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Safety of Rupatadine Administered Over a Period of 1 Year in the Treatment of Persistent Allergic Rhinitis

A Multicentre, Open-Label Study in Spain

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Abstract

Background: Rupatadine (Rupafin®), a novel antihistamine approved recently in Europe for the treatment of allergic rhinitis (AR) and chronic idiopathic urticaria in patients aged ≥12 years, has been shown to be highly efficacious, and as safe and well tolerated as other commonly employed antihistamines in the treatment of allergic disease. There are, however, few data on the long-term safety of these antihistamines derived in accordance with the clinical safety recommendations of the European Agency for the Evaluation of Medicinal Products (EMEA) and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline.

Objective: To assess the safety and tolerability of treatment with rupatadine 10 mg/day for 12 months in subjects with persistent AR (PER).

Methods: A multicentre, open-label, phase IV study in patients recruited from 33 centres in Spain, from September 2002 to November 2005. The study enrolled 324 male and female patients (aged 12–70 years) with a medical history of PER for at least 12 months and a documented positive skin-prick test to an appropriate allergen. On 4 of the 7 days prior to start of treatment, the patients were required to have a minimum total nasal symptom score (TNSS [for sneezing, rhinorrhoea, nasal obstruction/congestion and nasal itching]) of ≥5. Of the 324 eligible patients starting treatment, 120 needed to be treated for more than 6 months and were followed up until the end of 12 months. All patients received rupatadine 10 mg/day and were allowed to continue their normal concomitant medication for all conditions, other than rhinitis, for up to 6 or 12 months. Safety was assessed by means of adverse events (AEs)

reported by patients or detected by investigators, scheduled centralized ECG with special attention to Bazzet corrected QT interval (QTcB) and standard laboratory investigations.

Results: Assessment of treatment compliance rates indicated 90% and 83% of patients to be compliant during the 1–6 months and 1–12 months treatment periods, respectively, with compliance rates >80% being associated with the majority of the study population reporting at least one AE. Overall, 74.1% and 65.8% of the patients reported at least one AE during the 1–6 months and 1–12 months treatment periods, respectively, compared with 20.4% and 10.8% of patients reporting at least one treatment-related AE during these periods. Disorders of the nervous system and respiratory thoracic and mediastinal system, in particular headache, somnolence and catarrh, were the three most common AEs reported by >5% of the patients during both treatment periods. Detailed ECG assessments demonstrated no clinically relevant abnormal ECG findings, nor any QTcB increases >60 msec or QTcB values >470 msec for any patient at any time during treatment. Serious AEs were reported in seven patients, of whom six were considered as unlikely to be related to rupatadine treatment, whereas one involving increased blood enzyme levels was considered as possibly related to rupatadine treatment.

Conclusion: This study confirmed the good long-term safety and tolerability of rupatadine at the therapeutic dose of 10 mg/day in patients with PER.

Background

Allergic rhinitis (AR), a common chronic disease characterized by rhinorrhoea, nasal congestion, sneezing and itching of the nose and eyes,[1-3] has increased in prevalence over the last 2–3 decades, affecting up to 20–30% of the population worldwide.[1,4] Moreover, increasing evidence suggests that a large number of modern-day patients may experience more persistent and more severe disease symptoms[5-7] compared with a few years ago. Although AR is not life threatening, when left untreated, the condition substantially impairs the quality of life of affected individuals.[8-10]

Studies investigating the mechanisms underlying the aetiology of AR have shown that histamine is a primary and most abundant mediator involved in the pathogenesis of AR in the early-phase reaction.[11,12] Histamine, acting in concert with other mediators, is also thought to impact the progression of disease.[13] In this regard, it has been demonstrated that the interaction between histamine and platelet-activating factor (PAF), a mediator synthesized *de novo* in response to antigenic challenge[14] and thought to be capable of eliciting allergen-induced bronchoconstriction, mucosal oedema, eosinophil infiltration and airway hyperresponsiveness,[15] may be particularly important because each mediator can promote the release of the other from different tissues and cells.[16]

