
Comparison of ebastine to cetirizine in seasonal allergic rhinitis in adults

Pierre Gehanno, MD*; Clothilde Bremard-Oury, MD†; and Philippe Zeisser, MD†

Background: Second-generation histamine H₁-receptor antagonists are accepted first-line systemic therapy for seasonal allergic rhinitis. Ebastine is a new histamine H₁-receptor blocker that may differ in efficacy from currently used second-generation agents.

Objective: To compare the efficacy of daily treatment with ebastine, 10 mg, ebastine, 20 mg, or cetirizine, 10 mg, for relieving symptoms of seasonal allergic rhinitis in adults.

Methods: In this multicenter, double-blind study, outpatients were randomized to one of three parallel treatment groups: ebastine, 10 mg, ebastine, 20 mg, or cetirizine, 10 mg once daily in the morning for a 2-week period. Patients were evaluated clinically according to symptoms, discomfort, and a global assessment at baseline and on days 8 and 15 of treatment. The total symptom score, defined as the sum of the total morning score on the day of evaluation and the total evening score on the preceding day, was the primary efficacy parameter.

Results: Ebastine, 20 mg (n = 111), ebastine, 10 mg (116), and cetirizine, 10 mg (116), were all effective for improving nasal and ocular symptoms. There was, however, a general trend towards more rapid relief of symptoms with ebastine, 20 mg, and this reached statistical significance in some efficacy parameters after the first week of treatment. In a subpopulation of 158 patients who presented with more severe symptoms, statistically significantly greater improvement was seen with ebastine, 20 mg, compared with ebastine, 10 mg, as indicated by the mean change from baseline in the total symptom score averaged over the treatment period (-13.7 ± 4.7 vs -11.8 ± 3.8 ; $P = .027$) and in the morning symptom score (-6.7 ± 2.7 vs -5.7 ± 2.2 ; $P = .042$). All three treatments were well tolerated. Dry mouth, headache, and somnolence were the most common adverse events.

Conclusion: Ebastine (10 mg), cetirizine (10 mg), and ebastine (20 mg) administered orally once daily for 2 weeks all appear to be effective for relieving the symptoms of seasonal allergic rhinitis. Ebastine, 20 mg, may have advantages over ebastine, 10 mg, and cetirizine, 10 mg, in terms of a reduced time to achieve maximal efficacy and a superior level of efficacy in patients with more severe symptoms.

Ann Allergy Asthma Immunol 1996;76:507-12.

INTRODUCTION

Histamine H₁-receptor antagonists have an established role in the treatment of seasonal allergic rhinitis.¹

Compared with older compounds of this class of drugs, the newer, second-generation H₁-receptor antagonists have a more favorable safety profile, most notably a lack of sedation. They also appear to have anti-allergy effects in addition to histamine blockade. These effects may include inhibition of release of inflammatory mediators, antagonism of these mediators, and inhibition of eosinophil recruitment.

Ebastine, 4-diphenylmethoxy-1-[3-(4-terbutylbenzoyl)-propyl]piperidine, is a selective and potent H₁-receptor

antagonist with no anticholinergic or sedative effects at therapeutic dosages.²⁻⁵ Its chemical structure resembles those of terfenadine, the first nonsedating antihistamine, and diphenylpyriline, a classical antihistamine. Ebastine is metabolized by the liver to the active compound carebastine which has an elimination half-life of 10 to 16 hours, thereby facilitating once daily administration in the clinical setting.^{6,7} In vitro, ebastine was at least as potent as terfenadine and astemizole for inhibiting histamine-induced contractions of guinea-pig isolated ileum. In vivo it was more active than either agent for protecting against histamine-induced bronchoconstriction in conscious guinea pigs.^{2,3} In human volunteers, an oral dose of ebastine, 10 mg, produced optimal inhibition of histamine-induced skin wheals.^{6,7} Ebastine, 10 to 40 mg/day orally, has been shown to be effective in the treatment of seasonal and perennial allergic rhinitis.⁸⁻¹⁰ The aim of this study was to evaluate the efficacy of ebastine, 10 mg, relative to that of ebastine, 20 mg, once daily in relieving symptoms of seasonal allergic rhinitis in adults, and to compare these dosages directly with cetirizine, 10 mg daily, a reference second-generation antihistamine.

