

Original article

Mizolastine in the treatment of seasonal allergic rhinoconjunctivitis: a European clinical experience with 5408 patients managed in daily practice (PANEOS SAR Study)

Background: Mizolastine, a potent H₁ antihistamine with additional antiallergic properties, is marketed for the treatment of allergic rhinoconjunctivitis and urticaria. The objective was to investigate the safety and effectiveness of mizolastine under conditions of daily practice in patients with seasonal allergic rhinoconjunctivitis (SAR).

Methods: In an open multicenter study, mizolastine 10 mg daily was administered for 14 days during the pollen season. Nasal and ocular symptoms, time to onset of symptom relief, and effect of the drug on diurnal alertness were evaluated. Safety was evaluated on the basis of self-reported adverse events (AE).

Results: A total of 5408 patients (36 ± 14 years of age, females = 57%) with a history of SAR for 8 ± 9 years were treated for a mean of 17.1 ± 5.0 days. SAR symptoms improved in 93% and decreased by at least 50% in 86% of patients; 78% reported improvement after the first drug intake and 51% from the first hour. Sixty-nine percent considered mizolastine more effective than other antihistamines taken previously. The incidence of AE was low (3.8%).

Conclusions: The high responder rate, the rapid onset of action, and the low incidence of AE observed in this large multicenter study confirm the previously reported beneficial efficacy and safety of mizolastine in the management of SAR.

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Allergic rhinitis is an IgE-mediated inflammatory disease characterized clinically by nasal pruritus, sneezing, rhinorrhea, and nasal obstruction, and is usually accompanied by conjunctival symptoms. It may be seasonal and/or perennial, depending on the causative allergens: grass, tree, or weed pollens in seasonal allergic rhinoconjunctivitis (SAR); house-dust mites, mold spores, or animal dander in perennial allergic rhinitis (PAR) (1). It has been estimated that SAR affects as many as 10% of the European population (2), and there are reports suggesting a substantial increase in the prevalence of allergic conditions over the past few decades. For example, surveys in Switzerland show that the prevalence of SAR increased from 0.28% in 1926 to 14.2% in 1995 (3). It tends to affect younger persons more than older adults, the prevalence being highest among patients aged 15–19 years, and it decreases after the age of 40 (2). Patients with allergic rhinitis are reported to have impaired quality of life (4), resulting in an important loss of productivity and in absenteeism from workplace and

classroom, contributing to the high economic and personal costs of allergic rhinitis (5). Thus, relief of symptoms is a priority for patients with SAR. It is generally agreed that H₁ antihistamines are the first-line treatment for patients with mild to moderate SAR (6).

Currently marketed in most European countries, mizolastine is a potent, specific, and selective histamine H₁-receptor antagonist with additional antiallergic properties (7, 8). Its efficacy in the treatment of SAR and PAR, as well as urticaria, has been extensively demonstrated in controlled clinical trials (9–15). However, these studies included rather highly selected patient populations. Therefore, further confirmation of the drug's effectiveness and safety in a wider population under day-to-day conditions of daily medical practice is deemed desirable (16). The present study was designed to investigate the effectiveness and safety of mizolastine in the treatment of SAR under conditions of daily practice in a large population that more closely reflect the reality of medical practice.

Material and methods

Study design

This was an open, noncontrolled multicenter, observational, cohort study conducted during the 1998 pollen season in four European countries. Due to the wide dispersion of the 1083 participating centers, pollen counts were not performed. However, only those potential study patients presenting with typical SAR symptoms when seen by the investigator were included. Written informed consent was obtained from patients, and local ethics committees approved the study protocol (where applicable). The patients were recruited in either hospital- or community-based practices by the investigators, who were general practitioners, allergists, dermatologists, ENT specialists, and pulmonologists.

The patients were seen twice, first on the day of inclusion (D0) and then 14 days later (Dend) (28 days in Switzerland). At each of these visits, the investigators questioned the patients about the severity of their present and, on D0, past SAR symptoms, following a semistructured outline. At each visit, the patients were asked to rate the severity of their nasal symptoms (itchy nose, runny nose, sneezing, and nasal obstruction) and ocular symptoms (itchy eyes, watering of the eyes, and redness of the eyes) over the previous 7 days, on a four-point scale for each of these symptoms: 0=absent; 1=symptom present, but does not bother the patient; 2=symptom moderate, but does not prevent the patient from carrying out normal activity nor interfere with sleep; 3=symptom severe, and prevents the patient from performing normal activities and/or interferes with sleep. The sum of the scores of the nasal symptoms, including obstruction, could range from 0 to 12, and it could range from 0 to 9 for the three ocular symptoms.

