134	134	136	133
Randomized	134	134	136	133
Withdrawn	23	23	14	19
Did not receive study drug	1	0	0	1
Adverse event	9	14	4	10
Personal reasons	3	1	3	2
Poor compliance	3	2	1	1
Therapeutic failure	4	1	2	0
Other	3	5	4	5
Completed trial	111	111	122	114

zole (Prevacid; TAP Pharmaceutical Products Inc, Lake Forest, Ill) (15 and 30 mg) with the full therapeutic dose of misoprostol (800 µg/d) and placebo for preventing ulcer relapse among patients who continued NSAID use and were known to be free of *H pylori*.

RESULTS

A total of 537 patients were randomized to receive placebo (n=134), 200 µg of misoprostol 4 times a day (n=134), 15 mg of lansoprazole once daily (n=136), or 30 mg of lansoprazole once daily (n=133) for 12 weeks. Two patients (1 each in the placebo and 30-mg lansoprazole groups) who did not take study medication were not included in the intent-to-treat analysis of ulcer occurrence or adverse events (**Table 1**). Eighty-two (15%) of the 537 enrolled patients were excluded from the per-protocol analyses because of noncompliance (eg, fewer than 14 days and/or less than 67% of prescribed study medication taken during the treatment period; n=33), no evaluable endoscopy after the initiation of treatment (n=21), positive for *H pylori* at baseline (n=15), inappropriate ulcer history (n=6), and other reasons (n=10). (Three patients were excluded in 2 categories but were counted once in the total of 82 excluded patients.) The reasons for exclusion from the per-protocol analyses were generally balanced across the treatment groups with the exception that more patients in the misoprostol group did not take the minimum amount and/or complete the minimum duration necessary for evaluability (7, 19, 1, and 6 patients in the placebo, misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups, respectively).

The treatment groups were well matched at baseline, including demographic characteristics, social history, previous history of gastrointestinal disorders, recent treatment for an NSAID-associated gastric ulcer, and severity of symptoms (**Table 2**). Most patients reported no daytime or nighttime abdominal pain at baseline. Forty percent of the patients used ibuprofen, 35% used naproxen, 32% used diclofenac, 22% used aspirin or aspirin combinations, 17% used piroxicam, and 34% used other NSAIDs. The distribution across treatment groups was similar. Patients could have taken more than 1 NSAID.

ULCER PREVENTION

Evaluable patients taking an NSAID in the 15- and 30-mg lansoprazole groups remained free from gastric ulcer significantly longer than those who received placebo ($P<.001$). There was no difference between lansoprazole dosage groups ($P=.62$). Evaluable patients in the misoprostol group remained free of gastric ulcer significantly longer than those who received placebo ($P<.001$), 15-mg lansoprazole ($P=.01$), or 30-mg lansoprazole ($P=.04$). These observations were unaffected after adjustment for potentially influential factors, including age, sex, race, treatment for an acute NSAID-associated gastric ulcer before study enrollment, hiatal hernia, investigator, and alcohol, tobacco, or caffeine use. There were no statistically significant differences between any of the active treatment groups after adjusting for acute baseline gastric ulcer size. Similar trends were observed in the results of the intent-to-treat analysis of gastric ulcer prevention data throughout the 12-week treatment period.

Absence of a gastric ulcer after 8 or 12 weeks of treatment was different among those receiving placebo, misoprostol, or lansoprazole. By week 12, the percentages of evaluable patients who were free of gastric ulcer were 51% (95% confidence interval [CI], 41.1%-61.3%), 93% (95% CI, 87.2%-97.9%), 80% (95% CI, 72.5%-87.3%), and 82% (95% CI, 75.0%-89.6%) for the respective treatment groups (**Figure 1**).

When prevention rates were analyzed based on the development of gastric or duodenal ulcers (gastroduodenal ulcers), those in the misoprostol, 15-mg lansoprazole, or 30-mg lansoprazole groups remained free of ulcer for a significantly longer period compared with those who received placebo ($P<.001$). There was no statistical difference between any 2 of the active treatments for time to occurrence of gastroduodenal ulcers (**Figure 2**).

To evaluate the impact of the early patient withdrawals from the misoprostol group, the worst-case scenario, where patients who withdrew from the study prematurely (eg, because of an adverse event) were classified as a treatment failure (eg, equivalent to having a gastric ulcer), was evaluated. In this scenario, the proportion of patients who were treatment successes