PATIENTS AND METHODS

In this multicenter, double-blind study, patients were randomized to one of three parallel treatment groups to receive ebastine, 10 mg, ebastine, 20 mg, or cetirizine, 10 mg, once daily in the morning for a 2-week period.

Patients aged 18 to 65 years were recruited by 46 investigators in France. Inclusion criteria were as follows: diagnosis of seasonal allergic rhinitis of at least 1 year's duration, with pollen sensitization documented by positive skin prick test and/or RAST class 3-4;

* Assistance Publique Hôpitaux de Paris, Bichat-Claude-Bernard, 46 rue Henri-Huchard, 75877 Paris Cedex 18, France.

† Rhône-Poulenc Rorer, 20, Avenue Raymond Aron, 92165 Antony Cedex, France.

Rhône-Poulenc Rorer provided sponsorship for this study.

Received for publication June 16, 1995.

Accepted for publication in revised form October 5, 1995.

a minimum of two nasal symptoms rated as moderate or severe (two or three respectively on a 4-point severity scale) at the commencement of the study; and a total symptom score of ≥ 12 of 20 (sum of the scores of the five nasal and ocular symptoms rated on a 4-point severity scale on the evening preceding and on the morning of the first consultation). Patients were excluded from the study if they were pregnant or lactating, known to have allergic sinusitis requiring treatment with corticosteroids, had a diagnosis of acute asthma or nasal polyps, or if they had an upper respiratory tract infection, otitis media, or pharyngitis. Patients also excluded from the study were those with known hypersensitivity to H_1 -receptor antihistamines, desensitization to pollens during the past year or anticipated during the study period, or serious concurrent disease (renal dysfunction, hepatitis, etc), and those receiving concomitant medication(s) capable of interfering with the study medication or with evaluations (xanthine derivatives, immunoglobulins, local or systemic corticosteroids, etc). All patients freely gave their written informed consent before participating in the study. Recruitment began after the study protocol was formally approved by the ethics committee of the Versailles Hospital. The study was conducted between April 20 and July 29, 1993.

After a wash-out period that varied from 24 hours to 3 months depending upon the particular medication a patient had been receiving previously, patients were randomized to receive ebastine, 10 mg, ebastine 20 mg, or cetirizine, 10 mg daily. Placebo tablets matching ebastine, 10 mg, and placebo capsules matching cetirizine were administered to ensure double-blinding. Two tablets and one capsule were taken as a single dose in the morning on an empty stomach before breakfast for 2 weeks.

Patients were assessed at baseline (day 1) and on day 8 and day 15 of treatment. Clinical efficacy was evaluated in three ways: symptoms, discomfort, and global assessment. Patients

recorded a symptom score for nasal symptoms (nasal discharge, nasal stuffiness, sneezing, itchy nose) and for ocular symptoms (itchy/watery eyes) twice daily on a diary card using a 4-point severity scale: 0 (absent) = no symptom; 1 (mild) = symptom is present but not annoying to self; 2 (moderate) = symptom is present and annoying to self; 3 (severe) = symptom interferes with/or prevents activities of daily living. Baseline scores were recorded at entry in the presence of the investigator.

The patient also rated overall discomfort, overall nasal discomfort, and overall eye discomfort using a visual analogue scale (0 mm = no trouble; 100 mm = trouble maximal) at each visit in the presence of the investigator. In addition, both the patient and the investigator made a global assessment of treatment efficacy at the end of treatment using a 4-point scale: 0 = no effect of the medication on allergic rhinitis symptoms or impairment of symptoms; 1 = some allergic symptoms improved but overall discomfort unchanged; 2 = allergic rhinitis symptoms and overall discomfort improved; 3 = allergic rhinitis symptoms and overall discomfort greatly improved. Patients were followed up 1 week after discontinuation of study medication to assess whether their symptoms had recurred.