Studies of rupatadine, a novel antihistamine approved recently in 22 European countries for the treatment of seasonal AR (SAR), perennial AR (PAR) and chronic idiopathic urticaria in patients aged ≥12 years, have demonstrated that this agent has dual activity as both a histamine H_1- and PAF-receptor antagonist.[12,17] Clinical trials have indicated that rupatadine 10 or 20 mg/day is significantly more effective than placebo and equally as effective as loratadine, desloratadine, cetirizine or ebastine in improving the symptoms of AR in patients with SAR, PAR

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and persistent AR (PER) and improves the health-related quality of life to a greater extent than placebo and to a similar extent as cetirizine over a period of 12 weeks in patients with PER.[12,17] Moreover, rupatadine has also been shown to be equally well tolerated as the comparator antihistamines, and additionally does not show any evidence of cardiotoxicity at doses up to ten times the recommended therapeutic dose of 10 mg/day.[18] This is especially important because life-threatening cardiac adverse effects such as prolongation of the QT interval and the development of *torsades de pointes*, a potentially fatal ventricular arrhythmia, have been associated with some second-generation antihistamines, notably terfenadine and astemizole.[19,20] These adverse events (AEs) are associated with greatly elevated blood levels of these agents (resulting from drug overdose, hepatic insufficiency [dysfunction] or interactions with other drugs that inhibit their metabolism), which lead to blockade of specific cardiac K^+ channels resulting in delayed ventricular repolarization and QT-interval prolongation.

Despite the well documented tolerability and safety of commonly employed antihistamines and rupatadine in patients with AR, there are few data on the long-term safety of antihistamines in accordance with the clinical safety recommendations of the European Agency for the Evaluation of Medicinal Products (EMEA)[21] and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline.[22] Recommendations from the EMEA in the guideline on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis have indicated that clinical safety evaluation data should include an appropriate number of patients evaluated for 6 months and a suitable number of patients evaluated for 1 year.[21] These recommendations refer to the ICH Tripartite Guideline concerning the extent of population exposure to assess clinical safety for drugs intended for the long-term treatment of non-life-threatening conditions,[22] which suggested that at least 300 patients were required to be treated during 6 months and at least 100 patients to be treated during 1 year in order to study the long-term safety. The primary objective of this study was therefore to assess the safety and tolerability of rupatadine (Rupafin®) 10 mg/day in the treatment of PER over a period of 6 and 12 months in accordance with these guidelines.

Materials and Methods

Patients

Male and female patients aged 12–70 years were recruited from 33 centres in Spain, from September 2002 to November 2005. All patients had a positive medical history of PER for at least 12 months prior to inclusion in the study and a documented positive skin-prick test to an appropriate allergen at the beginning of the study or within the past 12 months. Patients were required to have a minimum total nasal symptom score (TNSS [for sneezing, rhinorrhoea, nasal obstruction/congestion and nasal itching]) of ≥5 on 4 of the 7 days prior to start treatment at visit 1, Bazett corrected QT interval (QTcB) values below 450 msec in men and 470 msec in women and an ECG with no other clinically important abnormalities.

Patients with a history of non-allergic rhinitis (vasomotor, infectious, drug-induced, etc.) were excluded, as were patients with any significant concomitant medical conditions, including obstructive nasal polyps, significant deviation of the nasal septum, cognitive disorders or any other condition that could interfere with the appropriate assessment. Pregnant and lactating women and patients with clinically significantly abnormal ECGs or abnormal clinical laboratory tests were also excluded. In order to encourage the patients to remain in the study and to assess the safety of rupatadine under more common clinical practice conditions, they were allowed to continue with their normal concomitant medications, except intranasal, systemic and topical (nasal and ocular) antihistamines and medication whose metabolism could interfere with cytochrome P450 3A4, such as macrolide-type antibiotics

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(e.g. erythromycin), antifungal agents (e.g. ketoconazole) and/or antidepressants (e.g. tricyclic derivatives such as imipramine and amitriptyline).

Study Design

This was a multicentre, open-label, phase IV study designed to evaluate the long-term safety and tolerability of rupatadine 10 mg/day, as recommended by the EMEA[21] and ICH[22] guidelines. A sample size of 316 patients, assuming a 5% withdrawal rate in the first 6 months of the study, was estimated according to these guidelines, which suggested that 300 patients were required to be treated for 6 months and 100 patients treated for 1 year in order to study the long-term safety of rupatadine. All eligible patients providing written informed consent were enrolled into the study and received rupatadine 10 mg/day for 6 or 12 months. The patients attended the clinic on six scheduled visits (inclusion visit; at 1 month; at 3 months; at 6 months; at 9 months; and final visit at 12 months after the start of treatment) during which they underwent a physical examination and assessment for any emergent AEs. Furthermore, patients also underwent centralized ECG assessments and provided blood samples for assessment of clinical laboratory tests at inclusion, 6 and 12 months. Only patients with evidence of clinical symptom severity that would require treatment for more than 6 months according to the investigator criteria were followed up until the end of the study at 12 months. Compliance was assessed throughout the study by means of a pill count at each visit.

