A Comparison of the Efficacy of Fluticasone Propionate Aqueous Nasal Spray and Loratadine, Alone and in Combination, for the Treatment of Seasonal Allergic Rhinitis

Paul H. Ratner, MD; Julius H. van Bavel, MD; Bruce G. Martin, DO; Frank C. Hampel, Jr., MD; William C. Howland, III, MD; Paula R. Rogenes, PhD; Ronald E. Westlund; Brian W. Bowers, PharmD; and Cindy K. Cook
San Antonio, Austin, and New Braunfels, Texas; and Research Triangle Park, North Carolina

BACKGROUND. Intranasal corticosteroids and oral antihistamines are both effective in the treatment of seasonal allergic rhinitis, although the therapeutic value of administering the two types of agents concurrently has rarely been evaluated. This study was designed to compare the efficacy, safety, and impact on quality of life of fluticasone propionate aqueous nasal spray (FP ANS), loratadine, FP ANS plus loratadine, and placebo (an aqueous nasal spray plus tablet) in the treatment of seasonal allergic rhinitis during the mountain cedar allergy season in south central Texas.

METHODS. Six hundred patients with seasonal allergic rhinitis were treated for 2 weeks with either FP ANS 200 µg once daily, loratadine 10 mg once daily, the FP ANS and loratadine regimens combined, or placebo in a multicenter, randomized, double-blind, double-dummy, parallel-group study.

RESULTS. Clinician- and patient-rated total and individual nasal symptom scores after 7 and 14 days of therapy and overall evaluations were significantly lower ($P < .001$) in the FP ANS and FP ANS plus loratadine groups compared with the loratadine only and placebo groups. Loratadine was not statistically different from placebo in clinician and patient symptom score ratings nor in overall clinician and patient evaluations. FP ANS plus loratadine and FP ANS monotherapy were comparable in efficacy in almost all evaluations; for some patient-rated symptoms the combination was found superior. Mean score changes in the Rhinoconjunctivitis Quality of Life Questionnaire from baseline to day 14 showed significantly greater improvement ($P < .001$) in quality of life in the FP ANS group than in the group of patients receiving loratadine only or placebo, and no significant benefit was demonstrated in the FP ANS plus loratadine group over the FP ANS monotherapy group. No serious or unusual drug-related adverse events were reported. Combining loratadine with FP ANS did not alter the adverse events profile or frequency.

CONCLUSIONS. In the treatment of seasonal allergic rhinitis, FP ANS is superior to loratadine and placebo, and adding loratadine to FP ANS does not confer meaningful additional benefit.

KEY WORDS. Rhinitis, allergic, seasonal; loratadine; antihistamine; fluticasone propionate aqueous nasal spray [non-MeSH]. *(J Fam Pract 1998; 47:118-125)*

Intranasally administered corticosteroids and nonsedating, second-generation oral antihistamines currently form the core of pharmacotherapy for seasonal allergic rhinitis.[1,2] Both treatments have been shown to alleviate or significantly reduce the rhinorrhea, sneezing, and nasal itching characteristics of allergic rhinitis.[2] While intranasal corticosteroids reduce nasal blockage more effectively than oral antihistamines,[1] antihistamines tend to have a more pronounced effect on eye symptoms.[1,3] The choice of one mode of pharmacotherapy over the other is generally based on patient preference, with the goal of achieving the most effective control of rhinitis symptoms with the fewest side effects.

One currently available intranasal corticosteroid preparation, fluticasone propionate aqueous nasal spray (FP ANS) (Flonase Nasal Spray, 0.05% w/w, Glaxo Wellcome Inc, NC), was developed to provide a high ratio of local anti-inflammatory to systemic activity.[4-7] In clinical trials of 2 to 4 weeks' duration comparing FP ANS with oral antihistamines, FP ANS demonstrated significantly greater effectiveness than loratadine,[8-11] terfenadine,[12-14] astemizole,[15] and cetirizine[16] in relieving nasal symptoms of rhinitis.