Spontaneously reported adverse events were recorded and routine laboratory tests were performed at the beginning and the end of the study period.

The primary efficacy criterion was the total symptom score, defined as the sum of the total morning score (sum of the five morning symptoms) on the day of evaluation and of the total evening score (sum of the five evening symptoms) on the preceding day. For each treatment group, the mean change from baseline in the total symptom score averaged over the treatment period was calculated and analyzed on a two-by-two basis using the Student's *t* test. All *P* values reported are two-tailed and a *P* value below .05 was considered to indicate statistical signifi-

ficance. Total morning, total evening, and individual nasal and ocular symptom scores were also assessed using this method. The treatment groups were also compared with respect to patient's discomfort (Student's *t* test) and global assessments of treatment efficacy (Wilcoxon test). Descriptive analysis was used for safety data.

RESULTS

A total of 343 patients were recruited for the study, which was conducted during the pollinating season (April–June), and were the basis for the intent-to-treat analysis which included all randomized patients. The three treatment groups were well matched at baseline in terms of demographic variables and history of seasonal allergic rhinitis (Table 1). Although the ratio of women to men was higher in the cetirizine group than the ebastine treatment groups, this difference was not statistically significant. Major protocol violations necessitating exclusion from the per-protocol analysis occurred in 42 cases, thus the per-protocol population consisted of 301 patients. Overall, major protocol deviations were distributed equally among the treatment groups and were related mainly to non-compliance with the washout period for previous treatment, use of prohibited medication during the treatment period, and missing diary cards.

Efficacy

The key results of the analyses performed on the intent-to-treat population are summarized in Table 2. For each treatment group, there was improvement from baseline in the total, morning, and evening symptom scores. Although the decrease in symptom scores was more marked in the ebastine, 20-mg group than in the ebastine, 10-mg and cetirizine, 10-mg treatment groups, the between-group differences in the mean change in the scores from baseline averaged over the 2-week treatment period were not statistically significant. Fewer patients in the ebastine groups than in the cetirizine, 10-mg group discontinued treatment because of lack of efficacy (Table 3).

Table 1. Demographic Data and Seasonal Allergic Rhinitis History of 343 Patients in the 'Intent-to-Treat' Population

	Ebastine, 10 mg n = 116	Ebastine, 20 mg n = 111	Cetirizine, 10 mg n = 116
Age,* yr	35.2 ± 11.7	35.0 ± 11.9	34.4 ± 9.7
Sex, male/female	53/63	56/55	41/75
Weight,* kg	66.3 ± 13.4	69.1 ± 12.3	63.3 ± 12.2
Height,* cm	167.5 ± 9.0	168.7 ± 9.0	166.7 ± 8.4
Duration of seasonal allergic rhinitis,* yr	9.1 ± 6.9	9.5 ± 7.4	9.0 ± 6.2
Duration of current episode,* days	26.4 ± 25.2	25.4 ± 20.7	28.4 ± 23.0
Associated conjunctivitis	68 (58.6%)	71 (64.0%)	68 (58.6%)

* Mean ± SD.

Table 2. Patient-Rated Symptom Scores at Baseline and the Mean Change from Baseline (± SD) Averaged Over the 2-Week Treatment Period in the 'Intent-to-Treat' Population

	Ebastine, 10 mg n = 116	Ebastine, 20 mg n = 111	Cetirizine, 10 mg n = 116
Total score (morning + evening scores) at baseline	18.7	19.0	19.0
Mean change ± SD	-9.8 ± 4.6	-10.6 ± 5.4	-9.7 ± 5.0
Morning score* at baseline	9.2	9.6	9.5
Mean change ± SD	-4.9 ± 2.4	-5.0 ± 3.1	-4.6 ± 3.0
Evening score* at baseline	9.4	9.5	9.5
Mean change ± SD	-4.9 ± 2.8	-5.5 ± 2.8	-5.0 ± 2.7

* Sum of five individual symptom scores (nasal discharge, nasal stuffiness, sneezing, itchy nose, and itchy/watery eyes).