Table 2. Pretreatment Characteristics of Intent-to-Treat Patients*

Characteristic	Placebo (n = 133)	Misoprostol, 200 µg 4 Times Daily (n = 134)	Lansoprazole, 15 mg/d (n = 136)	Lansoprazole, 30 mg/d (n = 132)
Age, mean ± SD, y	60.5 ± 11.8	59.4 ± 12.0	61.6 ± 12.1	60.2 ± 11.8
Sex				
Female	87 (65)	91 (68)	86 (63)	84 (64)
Male	46 (35)	43 (32)	50 (37)	48 (36)
Race				
White	118 (89)	125 (93)	124 (91)	117 (89)
Black	10 (8)	3 (2)	8 (6)	10 (8)
Other	5 (4)	6 (4)	4 (3)	5 (4)
Smoker†	38 (29)	26 (19)	24 (18)	23 (17)
Alcohol use‡	50 (38)	49 (37)	48 (35)	39 (30)
Previous gastrointestinal disease				
Reflux esophagitis	79 (59)	84 (63)	77 (57)	76 (58)
Duodenal ulcer	69 (52)	70 (52)	65 (48)	63 (48)
Gastric ulcer	131 (98)	131 (98)	135 (99)	132 (100)
Previous treatment§	53 (40)	50 (37)	49 (36)	52 (39)
Daytime abdominal pain				
None	79 (59)	73 (54)	79 (58)	71 (54)
Mild to moderate	51 (38)	58 (43)	57 (42)	58 (44)
Severe	3 (2)	3 (2)	0	3 (2)
Nighttime abdominal pain				
None	92 (69)	96 (72)	92 (68)	83 (63)
Mild to moderate	38 (29)	33 (25)	42 (31)	46 (35)
Severe	3 (2)	5 (4)	2 (1)	3 (2)

*Data are given as number (percentage) of patients unless otherwise indicated.

†Smoker defined as any tobacco use.

‡Alcohol use defined as consumption of any quantity of alcohol on a routine basis.

§Patient received either lansoprazole or ranitidine during the 8 weeks before study enrollment for healing of a nonsteroidal anti-inflammatory drug-associated gastric ulcer.

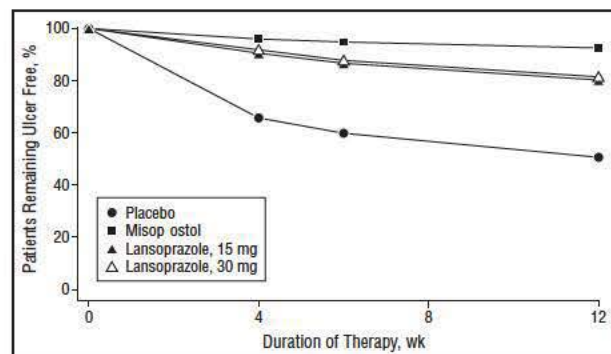


Figure 1. Percentage of evaluable patients remaining free from gastric ulcer disease during therapy as calculated by life table methods. Patients in the misoprostol group remained free of gastric ulcer significantly longer than those who received placebo ($P < .001$), 15 mg of lansoprazole ($P = .01$), or 30 mg of lansoprazole ($P = .04$). The proportions of intent-to-treat patients remaining ulcer free at the final evaluation were 51%, 92%, 83%, and 79% for the placebo, misoprostol, 30-mg lansoprazole, and 15-mg lansoprazole groups, respectively.

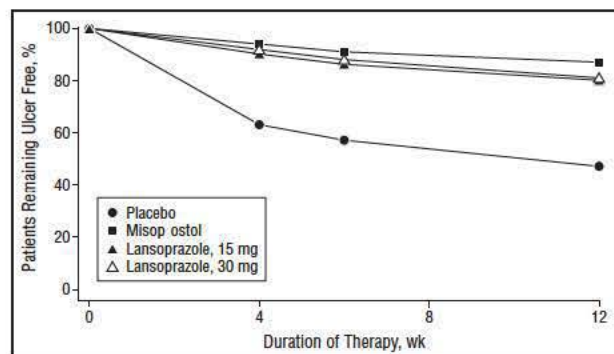


Figure 2. Percentage of evaluable patients remaining free from gastric and duodenal ulcer disease during therapy as calculated by life table methods. Those in the misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups remained ulcer free for a significantly longer period compared with those who received placebo ($P < .001$). The difference between any 2 of the active treatments for time to occurrence of gastroduodenal ulcer was not statistically significant. The proportions of intent-to-treat patients remaining ulcer free at the final evaluation were 47%, 88%, 83%, and 79% for the placebo, misoprostol, 30-mg lansoprazole, and 15-mg lansoprazole groups, respectively.

were identical for the misoprostol and lansoprazole groups and 2-fold higher than that for the placebo group (69% for each treatment group vs 35% for placebo). When those patients withdrawing prematurely were classified as the worse case (ie, having had a gastric or duodenal ulcer), the percentages of patients remaining free from gastroduodenal ulcer disease throughout the study period were 34%, 67%, 69%, and 68% for the placebo, misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups, respectively.