Inclusion criteria

Children of at least 12 years of age and adults seen by the investigators for treatment of current SAR were considered to be candidates for inclusion. They had to be symptomatic on D0. The diagnosis of SAR was confirmed by positive skin test and/or serologic assay for specific IgE and/or a nasal allergen challenge test with pollen.

Exclusion criteria

As for any observational cohort study, patients were excluded if they were receiving drugs that are subject to contraindications or special precautions according to the drug's summary of product characteristics (i.e., macrolid antibiotics or systemic imidazol antifungals). Women who were pregnant were excluded. Patients with associated asthma were not excluded, even though their asthma was not assessed in this study.

Treatment

The study drug, mizolastine, was administered at the recommended dose (one 10-mg tablet once a day in the morning or evening at patient's convenience) for 14 days, except in Switzerland, where it was taken for 28 days. Patients were required to discontinue any other antihistamine being taken before D0, but they were not required to stop taking other nonantihistamine drugs during the study period.

Assessment of efficacy

The primary outcome measure was the assessment of the severity of the nasal and ocular symptom scores on D0 and Dend over the past 7 days. In addition, on the first day, the patients were asked to judge the time to onset of symptom relief, if any, either 30 min, 1 h, 2 h, or more than 2 h after the first dose of mizolastine. They were asked to report their consumption of other drugs that may have been taken

for treatment of nasal and ocular symptoms during the present study period. They were asked to make a global assessment of the effectiveness of mizolastine, using the following options: symptoms improved, were unchanged, or were worse than before. They were also asked to give their opinion of the efficacy of mizolastine in comparison with previous oral antihistamines they may have taken for treatment of their symptoms. In addition, the investigators asked the patients about possible diurnal alertness problems during the previous week as a result of the nasal and ocular symptoms (0=not troubled, up to 6=extremely troubled).

Assessment of safety

Safety was evaluated on the basis of spontaneously reported adverse events (AE). Those reported by the patient and/or by the investigator were recorded at the end of the study.

Statistical analysis

Clinical efficacy data were analyzed on an "intent-to-treat" population, defined as patients who presented with the study disorder (SAR), those who had taken at least one dose of the study treatment, and those who had had a second visit. The primary criteria of effectiveness were based on the difference from baseline in the mean total symptom score (TSS), defined as the sum of the nasal and ocular scores and in the mean severity of the individual nasal and ocular scores. In addition, an analysis was made of subgroups defined before the statistical analysis, on the basis of the severity of ocular and nasal symptoms on D0. The change from baseline of the severity of the individual symptoms was also measured. Responders were defined as patients whose TSS on Dend was at least 50% less than that on D0. For the difference between D0 and Dend, a *P* value of <0.05 was considered statistically significant. Assessment of safety was based on data collected from all patients who had taken at least one dose of mizolastine.

Results

The demographic characteristics and baseline (D0) symptom scores are summarized in Table 1. The included population was representative of the general population of patients with SAR who use antihistamines, with respect to mean age, sex ratio, associated allergic diseases, perennial allergy, pollen sensitivity, and previous and current treatments. Of the 5408 patients included (2845 in Germany, 1800 in Spain, 557 in Greece, and 206 in Switzerland), 4584 (84.7%) completed the study. As observed in Fig. 1, 431 patients (7.9%) did not complete the study for various reasons, including 132 (2.4%) who discontinued the treatment because of an apparent lack of efficacy. Eighty-one patients (1.8%) were subsequently found not to be suffering from SAR at the moment of inclusion and were therefore excluded from the analysis. A total of 5084 patients (94%) were included in the "intent-to-treat" population analysis. No country effect was observed on any of the parameters investigated.