Table 3. Number of Patients Who Withdrew from Treatment for Seasonal Allergic Rhinitis Because of Lack of Efficacy

	Ebastine, 10 mg n = 116	Ebastine, 20 mg n = 111	Cetirizine, 10 mg n = 116
Withdrawal for lack of efficacy	2 (1.7%)	1 (0.9%)	5 (4.3%)

Dropouts due to lack of efficacy generally occurred during the first week of treatment. Ebastine, 20 mg appeared to achieve maximal efficacy more quickly than either ebastine, 10 mg, or cetirizine, 10 mg (Fig 1). After 1 week of treatment, the mean change in the total symptom score from baseline was significantly greater in the ebastine, 20-mg group than in the ebastine 10-mg and cetirizine, 10-mg groups (-11.9 vs -10.0 [$P = .030$] and -9.9 [$P = .027$], respectively). The results of the per-protocol analysis were similar to those of the intent-to-treat analysis.

Individual nasal and ocular symptom scores followed the same trend as total symptom scores. There was a statistically significant difference between ebastine, 20 mg, and ebastine,

10 mg, in the mean change from baseline in the scores for itchy/watery eyes (-1.0 vs -0.7; $P = .035$).

An improvement in patient's discomfort as assessed by the visual analogue scale was observed in all treatment groups (Fig 2), with ebastine, 20 mg, being significantly more effective than cetirizine, 10 mg, after the first week of treatment ($P = .048$). There was also greater improvement in patient's discomfort in the ebastine, 10-mg group compared with the cetirizine group, but the difference did not reach statistical significance.

The global assessment of efficacy by both the investigator and the patient at the end of treatment favored ebastine, 20 mg; the difference was statistically significant vs cetirizine, 10 mg, in the investigator's opinion ($P =$

.048). Overall, the investigators observed an improvement in both allergic rhinitis symptoms and overall discomfort in 84.6% of patients in the ebastine, 20-mg group, compared with 77.8% in the ebastine, 10-mg group, and 72.7% in the cetirizine, 10-mg group.

A subgroup analysis was performed in patients with more severe symptoms at baseline. This subgroup was defined retrospectively as those patients with a baseline symptomatic score greater than the mean of the entire patient population (ie, 18.8). The subpopulation comprised 158 patients: ebastine, 20 mg ($n = 57$), ebastine, 10 mg (51), and cetirizine (50). Ebastine, 20 mg, was significantly superior to ebastine, 10 mg, as indicated by the mean change from baseline in the total symptom score averaged over the treatment period (-13.7 ± 4.7 vs -11.8 ± 3.8; $P = .027$) and in the morning symptom score (-6.7 ± 2.7 vs -5.7 ± 2.2; $P = .042$). There was a similar trend favoring ebastine, 20 mg, over cetirizine, 10 mg, for the total symptom score (-13.7 ± 4.7 vs -11.8 ± 5.9; $P = .07$) and morning symptom score

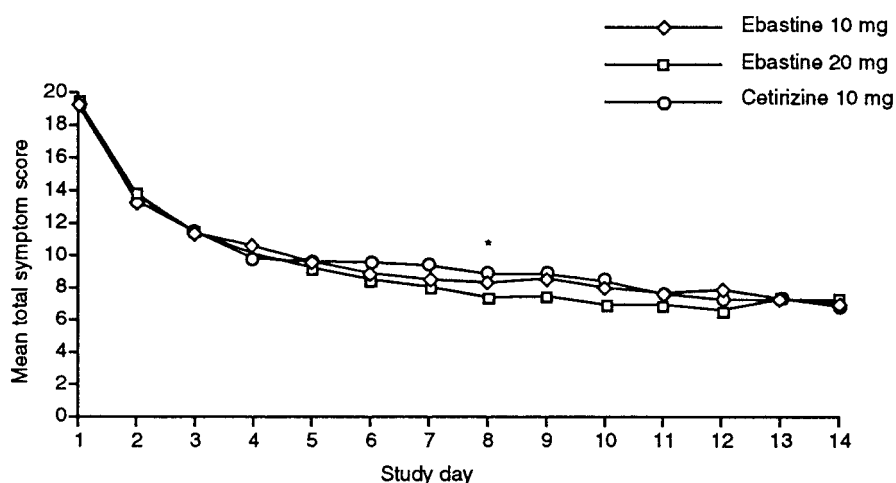


Figure 1. Mean total symptom scores (intent-to-treat analysis) for 343 patients with seasonal allergic rhinitis treated with ebastine, 10 mg, ebastine, 20 mg, or cetirizine, 10 mg once daily for 2 weeks; * $P = .03$ for ebastine, 20 mg, vs ebastine, 10 mg, and for ebastine, 20 mg, vs cetirizine, 10 mg.