The study was approved by the appropriate local ethics committees and performed in accordance with the Declaration of Helsinki and in compliance with informed consent regulation, the ICH Good Clinical Practices and Good Laboratory Practices.

Safety Assessments

Safety was assessed by means of AEs reported by patients or detected by investigators, as well as by ECG, with special attention to QTcB and standard laboratory investigations. When patients were attending the scheduled visits they were asked about any AE. Moreover, patients could contact the investigator at any time in case of any AE occurring during the study period.

AEs were coded according to the Preferred Term and System Organ Class in MedDRA (Medical Dictionary for Regulatory Activities) [version 8]. The causality relationship was assessed as certain, probable, possible, unlikely, conditional/unclassified or unassessable/unclassifiable, according to the WHO causality categories,[23] and an AE was considered related to treatment if the causality assessment was defined at least as possible. An AE was considered as a serious AE (SAE) if identified according to any one of the following standard criteria:[24,25] resulted in death, was life threatening, required inpatient hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or was considered an important medical event. Non-serious AEs were defined as any AE that did not fit into any of the preceding categories and causality was assessed using the WHO modified algorithm.

Twelve-lead ECGs were performed on each patient for overall evaluation and for assessment of change from baseline in QTcB values. In case of detection of any clinically relevant ECG abnormalities, the ECG was repeated and the patient was subjected to further testing and follow-up until normal values or values similar to baseline were attained. A scheduled centralized ECG reading laboratory was used to read ECGs and to minimize inter-reader variability.

Similarly, whole blood and serum were collected at each study centre according to a standardized protocol and shipped to a central laboratory for evaluation of serum glucose, sodium, potassium, chloride, ALT, AST, γ-glutamyl transpeptidase, total bilirubin, alkaline phosphatase, total protein, urea, creatinine, total cholesterol, triglycerides, creatine phosphokinase, pregnancy and a standard haemogram.

Physical examinations included clinical anamnesis and physical examination by organ system.

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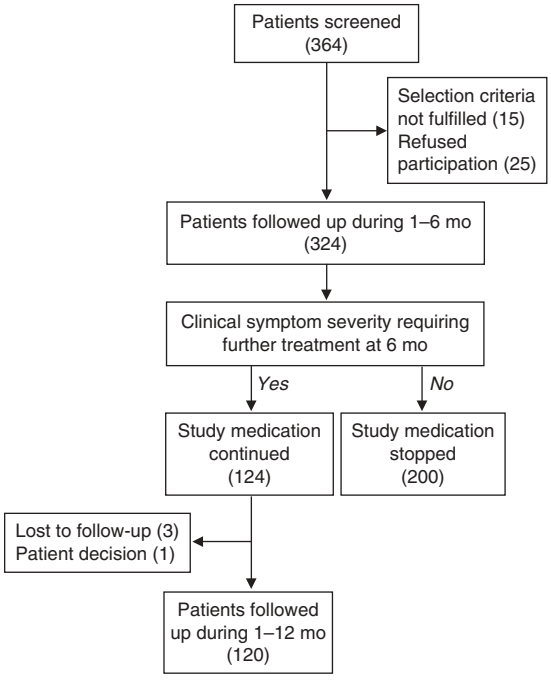

Fig. 1. Study profile.

Statistical Analysis

AEs were summarized according to the system organ class and a preferred treatment-related term (MedDRA version 8), with any AE occurring more than once in any one organ class and preferred term in the same patient being recorded as a single AE. All data were analysed using descriptive analyses to calculate the proportion of patients reporting at least one AE over a course of 1–6 months and 1–12 months.