Drouin and colleagues[17] have suggested that the concomitant administration of an intranasal corticosteroid regimen with an oral antihistamine regimen

Submitted, revised, May 7, 1998. *From Sylvana Research, San Antonio, Texas (P.H.R.); Allergy Associates of Austin Diagnostic Clinic (J.H.V.) and HealthQuest Research (W.C.H), Austin, Texas; Southwest Allergy and Asthma Research Center, San Antonio, Texas (B.G.M.); and Central Texas Health Research, New Braunfels (F.C.H.); Glaxo Wellcome Inc, Research Triangle Park, North Carolina (R.E.W., B.W.B., P.R.R., C.K.C.). Requests for reprints should be addressed to Paul H. Ratner, MD, Sylvana Research, 7711 Louis Pasteur Drive, Suite 406, San Antonio, TX 78229.*

theoretically should result in greater relief of both nasal and ocular rhinitis symptoms than is achievable with either regimen alone. Although several clinical trials have evaluated the efficacy of intranasal beclomethasone dipropionate in combination with an oral antihistamine,[17-19] and one study has investigated an FP ANS–cetirizine combination,[20] there have been no studies to date evaluating a combination of FP ANS and loratadine. The purpose of the present study was to compare the efficacy, safety, and impact on quality of life of FP ANS, loratadine, FP ANS combined with loratadine, and placebo over a 2-week period in the treatment of nasal symptoms of seasonal allergic rhinitis due to mountain cedar pollen.

METHODS

PATIENTS

Male and nonpregnant female outpatients, aged 12 years or older, were eligible for the study if they had moderate to severe seasonal allergic rhinitis diagnosed according to four criteria: (1) positive (a 2+ reaction, scored on a scale of 0 to 4, defined as a wheal diameter at least 3 mm greater than diluent control) skin test reaction to mountain cedar (*Juniperus ashei*) allergen within 12 months; (2) appearance of the nasal mucosa consistent with a diagnosis of seasonal allergic rhinitis; (3) a history of seasonal onset and offset of symptoms for at least two previous mountain cedar pollen seasons; and (4) moderate to severe symptoms of rhinitis evidenced by patient diary card ratings during a run-in. Patients were ineligible for the study if they had received, before the screening visit, treatment with loratadine within 1 week, astemizole within 6 weeks, cromolyn sodium within 2 weeks, over-the-counter or prescription medications that could affect rhinitis symptomatology (eg, nasal decongestants) within 72 hours, or inhaled, intranasal, or systemic corticosteroids within 1 month. Patients could not have either a septal deviation (>50% blockage) or a nasal polyp that could obstruct penetration of an intranasal spray. Patients were not included if they had a history of nasal septal surgery or nasal septal perforation. Patients were excluded if they had clinically significant physical examination findings at screening, had evidence of candidal infection, or were pregnant or lactating. Patients were also excluded if they had any condition or impairment that might affect their ability to complete the study or provide informed consent.

STUDY DESIGN

The protocol for this double-blind, placebo-controlled, parallel-group comparative trial was approved by an institutional review board for each of the five study sites. All patients or their guardians gave written informed consent. This study was a double-dummy design in which patients randomized to active oral medication received both a placebo nasal spray and active oral medication, and patients randomized to active nasal spray received both the active nasal spray and placebo oral medication. At the screening visit, clinicians evaluated potential study candidates by rating their nasal symptoms (sneezing, nasal blockage, rhinorrhea, and nasal itching) according to a visual analog scale, ranging from 0 (absent) to 100 (severe),[21] and by completing the following: a medical history, skin testing for allergy to mountain cedar allergen (if not done within previous 12 months), a physical examination, clinical laboratory tests, pregnancy test, and an examination of the nose and oropharynx for evidence of *Candida*. Patients who had symptoms began the 7- to 30-day run-in period immediately after screening, and patients who were free of symptoms were instructed to record their allergy symptoms associated with mountain cedar as soon as they began, so that the run-in period could be initiated.

During the run-in period and throughout the study, patients used the visual analog scale described above to rate their nasal symptoms daily on diary cards. Symptoms were rated in the evening to represent symptoms for the entire day. To qualify for enrollment, the total nasal symptom score (derived by adding individual symptom scores for nasal blockage, rhinorrhea, sneezing, and nasal itching for the day) was required to be at least 200 of a possible 400 on 4 of the 7 days immediately preceding enrollment.