(-6.7 ± 2.7 vs -5.7 ± 3.4 ; $P = .09$), but the differences observed were only numerical because of the greater standard deviation from the mean. All treatment groups showed similar results for the evening symptom scores.

A total of 302 patients completed diary cards for the week following the discontinuation of treatment; 35% of these patients were prescribed medication to treat recurring symptoms of allergic rhinitis. This mean percentage is difficult to interpret since patients who finished the study during the pollen season were likely to be more prone to retreatment than those who finished at the end of the season.

Safety

The pattern and incidence of adverse events was similar in all three treatment groups (Table 4). The incidence of dry mouth, asthenia, and somnolence were lowest in the ebastine, 10-mg group. If asthenia and somnolence are considered together as representing sedative effects, the differences are more marked, with an incidence of 5.2% for the ebastine, 10-mg group, compared with 13.0% for the cetirizine, 10-mg group, and 9.9% for the ebastine, 20-mg group. The high incidence of headache reported in the ebastine, 20-mg group,

was unexpected since the incidence of headache at this dosage was no greater than that of placebo in previous clinical studies.^{8,11}

Two patients in the ebastine, 10-mg group, and one patient in the cetirizine, 10-mg group, discontinued treatment because of adverse events (hot flushes and an acute episode of asthma in the ebastine group; abdominal pain in the cetirizine group). Somnolence was also reported by one patient treated with ebastine, 10 mg, and by one patient treated with cetirizine, both of

whom discontinued treatment because of lack of efficacy.

There were no clinically relevant abnormalities related to drug treatment in routine laboratory tests. One patient in the cetirizine group was withdrawn from the study because of hepatitis A.

DISCUSSION

In earlier studies in patients with seasonal allergic rhinitis, ebastine, 10 mg once daily, was shown to be superior to placebo and equivalent to terfenadine, 60 mg twice daily, and equivalent to astemizole, 10 mg once daily.¹² There was no placebo group in the current study; the results demonstrate that ebastine, 10 and 20 mg once daily, are at least equivalent in efficacy to cetirizine, 10 mg once daily, for the treatment of seasonal allergic rhinitis in adults. Cetirizine is a second-generation antihistamine that has demonstrated efficacy at a dosage of 10 mg once daily in the treatment of seasonal allergic rhinitis¹³ and was marketed in Europe at the time the study was conducted. There was a general trend towards greater efficacy with ebastine, 20 mg, although statistical analyses revealed significant differences only for the reduction in patients' overall discomfort after the first week of treatment and for the investigators' global assessment of efficacy. Globally, ebas-

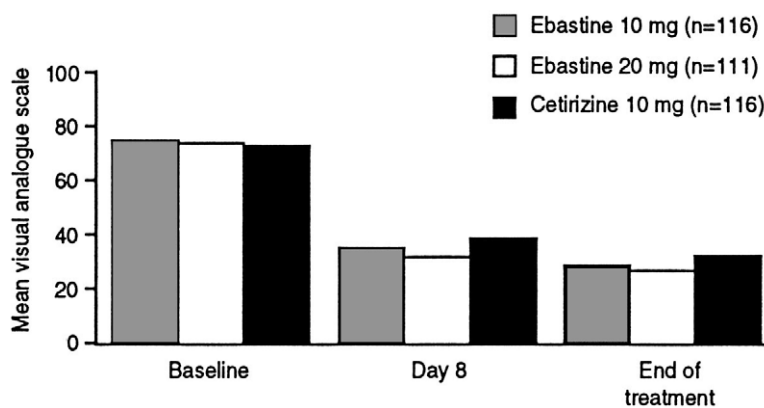


Figure 2. Mean visual analogue scale ratings (intent-to-treat analysis) for overall discomfort in 343 patients with seasonal allergic rhinitis treated with ebastine, 10 mg, ebastine, 20 mg, or cetirizine, 10 mg once daily for two week; * $P < .05$ for ebastine, 20 mg, vs cetirizine, 10 mg.