Efficacy

The average decrease of symptom scores from D0 to Dend is shown in Fig. 2. After 17.1 ± 5.0 days of mizolastine treatment, statistically significant decreases

Table 1. Demographic characteristics and baseline symptom scores of sample

Age mean $\pm$ SD (years)	36 $\pm$ 14
Sex n (%)	
M	2126 (43)
F	2851 (57)
Duration of SAR (years) mean $\pm$ SD	8 $\pm$ 9
Symptom scores (mean $\pm$ SD)*	
Total	12.0 $\pm$ 3.7
Nasal	7.8 $\pm$ 2.1
Ocular	4.5 $\pm$ 2.3
Diurnal alertness problems**	3.1 $\pm$ 1.4
Symptoms severity (moderate to severe) n (%)	
Nasal	3778 (75)
Ocular	2606 (52)
Pollen sensitivity n (%)	
Grass	2743 (54)
Trees	2662 (52)
Weeds	744 (15)
Associated allergic diseases n (%)	
Asthma	827 (17)
Perennial allergy	961 (21)
Others	661 (14)
Diagnostic methods n (%)	
Skin tests	3229 (63)
Specific IgE	1206 (24)
Others	410 (8)
Treatments n (%)	
Prior oral anti-H ₁	3844 (81)
Current anti-H ₁ (before study inclusion)	1638 (33)
Oral	1150 (70)
Nasal	880 (54)
Ocular	598 (36)
Concomitant treatment n (%)	2360 (55)
Nasal	1582 (67)
Ocular	978 (41)
Others	868 (37)

* Ranges: nasal (0–12); ocular (0–9), total (0–21).

** Ranges: 0–6.

+ 107 missing data.

from baseline were observed in mean TSS (-72%) and in the nasal (-70%) and ocular (-75%) symptom scores. A total of 4078 patients (86%) were responders; i.e., their total symptom score had decreased by at least 50%. Improvement of the TSS was significantly higher in patients with severe nasal, ocular, and nasal blockage scores at baseline in comparison with less severely symptomatic patients (Table 2).

The overall effect of mizolastine according to the patients' assessment was judged "improved" in 93%, "unchanged" in 6%, and "worsened" in 1% of the patients. The percentages of patients rating their nasal symptoms (itching, sneezing, rhinorrhea, and nasal obstruction) as absent (0), mild (1), moderate (2), or severe (3) on D0 and Dend are shown in Fig. 3. It is evident that the severity of each of these scores was reduced during the study period. In addition, 2655/3854 (69%) felt that mizolastine was more effective than the antihistamine they had used previously, 1122/3854 (29%) that it was similar to their previous antihistamine therapy, and 77/3854 (2%) that it was not as good as their previous antihistamine therapy.

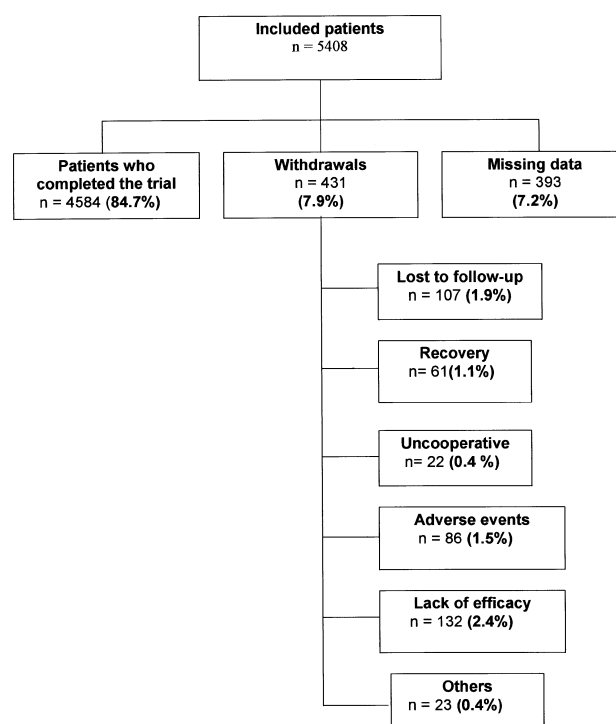


Figure 1. Patient outcome.

As shown in Fig. 4, symptom improvement was reported by 1709/3341 patients (51%) in the first hour after taking the first dose of mizolastine, and during the first day of treatment in 3400/4380 patients (78%). Moreover, mizolastine treatment was associated with a reduction in diurnal alertness impairment scores between D0 (3.1) and Dend (1.0).