Patients who met this criterion were randomly assigned on day 0 (baseline) to receive one of four regimens for 14 days: FP ANS 200 µg (two 50-µg sprays per nostril) plus one placebo capsule (to match the loratadine dosing form) once daily at 8 AM; placebo nasal spray (two sprays per nostril) plus one encapsulated loratadine 10-mg tablet once daily at 8 AM; FP ANS 200 µg (two 50-µg sprays per nostril) plus one encapsulated loratadine 10-mg tablet once daily at 8 AM; placebo spray (two sprays per nostril) plus one placebo capsule once daily at 8 AM. The formulation of loratadine used for encapsulation was Claritin tablets (Schering Corporation, Kenilworth, NJ). Dissolution testing confirmed that active capsules were comparable with unencapsulated tablets.

EFFICACY ANALYSIS

Patients recorded their nasal symptoms and use of study medication daily on diary cards throughout the treatment phase. Nasal symptoms were assessed by the clinician on day 0 (before the first dose of drug was administered), day 7, and day 14. During the treatment period, patients were not permitted to use any other medication that might affect rhinitis symptoms. At every clinic visit, clinicians recorded the occurrence of adverse events (defined as any untoward medical occurrence, drug-related or not), recorded concomitant medications used, checked compliance by diary

card and capsule counts, and examined patients for evidence of nasal and oropharyngeal *Candida*. On day 14, clinicians and patients independently recorded their overall evaluation of treatment, and patients underwent a final physical examination.

Quality-of-Life Analysis

At baseline and on day 14, patients completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[22] This 28-item, self-administered, disease-specific questionnaire measures quality of life globally and across seven different domains known to be affected by rhinoconjunctivitis: nasal symptoms; eye symptoms; activities; practical problems; sleep; emotional issues; and symptoms other than those involving the nose or eye, such as fatigue, irritability, and tiredness. Patients were asked to rate each item on a 7-point scale (where 0 = not troubled or none of the time and 6 = extremely troubled or all of the time), capturing the impact of rhinoconjunctivitis for each item over the previous 7 days. Each domain provides a scale score, and the mean of all the items provides an overall global score. An improvement in rhinoconjunctivitis quality of life was indicated by a decrease in domain and global scores at day 14.

TABLE 1

Demographic Characteristics and Disposition of Patients

	Placebo	Loratadine*	FP ANS*	FP ANS + Loratadine*
Number of patients	150	150	150	150
Mean age, yr	42.0	40.1	40.7	42.2
Range	16-74	15-70	13-80	15-78
Sex, no. (%)				
Male	61 (41)	69 (46)	68 (45)	74 (49)
Female	89 (59)	81 (54)	82 (55)	76 (51)
Ethnic origin, no. (%)				
White	115 (77)	110 (73)	117 (78)	120 (80)
Hispanic	30 (20)	28 (19)	22 (15)	26 (17)
Other	5 (3)	12 (8)	11 (7)	4 (3)
Compliance† (%)				
With capsule	97.5	97.0	97.8	98.0
With spray	97.9	96.8	97.9	98.2
Patients withdrawn, no. (%)	10 (7)	8 (5)	8 (5)	5 (3)
Adverse event	3 (2)	2 (1)	3 (2)	0 (0)
Failed to return	2 (1)	0 (0)	0 (0)	1 (<1)
Lack of efficacy	4 (3)	3 (2)	4 (3)	2 (1)
Other	1 (1)	3 (2)	1 (<1)	2 (1)

* FP ANS = fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage is 10 mg once daily.
† Percent of patients who took at least 80% of study medication.