Table 4. Most Commonly Reported Adverse Events in 343 Patients with Seasonal Allergic Rhinitis Treated with Ebastine, 10 mg, Ebastine, 20 mg, or Cetirizine, 10 mg, Once Daily for Two Weeks

Adverse Event	Ebastine, 10 mg n = 116 (%)	Ebastine, 20 mg n = 111 (%)	Cetirizine, 10 mg n = 116 (%)
Asthenia	1 (0.9)	3 (2.7)	6 (5.2)
Dry mouth	0 (0.0)	5 (4.5)	7 (6.0)
Headache	9 (7.8)	14 (12.6)	5 (4.3)
Somnolence	5 (4.3)	8 (7.2)	9 (7.8)
All events	35 (30.2)	39 (35.1)	31 (26.7)

tine, 10 mg, and cetirizine, 10 mg, appeared to possess similar efficacy. In addition, maximal efficacy may be achieved more quickly with ebastine, 20 mg, than with ebastine, 10 mg, or cetirizine, 10 mg. Subgroup analyses revealed that in patients with more severe symptoms at baseline, ebastine, 20 mg, was significantly more effective than ebastine, 10 mg, in improving symptoms.

In this study, both ebastine and cetirizine were well tolerated. The most commonly reported adverse events were dry mouth, headache, and somnolence. The incidence of somnolence and asthenia reported with cetirizine was higher than that associated with ebastine. The incidence of somnolence with cetirizine has also been noted to be higher than other second-generation antihistamines,^{1,14} with the incidence increasing in frequency at higher dosages as shown in the dosage range of cetirizine, 5 to 20 mg, in a placebo-controlled trial.¹⁵ In addition, a single 10-mg dose of cetirizine has been shown to cause mild impairment of performance, notably during car driving by healthy volunteers, with alcohol having additive effects to those of cetirizine.¹⁶ In contrast, in a similar clinical pharmacology study, ebastine (20 mg once daily for 1 week) did not impair skilled performance in objective and subjective tests, including simulated driving, and there was no clinically noteworthy interaction between ebastine and alcohol.¹⁷ The relatively high incidence of headache in the present study was probably an artifact of the study since previous studies have not

reported differences between ebastine and placebo with respect to the incidence of headache.

The second-generation antihistamines terfenadine and astemizole have the potential to prolong the QT_c interval and induce fatal ventricular arrhythmias, although this is generally associated with high plasma concentrations occurring in overdose situations or when terfenadine or astemizole is coadministered with drugs such as macrolide antibacterials, fluoxetine, itraconazole, and ketoconazole that inhibit hepatic microsomal enzymes.^{18,19} To date this has not been reported for ebastine. Indeed, pooled electrocardiogram results for 1076 patients enrolled in five multicenter clinical trials revealed no statistically significant differences in maximum observed QT_c intervals during the double-blind period for patients who received placebo (n = 360) compared with those who received ebastine, 10 mg (272) or ebastine 20 mg (444) once daily.²⁰ None of the patients experienced a QT_c interval greater than 500 msec or a change from baseline QT_c >15%. Furthermore, no serious cardiac events were noted in any of the 226 patients who underwent 24-hour Holter monitoring.

A characteristic feature of the symptom complex of seasonal allergic rhinitis is the variability in symptom severity.²¹ In this context, a second-generation antihistamine that could offer practitioners the option of modifying the daily dosage according to symptom severity, within a well-tolerated dosage range as is the case for ebastine, 10 to 20 mg, could provide

further advantages in the management of seasonal allergic rhinitis.