ECG data were assessed as changes from baseline values as well as absolute values and summarized using descriptive statistics. Changes in QTcB values were expressed as mean changes from baseline at different timepoints over the course of the study, and as categorized changes to calculate the percentages of patients demonstrating either a decrease or increase of <30 msec, increases between 30 and 60 msec, and increases >60 msec. QTcB values >470 msec were also summarized.

Data for clinical laboratory tests were also analysed using descriptive statistics and assessed for the number of patients with clinically relevant abnormal values for specific parameters at different timepoints. Similarly, data for physical examination were analysed using descriptive statistics and assessed for the number of patients with normal and abnormal findings.

Results

A total of 364 patients were screened and 324 were enrolled into the study and received rupatadine 10 mg/day for a period of 6 months. At the end of the 1–6 months treatment period, 120 of these patients were assessed as requiring further treatment and went on to receive an additional 6 months of treatment (figure 1). The demographic and baseline characteristics of the patient cohorts demonstrated that they were similar with respect to mean age, height and weight, although female patients formed a slightly higher proportion of the patient population during the treatment period (table I). Additionally, the patient group investigated during the 1–6 months treatment period included 28 adolescent patients (aged 12–17 years), of whom 15 also participated in the 1–12 months treatment period.

Compliance

Compliance could be determined in all except two cases from the cohort of 324 patients; the

Table I. Patient demographics and baseline characteristics

Characteristic	Patients treated with rupatadine 10 mg/day over a period of 1–6 mo (n = 324)	Patients treated with rupatadine 10 mg/day over a period of 1–12 mo (n = 120)
Age (y), mean ± SD [range]	29.10 ± 11.23 [12–67]	28.56 ± 12.22 [12–66]
% Female	57.4	63.33
% Caucasian	99.38	100
Height (cm), mean ± SD	166.01 ± 10.22	165.81 ± 10.43
Weight (kg), mean ± SD	67.85 ± 15.31	65.12 ± 16.03

SD = standard deviation.

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Table II. Percentage of patients with persistent allergic rhinitis compliant with rupatadine 10 mg/day for periods of 1–6 mo and 1–12 mo

Categorized compliance rate (%)	Patients compliant over a period of 1–6 mo[a] (n = 322[b]) [n (%)]	Patients compliant over a period of 1–12 mo[c] (n = 120) [n (%)]
>90	203 (63)	48 (40)
80–90	64 (19.9)	31 (25.8)
70–80	29 (9)	19 (15.8)
60–70	15 (4.7)	14 (11.7)
50–60	7 (2.2)	5 (4.2)
40–50	3 (0.9)	2 (1.7)
30–40	1 (0.3)	1 (0.8)

a The mean continuous compliance rate in patients treated over 1–6 mo was 89.62% ± 12.54.

b Compliance could not be determined in two patients.

c The mean continuous compliance rate in patients treated over 1–12 mo was 83.26% ± 14.12.

mean compliance rate was 89.6% in the 1–6 months treatment period and 83.3% in the 1–12 months treatment period (table II). Moreover, there appeared to be an association between compliance rates and the number of patients reporting at least one AE or treatment-related AE during both treatment periods (table III). Thus, while patients with compliance rates >80% comprised the majority of the study population reporting the incidence of at least one AE, patients with compliance rates under 50% comprised <5% of the study population. Although the incidence of treatment-related AEs was much smaller, the pattern for the association between compliance rate and the number of patients reporting such AEs was nevertheless similar (table III).

Adverse Events

Overall, a total of 74.1% of the patients reported at least one AE during the 1–6 months treatment period and 65.8% of patients during the 1–12 months treatment period, whereas 20.4% and 10.8% of patients reported at least one treatment-related AE during the 1–6 months and 1–12 months treatment periods, respectively (table III). Assessment of AEs reported during both treatment periods by >5% of the patients showed that the three most common AEs were headache, somnolence and catarrh (table IV). Moreover, the frequency of these AEs was similar over both treatment periods (table IV). While somnolence (7.7%) and headache (6.5%) were also reported as treatment-related AEs during the 1–6 months treatment period, only somnolence (5.8%) was reported as treatment-related AE during the 1–12 months treatment period (table IV). Although patients also reported AEs associated with several other system organ classes, none of the specific AEs, apart from sore throat, within any of these system organ classes was found to be reported by >5% of patients (table IV).