Statistical Analysis

All patients randomly assigned to treatment received at least one dose of the study drug, and reported baseline scores were included in the analysis. Patients remained in the analysis (daily and weekly timepoints) until their efficacy scores were missing because of withdrawal or loss to follow-up. All tests performed tested two-sided hypotheses, and a difference was considered statistically significant when the two-tailed *P* value was ≤.05. Efficacy measures were changes in mean clinician- and patient-rated nasal symptoms (both total and individual nasal symptom scores), and frequency of patient- and clinician-scored ratings of overall response to treatment. It was estimated that 150 patients per treatment arm would provide approximately 80% power to detect a difference between active treatments of at least 30 in mean change from baseline in clinician-rated and patient-rated total nasal symptom scores at a significance level of .05. Demographic and baseline disease characteristics of patients were summarized by treatment group. The chi-square test was performed to compare differences with respect to sex, ethnic origin, childbearing potential, pregnancy status, type of birth control used, and clinician- and patient-rated overall evaluations. The analysis of variance F test was used to compare differences with respect to age, sex, ethnic origin, and individual and total clinician- and patient-rated symptom scores. In the RQLQ, descriptive statistics were used to evaluate differences among treatment groups for baseline scores, and descriptive and inferential statistics were used to compare the mean change from baseline RQLQ scores among and between the four treatment groups.

Safety measures included the incidence of potentially drug-related adverse events. Fisher's exact test was performed on pairs of treatments to detect differences in the number of patients with potentially drug-related adverse events overall and by body system.

RESULTS

Patient Characteristics

Six hundred patients were enrolled in the study, and 569 (95%) completed it. Eight patients discontinued the study because of adverse events, 13 withdrew because of lack of efficacy, and seven withdrew for other reasons. Demographic characteristics and com-

	FP ANS*	FP ANS + Loratadine*
	150	150
	40.7 13-80	42.2 15-78
	68 (45) 82 (55)	74 (49) 76 (51)
	17 (78) 22 (15) 11 (7)	120 (80) 26 (17) 4 (3)
	97.8 97.9	98.0 98.2
	8 (5) 3 (2) 0 (0) 4 (3) (<1)	5 (3) 0 (0) 1 (<1) 2 (1) 2 (1)

oratadine dosage is 10 mg once

gin, childbearing potential, birth control used, and erall evaluations. The used to compare differ- ethnic origin, and indi- patient-rated symptom ve statistics were used treatment groups for e and inferential statis- ean change from base- etween the four treat-

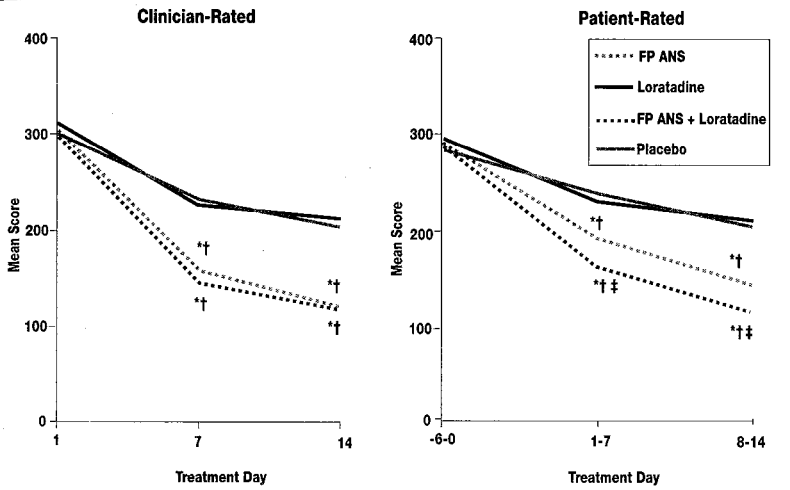
e incidence of poten- ts. Fisher's exact test ments to detect differ- with potentially drug- nd by body system.

CS

lled in the study, and patients discontinued events, 13 withdrew d seven withdrew for racteristics and com-

FIGURE 1

Clinician-rated and patient-rated total nasal symptom scores after 1 and 2 weeks of therapy for seasonal allergic rhinitis.



FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage, 10 mg once daily.
*P < .001 versus placebo.
†P < .001 versus loratadine.
‡P < .05 versus FP ANS for mean change from baseline.