ACKNOWLEDGMENTS

We thank the numerous investigators who participated in this study. We also acknowledge the assistance of Mrs. C. Vessereau for advice in statistical analysis.

REFERENCES

- Horak F. Seasonal allergic rhinitis. Newer treatment approaches. *Drugs* 1993;45:518-27.
- Roberts DJ, Spickett RWJ, Moragues J, et al. Ebastine, a new non-sedating antihistamine. Sydney. *Xth Int Cong Pharmacol* 1987:1006.
- Moragues J, Roberts DJ. Ebastine. *Drugs Fut* 1990;15:674-9.
- Vincent J, Sumner DJ, Reid JL. Ebastine: the effect of a new antihistamine on psychomotor performance and autonomic responses in healthy subjects. *Br J Clin Pharmacol* 1988;26:503-8.
- Hopes H, Meuret GH, Ungethüm W, et al. Placebo controlled comparison of acute effects of ebastine and clemastine on performance and EEG. *Eur J Clin Pharmacol* 1992;42:55-9.
- Torrent J, Barbanj MF, Izquierdo I, et al. Ebastine pharmacokinetics and antihistamine effect in man (Abstract). *N Engl Reg Allergy Proc* 1988;9:474.
- Vincent J, Limiñana R, Meredith PA, Reid JL. The pharmacokinetics, antihistamine and concentration-effect relationship of ebastine in healthy subjects. *Br J Clin Pharmacol* 1988;26:497-502.
- de Molina M, Cadahia A, Cano L, Sanz A. Efficacy and tolerability of ebastine at two dose levels in the treatment of seasonal allergic rhinitis. *Drug Invest* 1989;1:40-6.
- Picado Vallés C, Cadahia Garcia A,

-
- Cisteró Bahima A, et al. Ebastine in perennial allergic rhinitis. *Ann Allergy* 1991;67:615-8.
10. Ankier SI, Warrington SJ. A double-blind placebo-controlled study of the efficacy and tolerability of ebastine against hayfever in general practice patients. *J Intern Med* 1989;226:453-8.
 11. Luria X, Blakke O, Periz JP. Ebastine: a non sedative antihistamine H₁ with side effect profile similar to that of placebo. IV World Conference on Clinical Pharmacology and Therapeutics, Mannheim, 1989:04.31.
 12. Luria X, Bakke O. Ebastine (LAS W-090): Overview of clinical trials. *Drugs Today* 1992;28(Suppl B):69-79.
 13. Spencer CM, Faulds D, Peters DH. Cetirizine. A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs* 1993;46:1055-80.
 14. Backhouse CI, Renton R, Fidler C, Rosenberg RM. Multicentre, double-blind comparison of terfenadine and cetirizine in patients with seasonal allergic rhinitis. *Br J Clin Pharmacol* 1990;44:88-91.
 15. Falliers CJ, Brandon ML, Buchman E, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Ann Allergy* 1991;66:257-62.
 16. Ramaekers JG, Uiterwijk MM, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol* 1992;42:363-9.
 17. Mattila JM, Kuitunen T, Pletan Y. Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects. *Eur J Clin Pharmacol* 1992;43:179-84.
 18. Nightingale SL. Warnings issued on non-sedating antihistamines terfenadine and astemizole. *JAMA* 1992;268:705.
 19. Quinn DI, Day RO. Drug interactions of clinical importance. An updated guide. *Drug Saf* 1995;12:393-452.
 20. Connell L, Alderfer V, Garcia J. Electrocardiographic evaluation of ebastine in double-blind allergic rhinitis clinical trials [poster]. 16th European Congress of Allergology and Clinical Immunology, Madrid, 25-30 June, 1995.
 21. Ricketti AJ. Allergic rhinitis. In: Patterson R, eds. *Allergic diseases, diagnosis and management*. 4th edition. Philadelphia: JB Lippincott Company, 1993:225-53.

Request for reprints should be addressed to:
Prof. Pierre Gehanno
Assistance Publique Hôpitaux de Paris
Bichat-Claude-Bernard
46 rue Henri-Huchard
75877 Paris Cedex 18
France