On inclusion, 55% of the patients were using at least one other antiallergic treatment. During the trial, one-third (1426/4282) of those taking another drug for their

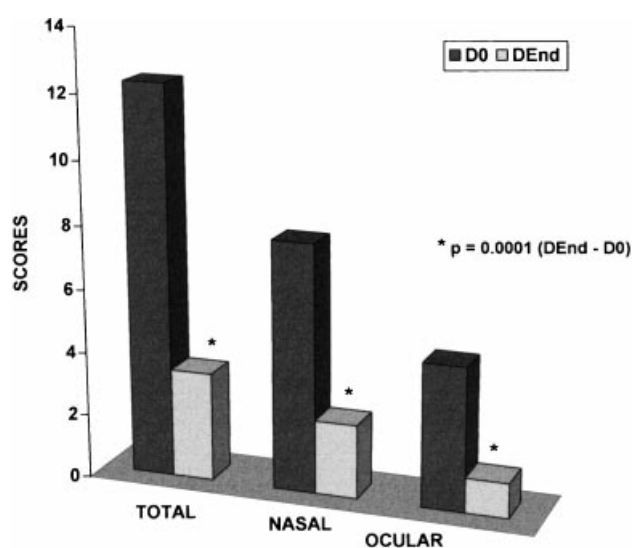


Figure 2. Mean reductions from baseline in total, nasal, and ocular scores.

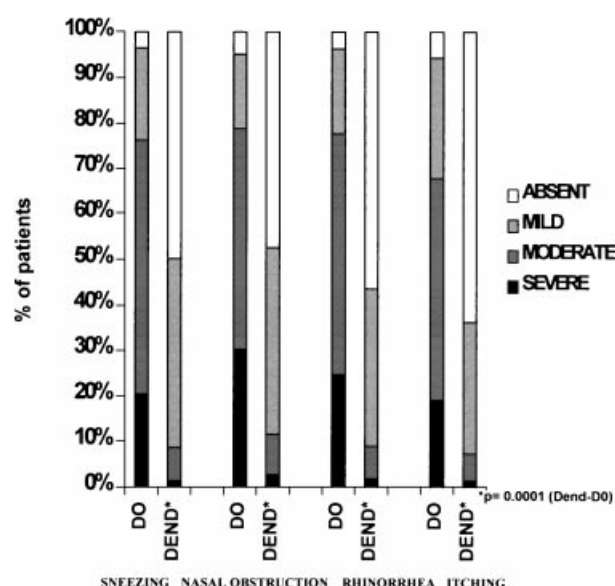


Figure 3. Changes in nasal individual symptoms. Percentage of patients.

nasal or ocular symptoms changed this treatment: 490/540 (91%) patients decreased or stopped a corticosteroid, 379/400 (95%) reduced or stopped a vasoconstrictor, 338/387 (87%) reduced or stopped a cromone treatment for nasal symptoms (Fig. 5), and 399/452 (88%) decreased or stopped their ocular cromone treatment.

Safety

Of the 5408 patients included in the safety analysis, 204 (3.8%) reported one or more emergent AE (Table 3). The most commonly reported AE are listed in Table 3. The incidence of these events was independent of the patient's age (Table 4). The severity of the reported AE was mild or moderate and resolved spontaneously, and the number of patients who discontinued treatment

Table 2. Changes in total symptom score between D0 and Dend (mean $\pm$ SD) according to score severity

	Total symptom score ^o (range, 0–21)
All patients <i>n</i> = 4741	$-8.9 \pm 4.3^*$
Patients with nasal score on D0 (range, 0–12)	
< 8 (<i>n</i> = 2072)	$-6.8 \pm 3.3^*$
≥ 8 (<i>n</i> = 2669)	$-10.6 \pm 4.2^*$
Patients with ocular score on D0 (range, 0–9)	
< 6 (<i>n</i> = 2946)	$-7.6 \pm 3.5^*$
≥ 6 (<i>n</i> = 1795)	$-11.2 \pm 4.5^*$
Patients with nasal obstruction score on D0 (range, 0–3)	
< 2 (<i>n</i> = 1021)	$-7.1 \pm 3.8^*$
= 2 (<i>n</i> = 2295)	$-8.7 \pm 3.8^*$
= 3 (<i>n</i> = 1425)	$-10.5 \pm 4.7^*$

^o Calculated from sum of nasal (including obstruction) and ocular scores.

* $P = 0.0001$.