TABLE 2

Baseline and Mean Change from Baseline at Day 7 and Day 14 for Clinician-Rated Nasal Symptom Scores

	Placebo Score (SE)	Loratadine Score (SE)	FP ANS Score (SE)	FP ANS + Lor Score (SE)
Total symptom score				
Baseline	302.4 (4.2)	313.3 (4.0)	304.9 (4.6)	304.9 (4.7)
Day 7	-71.0 (7.9)	-86.1 (8.6)	-149.0 (8.2) †‡	-158.0 (9.0) †‡
Day 14	-102.0 (8.8)	-102.0 (9.9)	-187.0 (8.5) †‡	-186.0 (9.4) †‡
Blockage				
Baseline	77.0 (1.4)	80.2 (1.2)	78.0 (1.4)	80.5 (1.4)
Day 7	-14.2 (2.2)	-16.8 (2.3)	-32.8 (2.2) †‡	-35.8 (2.5) †‡
Day 14	-20.0 (2.4)	-20.0 (2.6)	-42.5 (2.3) †‡	-42.6 (2.7)†‡
Discharge				
Baseline	81.3 (1.2)	85.0 (1.1)	82.8 (1.2)	83.0 (1.3)
Day 7	-18.1 (2.1)	-20.1 (2.4)	-38.5 (2.5) †‡	-40.7 (2.5) †‡
Day 14	-27.1 (2.5)	-26.9 (2.7)	-46.3 (2.6) †‡	-49.6 (2.7) †‡
Itching				
Baseline	76.0 (1.7)	76.3 (1.6)	74.4 (1.8)	73.6 (1.9)
Day 7	-19.9 (2.4)	-26.4 (2.5)	-38.6 (2.6) †‡	-41.0 (3.0)†‡
Day 14	-28.4 (2.6)	-29.3 (2.8)	-50.0 (2.5) †‡	-48.2 (2.7) †‡
Sneezing				
Baseline	68.1 (1.9)	71.7 (1.7)	69.7 (1.8)	67.8 (2.0)
Day 7	-18.9 (2.5)	-22.7 (2.7)	-38.8 (2.6) †‡	-40.1 (2.7)†‡
Day 14	-26.6 (2.7)	-26.3 (2.9)	-48.4 (2.6) †‡	-45.7 (2.9)†‡

Total symptom score is the sum of blockage, discharge, itching, and sneezing (maximum total possible = 400).
FP ANS denotes fluticasone propionate aqueous nasal spray; Lor, loratadine; SE, standard error.
† P <. 05 versus placebo.
‡ P < .05 versus loratadine.

pliance rates were similar among the treatment groups (Table 1). Approximately 90% of the patients enrolled were recruited from the offices of primary care physicians or were under no medical care for their rhinitis symptoms. Less than 10% of the patients enrolled in the study were recruited from the practices of allergists who participated in the study.

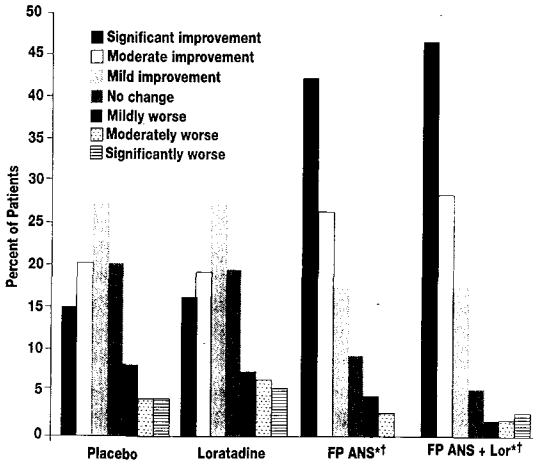
Efficacy Data

Nasal Symptoms Scores. At baseline, mean clinician-rated total nasal symptom scores were not significantly different between treatment groups. At clinic visits after 1 week of therapy (day 7), clinician-rated total nasal symptom scores were significantly lower (P < .001) in the FP ANS and FP ANS plus loratadine groups than in the loratadine only or placebo groups (Figure 1). At these timepoints, loratadine did not differ significantly from placebo aqueous nasal spray, and the FP ANS plus loratadine combination did not differ from FP ANS monotherapy (Table 2). After 2 weeks of therapy (day 14), total nasal symptoms were even further reduced in all treatment groups, with significantly lower scores in the FP ANS and FP ANS plus loratadine groups than in the loratadine or placebo groups. Again, loratadine did not differ significantly from placebo and there was no difference between the FP ANS plus loratadine combination and FP ANS monotherapy.