Detailed assessment of ECGs demonstrated that none of the abnormal ECG findings were clinically relevant. Furthermore, QTcB values >470 msec were not noted for any patient at any time over the course of treatment nor was the QTcB increased by >60 msec in any patient. Overall, 95–99% and 97–100% of patients treated with rupatadine 10 mg/day for 1–6 months and 1–12 months, respectively, demonstrated either a decrease or <30 msec increase in QTcB, at any given timepoint over the course of the study (table V). Similarly, increases in QTcB of between 30 and 60 msec were noted in <5% of patients at any timepoint during the 1–6 months treatment period and <2.5% of patients

Table III. Percentage of patients with persistent allergic rhinitis reporting at least any one adverse event (AE) and one treatment-related AE, based on the rate of compliance with rupatadine 10 mg/day for 1–6 mo and 1–12 mo

Compliance rate (%)	Patients experiencing at least one AE over the period 1–6 mo (n = 322[a])		Patients experiencing at least one AE over the period 1–12 mo (n = 120[b])	
	any	treatment-related	any	treatment-related
>90	46.27	13.98	25.83	7.50
80–90	16.15	3.73	19.17	0.83
70–80	5.28	0.93	6.67	0.00
60–70	3.42	0.62	8.33	0.83
50–60	1.55	0.62	3.33	0.83
40–50	0.93	0.62	1.67	0.83
30–40	0.31	0.00	0.83	0.00
Overall	**74.07**	**20.37**	**65.83**	**10.83**

a Mean number of any AE over a period of 1–6 mo was 3.54 ± 4.99 and mean number of treatment-related AEs was 0.55 ± 1.97. Compliance could not be determined for two patients.

b Mean number of any AE over a period of 1–12 mo was 2.75 ± 3.73 and mean number of treatment-related AEs was 0.15 ± 0.48.

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Table IV. Any adverse event (AE) and treatment-related AEs recorded by system organ class in patients with persistent allergic rhinitis treated with rupatadine 10 mg/day for 1–6 mo and 1–12 mo

System organ class classified according to MedDRA	1–6 mo treatment		1–12 mo treatment	
	most common AE in preferred term	no. of patients (%)	most common AE in preferred term	no. of patients (%)
At least one AE in system organ class				
Nervous system disorders		41.98 (136)		41.67 (50)
	Headache	33.02 (107)	Headache	32.50 (39)
	Somnolence	11.42 (37)	Somnolence	10.83 (13)
Respiratory, thoracic and mediastinal disorders		34.57 (112)		26.67 (32)
	Catarrh	10.19 (33)	Catarrh	9.17 (11)
			Sore throat	5.0 (6)
Infections and infestations		27.78 (90)		26.67 (32)
	Common cold	4.63 (15)	Influenza	4.17 (5)
Gastrointestinal disorders		18.21 (59)		11.67 (14)
	Odynphagia	4.01 (13)	Abdominal pain	3.33 (4)
Musculoskeletal and connective tissue disorders		13.89 (45)		15.83 (19)
	Back pain	1.54 (5)	Back pain, back ache, lumbar pain, knee pain, myalgia	1.67 (2) each
General disorders and administration site conditions		13.27 (43)		12.50 (15)
	Tiredness	2.78 (9)	Influenza-like illness	3.33 (4)
Reproductive system and breast disorders		7.72 (25)		5.0 (6)
	Dysmenorrhoea	4.93 (16)	Dysmenorrhoea	2.5 (3)
Skin and subcutaneous tissue disorders		7.41 (24)		6.67 (8)
	Rash, pruritus, crust and scab	0.62 (2) each	Rash	1.67 (2)
Eye disorders		5.86 (19)		
	Allergic rhinoconjunctivitis	1.85 (6)		
At least one treatment-related AE in system organ class				
Nervous system disorders		12.96 (42)		7.50 (9)
	Somnolence	7.72 (25)	Somnolence	5.83 (7)
	Headache	6.48 (21)		

MedDRA = Medical Dictionary for Regulatory Activities.

during the 1–12 months treatment period (table V). Furthermore, neither QTcB increases >60 msec nor QTcB values >470 msec were reported in any male or female patients.