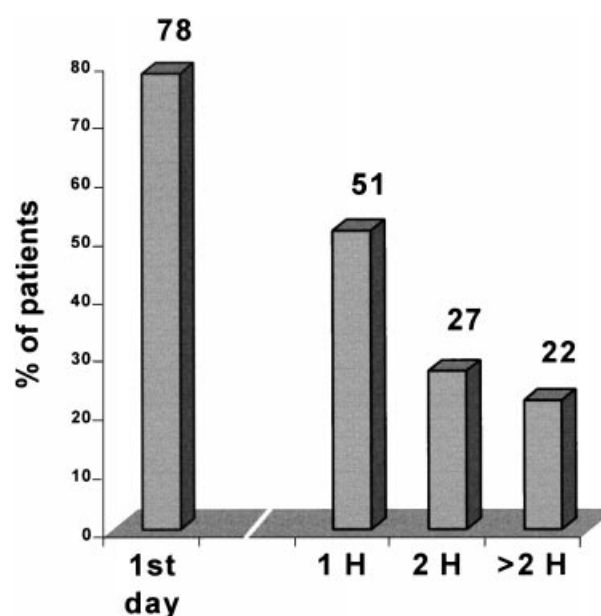


Figure 4. Patients' assessment on symptom relief onset action over first treatment day. Percentage of patients.

because of an AE was low (1.6%). Only one adverse event was reported as serious: one patient required hospitalization for aggravation of pre-existing asthma.

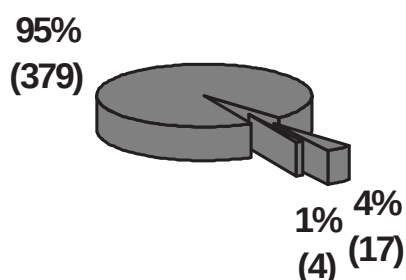
Discussion

This is the first study in which data were collected on the effectiveness and safety of mizolastine in the treatment of SAR in a large number of patients under conditions of daily practice. The duration of treatment in this study was similar to that usually recommended for patients with SAR, and it corresponds to the common demand of health authorities. Treatment efficacy was assessed on the basis of standard criteria that are commonly used in studies of this kind (17). The number of premature withdrawals remained low, indicating good acceptability of the drug and the study protocol.

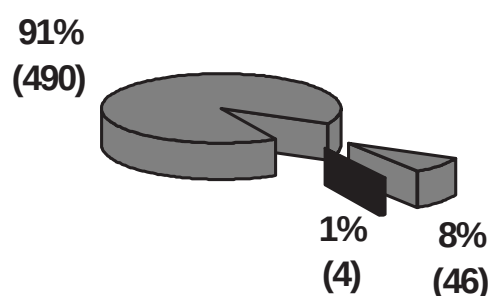
The data show that mizolastine is effective in the control of the most important symptoms of SAR under normal conditions of prescription in a majority of patients. Both nasal and ocular symptoms were significantly improved by mizolastine. Interestingly, improvement was greater in patients with the more severe symptoms at baseline. However, the lack of a control group does not allow us to exclude a simple "regression to the mean" effect as a possible explanation for this observation.

Most of the patients in the present study judged their rhinoconjunctivitis to be improved by mizolastine. This was confirmed by the fact that a majority of them could be classified as responders; that is, their total symptom score was at least 50% lower at the end of the treatment period than it was at baseline. In addition, only a small proportion of the patients withdrew from the study

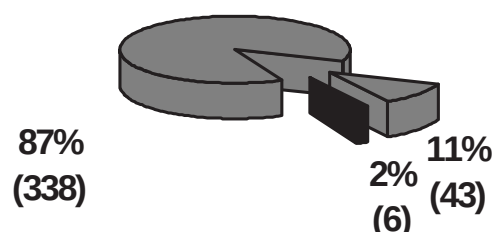
Vasoconstrictors



Corticosteroids



Cromones



■ Increased ■ Decreased or Stopped ■ Introduced

Figure 5. Changes in concomitant treatments – percentage of patients that increased, introduced and decreased, or stopped nasal treatment.

because of an apparent lack of efficacy. These results are in agreement with results of previously published clinical studies (9-11). It is of interest to note that the degree of symptom improvement reported here is higher than that reported in those earlier studies. Moreover, more than half of the patients in the present study reported symptom improvement within 1 h after taking the first dose of the drug, and symptoms were controlled during the first day of mizolastine treatment in nearly 80% of those who responded. The data also show that symptom relief observed on the first day persisted throughout the trial. These observations confirm the

rapid onset of action and the sustained efficacy of mizolastine. Rapid symptom relief had been demonstrated previously in a placebo-controlled study, with an onset of action within 2 h after the first dose of the drug, the first assessment point, and a greater symptom improvement than cetirizine, another second-generation antihistamine, on days 2 and 3 of treatment ($P=0.03$ and $P=0.05$, respectively) (11). A large proportion of patients in the present study considered mizolastine to be superior to their previous antihistamine treatment.