The data for clinician-rated individual nasal symptoms were similar to the total nasal symptom data (Table 2). At both the day 7 and day 14 assessments, scores in the FP ANS and FP ANS plus loratadine groups were significantly lower ($P \leq .05$) than loratadine alone and placebo group scores for blockage, discharge, itching, and sneezing. Clinician-rated scores for all individual nasal symptoms did not differ significantly between the FP ANS monotherapy and FP ANS plus loratadine combination treatment groups. Mean total and individual

FIGURE 2

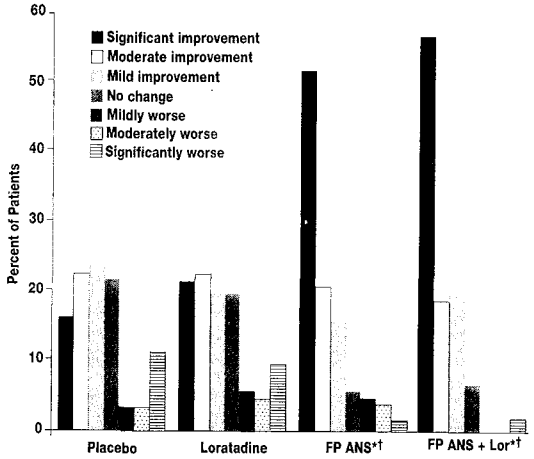
Clinician-rated overall response to therapy after 2 weeks of therapy for seasonal allergic rhinitis.



FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage, 10 mg once daily.
*P < .001 versus placebo.
†P < .001 versus loratadine.

FIGURE 3

Patient-rated overall response to therapy after 2 weeks of therapy for seasonal allergic rhinitis.



FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage, 10 mg once daily.
*P < .001 versus placebo.
†P < .001 versus loratadine.

nasal symptom scores for the loratadine and placebo treatment groups did not differ significantly at either the day 7 or day 14 evaluations.

The pattern of improvement observed in patient-rated total nasal symptom scores was similar to that reported in the clinician ratings, except that scores in the FP ANS plus loratadine combination group were significantly lower than those in the FP ANS monotherapy group at the evaluations on days 1 through 7 and days 8 through 14 (P values .006 and .017, respectively) (Figure 1). Individual nasal symptom score data generally conformed to a pattern similar to that seen for total nasal symptom scores; at days 1 through 7 and days 8 through 14, symptom scores in the FP ANS and FP ANS plus loratadine treatment groups were significantly lower than those in the loratadine only group (P <.05) and placebo group (P < .001). Individual nasal scores in the FP ANS plus loratadine group were significantly lower than those reported by patients in the FP ANS monotherapy group for nasal blockage, nasal discharge, and sneezing at days 1 through 7 and 8 through 14, and for nasal itching at days 1 through 7.

Clinicians' Overall Evaluation. In the clinician's overall evaluation at day 14, FP ANS and FP ANS plus loratadine were equivalent in efficacy and significantly more effective than placebo or loratadine only (P < .001)(Figure 2). No significant difference was observed between the loratadine and placebo treatment groups.

Patients' Overall Evaluation. Overall patient evaluations were in close agreement with overall clinical evaluations. FP ANS and FP ANS plus loratadine were significantly more effective than placebo or loratadine only (P < .001)(Figure 3), but were not significantly different from each other. No significant difference was observed between the loratadine and placebo treatment groups.

Patient-Rated Quality-of-Life Changes

At baseline, the mean global RQLQ scores and scores on each of the seven domains did not differ between or among the four treatment groups (Table 3). Significantly greater improvements in mean global RQLQ scores from baseline to day 14 were observed in the FP ANS treatment group than in the placebo and loratadine only treatment groups (P <. 001). There were no significant differences in the mean change from baseline RQLQ scores between the loratadine only and placebo groups. Significantly greater improvements were seen in the FP ANS plus loratadine group than in either the loratadine only or placebo treatment groups (P<.001); however, the RQLQ scores did not differ significantly between the FP ANS plus loratadine and FP ANS monotherapy groups.

Safety Data

The incidence and pattern of drug-related adverse events did not differ among the treatment groups.

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.