PATIENT DIARY RESULTS

Lansoprazole-treated patients experienced significantly less severe and significantly fewer days with daytime abdominal pain than evaluable misoprostol-treated patients based on analyses of patient diaries (**Table 3**). Patients in the 15-mg lansoprazole group also had significantly less severe ($P = .01$) and significantly fewer days ($P = .001$) with nighttime abdominal pain than those in the misoprostol group. Antacid use was significantly

Table 3. Mean Diary Results During the 12-Week Treatment Period

Variable	Placebo (n = 113)	Misoprostol, 200 µg 4 Times Daily (n = 108)	Lansoprazole, 15 mg/d (n = 126)	Lansoprazole, 30 mg/d (n = 119)
Daytime abdominal pain				
Days with pain, %	34.5	41.0	27.5†	30.8§
Average pain severity per day*	0.51	0.60	0.39‡	0.46§
Nighttime abdominal pain				
Nights with pain, %	30.4	32.7	22.2‡	27.1
Average pain severity per night*	0.45	0.49	0.32§	0.41
Antacid use				
Days used, %	37.1	41.6	24.6†	24.7†
Average number per day	1.24	1.35	0.72†	0.72†

*Severity was scored as follows: 0, none; 1, mild; 2, moderate; and 3, severe.

† $P < .001$ vs misoprostol.

‡ $P < .01$ vs misoprostol.

§ $P < .05$ vs misoprostol.

|| $P < .01$ vs placebo.

less ($P < .001$ for each pairwise comparison) among patients in the lansoprazole groups compared with patients in the misoprostol and placebo groups based on fewer antacid tablets taken per day and a smaller percentage of days of antacid use. Similar trends were observed in the results of the intent-to-treat analysis of diary data throughout the 12-week treatment period.

COMPLIANCE AND ADVERSE EFFECTS

More than 90% of patients in the placebo and 15- and 30-mg lansoprazole groups were compliant with study medication, compared with 73% of patients in the misoprostol group ($P < .001$). Thirty-eight (7%) of the 535 patients discontinued use of the study medication prematurely primarily because of an adverse event (9, 14, 4, and 10 patients in the placebo, misoprostol, 15-mg lansoprazole, and 30-mg lansoprazole groups, respectively).

A significantly higher percentage of patients in the misoprostol group (31%, 41/134) reported a treatment-related adverse event compared with each of the other treatment groups: 13 (10%) of 133 patients in the placebo group, 10 (7%) of 136 patients in the 15-mg lansoprazole group, and 21 (16%) of 132 patients in the 30-mg lansoprazole group ($P < .001$ for misoprostol vs placebo and vs 15-mg lansoprazole; $P = .006$ for misoprostol vs 30-mg lansoprazole; $P = .04$ for 15-mg lansoprazole vs 30-mg lansoprazole). The most commonly reported treatment-related event was diarrhea, which was more common in the misoprostol group (22%, 29/134) compared with the placebo (3%, 4/133), 15-mg lansoprazole (3%, 4/136), and 30-mg lansoprazole (7%, 9/132) groups ($P \leq .001$ for each comparison vs misoprostol). Patients in the misoprostol group also had a significantly greater incidence of treatment-related abdominal pain (6%, 8/134) and nausea (4%, 6/134) compared with patients in the 15-mg lansoprazole group (0/136 for both symptoms) ($P = .003$ and $P = .01$, respectively). One patient (in the 15-mg lansoprazole group) experienced an upper gastrointestinal tract hemorrhage during the study.

COMMENT

Studies designed to evaluate ulcer prevention among long-term users of NSAIDs have varied regarding study design, data analysis, and results presented. Several trials with antisecretory drugs showed the outcome differed with gastric ulcers compared with duodenal ulcers and *H pylori*-infected ulcers compared with ulcers not infected with *H pylori*.^{11,15-17} None were randomized with regard to *H pylori* status. That is unfortunate since randomization would have ensured that if there were a difference in outcome in relation to *H pylori* status, the overall results of the study would not hinge on the proportion of patients with (or without) the infection. A study conducted in Hong Kong of patients with bleeding ulcers who were long-term users of NSAIDs shows the importance of this stratification. Even though the background rate of *H pylori* infection is high in Hong Kong (>80%), the proportion of study patients with complicated ulcer and *H pylori* infection was only 45.5%.³³ Similarly, reanalysis of the outcomes of the OMNIUM¹⁰ and ASTRONAUT¹⁸ trials showed that *H pylori* infection has an important impact on outcome.²⁴ The lowest effective dose of misoprostol (400 µg/d) was superior to omeprazole (8.2% vs 16.6%, respectively, developed gastric ulcers) ($P = .04$) and low-dose ranitidine (150 mg twice daily) was equivalent to omeprazole (14.6% vs 11.6%, respectively) ($P = .56$) for the prevention of gastric ulcers in patients with unequivocal NSAID ulcers who were long-term users of NSAIDs. Among those with *H pylori* infection, misoprostol was similar to omeprazole (5.7% vs 9.2%, respectively) ($P = .48$), and omeprazole was superior to low-dose ranitidine (1.9% vs 17%, respectively) ($P = .001$).²⁴

The present study was designed to avoid those shortcomings by comparing 2 doses of a proton pump inhibitor (lansoprazole) with the full therapeutic dose of misoprostol and placebo in patients with unequivocal NSAID-associated ulcers. As with omeprazole, lansoprazole was superior to placebo, with no evidence of a major dose response effect. We confirmed that gastric ulcers recurred during the 12-week follow-up in a greater percent-

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.