SAEs were reported in seven patients and included cyst of the bone, breast neoplasm, obstructive chronic bronchitis, rib injury, exeresis of cutaneous melanoma, ligament sprain and one asymptomatic case of increased levels of blood enzymes (ALT, AST and blood creatine kinase). The former six SAEs were considered as unlikely to be related to the study drug. An increased level of blood enzymes was considered possibly related to the study drug. This SAE was reported in an 18-year-old male patient after 1 year of treatment. Of interest is that this patient was included in the study with an elevated value of blood creatine kinase (before starting the treatment). Although the patient recovered after the treatment was withdrawn, serum creatine kinase levels did not achieve the normal range. For these reasons, a myopathy present at baseline should

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Table V. Change in Bazzet corrected QT interval (QTcB) in patients with persistent allergic rhinitis treated with rupatadine 10 mg/day over a period of 12 mo

Group	Visit				
	1 mo	3 mo	6 mo	9 mo	12 mo
QTcB msec (mean ± SD)	2.3 ± 9.84	1.76 ± 12.27	3.53 ± 12.47	3.39 ± 0.76	–0.76 ± 13.77
% Patients with decrease or <30 msec increase in QTcB					
1–6 mo treated group	98.76	98.69	95.96	NA	NA
1–12 mo treated group	NA	NA	NA	97.70	99.17
% Patients with 30–60 msec increase in QTcB					
1–6 mo treated group	1.24	1.31	4.04	NA	NA
1–12 mo treated group	NA	NA	NA	2.30	0.83

NA = not applicable; **SD** = standard deviation.

have been ruled out. Unfortunately, the patient did not attend their scheduled appointments in the Neurology Department and an aetiological diagnosis was not performed.

Discussion

The main objective of this study was to evaluate the long-term safety of rupatadine 10 mg/day in the treatment of patients with PER, as recommended by international guidelines.[21,22] The study demonstrated that rupatadine 10 mg/day had a good safety and tolerability profile, as indicated by a low incidence of SAEs and non-serious AEs, no fatalities, no abnormalities in ECGs and no safety issues identified from laboratory tests or physical examinations. The overall compliance rate could be determined for the majority of the study population and was >80%. This high compliance rate is in agreement with the results published by other authors that also found compliance rates higher than 80% in patients treated with other antihistamines.[26]

Somnolence was the only treatment-related AE reported by the patients over the entire course of the study, while headache was reported only in the first 6 months. ECG evaluation demonstrated no evidence of serious arrhythmias and neither QTcB values over 470 msec nor QTcB increases of 60 msec or greater were reported, suggesting lack of cardiotoxicity at the therapeutic dose of rupatadine 10 mg. Indeed, this has been confirmed more recently in a study that specifically investigated any threshold pharmacological effect of rupatadine 10 mg and rupatadine 100 mg on cardiac repolarization, as detected by QT/corrected QT interval prolongation in 160 volunteers.[18] The study demonstrated that neither dose of rupatadine led to any abnormal effects on the ECGs.

Our findings for the safety and tolerability of rupatadine are also in accordance with the findings for other commonly used, second-generation H_1 antihistamines for the treatment of AR.[27,28] The majority of studies with the other antihistamines, however, have been comparatively short-term studies. Moreover, an increasing trend in long-term use of antihistamines suggests that safety and tolerability issues are even more relevant, particularly as there might be an increased potential for cardiotoxicity and drug-drug interactions, as well as age- or disease (renal and hepatic disease)-related complications, with prolonged treatment with some antihistamines. Although a few studies have investigated the effects of long-term treatment with antihistamines in adult patients with AR[29-31] and healthy subjects,[32] none of these studies was designed to specifically investigate the safety and tolerability of the active drug as the primary endpoint. In this respect, the present study is the first to investigate the long-term safety of an antihistamine drug as the primary endpoint in patients with PER, and performed according to EMEA[21] and ICH guidelines.[22]

Even though this study is somewhat limited because of its open-label treatment design, the findings of this study are clinically relevant because safety and tolerability were determined by the use of objective tests, particularly ECG and

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laboratory tests, in addition to subjective recording of AEs. Moreover, despite the absence of a placebo comparator, the findings for the AEs are also relevant because both the incidence and the specific type of any treatment- or non-related AEs recorded by a majority of patients were consistent for both study cohorts investigated during the 1–6 months and 1–12 months treatment periods.

Conclusion

This study confirmed the good long-term safety and tolerability of rupatadine at the therapeutic dose of 10 mg/day in patients with PER.

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