Between 40% and 65% of patients with allergic rhinitis have nasal congestion (18). This symptom can produce quite severe impairment of physical and mental functioning in patients with allergic rhinitis, and many patients report poor quality of life, including difficulty

Table 3. Safety data (adverse event [AE])

Number of patients exposed	5408
Average duration of treatment (days)	17.1 ± 5.0
Number of patients with ≥ 1 AE (%)	204 (3.8)
Number of patients with ≥ 1 AE leading to withdrawal (%)	86 (1.6)
Number of patients with serious AE (%) (aggravation of pre-existing asthma)	1 (0.02)
AE reported more than once – n (%) (tiredness, asthenia, fatigue)	86 (1.6)
Other AE reported occasionally n (%)	
Headache	16 (0.3)
Increased appetite	23 (0.3)
Drowsiness/somnolence	18 (0.4)
Dry mouth	11 (0.2)

Table 4. Distribution of adverse events according to age group

Age (years) (n*)	n (%) of patients reporting ≥ 1 AE
Total population (5408)	204 (3.8)
< 25 (1172)	39 (3.3)
25–39 (2216)	85 (3.8)
40–64 (1710)	75 (4.4)
65–74 (132)	4 (3.0)
> 75 (42)	1 (2.3)

* 136 missing data.

in sleeping or somnolence, due to nasal obstruction (18). This important symptom was reported by a majority of the patients in the present study, and it was effectively relieved by mizolastine, as had been demonstrated in an earlier placebo-controlled study in patients suffering from PAR (12). This clinically relevant effect might be related to the inhibitory effect of mizolastine on 5-lipoxygenase (8), an enzyme that is involved in the synthesis of cys-leukotrienes. These mediators are believed to have a role in the pathogenesis of nasal obstruction (19).

Among other classes of drugs currently used to treat SAR, topical nasal vasoconstrictors have a limited place; they should not be prescribed for more than 7-10 days because of the risk of inducing rhinitis medicamentosa. Mast-cell stabilizers, such as cromones, are safe topical drugs, primarily used prophylactically. However, since they must be administered four times per day, poor patient compliance is often associated with their use. Topical corticosteroids are particularly useful for treating patients with more severe allergic rhinitis (6). In the present study, mizolastine favorably reduced the use of nasal vasoconstrictors and corticosteroids, as well as nasal and ocular cromones. The reduction of concomitant drug consumption could contribute to a significant reduction in expenditures associated with the treatment of SAR.

Patients with allergic rhinitis not only experience nasal and ocular symptoms but may also suffer from sleep disturbance and daytime fatigue secondary to sleep fragmentation (18). In the present study, this disease-related impairment of these symptoms was reduced by mizolastine, as previously demonstrated (20).

Mizolastine was well tolerated, and no major AE were reported. Only one AE that could be rated as serious, aggravation of pre-existing asthma, occurred during the study. Finally, the proportion of patients reporting an AE leading to withdrawal from the study was low. This is in agreement with results reported on

approximately 2000 patients who had received mizolastine in 30 different phase II and III double-blind clinical trials (21).

With respect to the safety of other second-generation antihistamines, that of loratadine has been evaluated in 15 open, postregistration phase, clinical trials. The drug was well tolerated in the majority of patients treated with this drug. In one of these trials, which included 3689 patients with SAR who took the drug for 10 days, the AE reported most frequently were dry mouth (3.2%), somnolence (3.1%), fatigue (2.7%), and gastrointestinal upset (1.4%). In another study of the same drug, carried out on 2603 patients with SAR, the AE reported most frequently were headache (6%), somnolence (5%), nausea (3%), and dry mouth (2%) (22). Similarly, in 1251 patients with SAR who were treated for 4 weeks with cetirizine, another second-generation antihistamine, 5.7% reported AE, including CNS effects (fatigue and/or sleep disorders) in 2.8%; headache in 0.3%; abdominal symptoms, including abdominal pain in 0.03%, nausea in 0.1%; diarrhea in 0.1%; and ENT disorders (dry nose and throat) in 0.4% (23). It should be noted that the frequency of AE reported in these studies on loratadine and cetirizine was higher than those we observed with mizolastine in the present study.

In conclusion, in this open, multicenter observational cohort study of the second-generation antihistamine, mizolastine, carried out in a large number of patients under conditions of daily practice, the rapid and significant relief of symptoms in a majority of the patients and the low incidence of AE provide additional strong evidence of the effectiveness and safety of mizolastine in the management of SAR.

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