

Main Rupatadine References

Contents:

<i>Pharmacodynamics / Pharmacokinetics</i>	2
<i>Clinical Efficacy</i>	10
1. Adults	10
1.1. Allergic Rhinitis	10
1.2. Urticaria	20
1.3. Others – Allergy by mosquito bites	24
2. Children	25
2.1. Allergic Rhinitis	25
2.2. Urticaria	26
<i>Clinical Safety</i>	27
1. General	27
2. Cardiac Safety	28
3. CNS Effects	30
4. Drug Interactions	32
<i>Review Articles</i>	34

Pharmacodynamics / Pharmacokinetics

Dual effect of a new compound, rupatadine, on edema induced by platelet-activating factor and histamine in dogs: Comparison with antihistamines and PAF antagonists.

Queralt M, Merlos M, Giral M, Puigdemont A. *Drug Dev Res* 1996; 39 (1): 12-8.

The antihistamine-H1 and antiplatelet activating factor (PAF) activities of seven compounds, including rupatadine, a new antiallergic drug, were studied in healthy beagle dogs using a new experimental model that allows simultaneous testing of PAF and histamine reactions in the same animal. The method was based on the measurement of wheal area induced in dogs' skin by intradermal injection of PAF (1.5 mug) or histamine (2.5 mug). Rupatadine and the H1-antihistamine drugs cetirizine, levocabastine, and loratadine, administered orally at doses of 1 or 10 mg/kg showed similar maximum potencies (75-85% of wheal inhibition) 4-8 h after treatment. Levocabastine was the longest-acting compound (55% and 69% inhibition 24 h after administration of 1 or 10 mg/kg, respectively). Rupatadine, loratadine, and cetirizine behaved similarly, showing 34% and 58% inhibition at 24 h at the same doses. Dual PAF and histamine antagonist SCH-37370 exhibited mild anti-H1 activity, the maximum effect being 27% at 10 mg/kg. Pure PAF antagonists WEB-2086 and SR-27417 showed no effect against histamine-induced wheals.

Only rupatadine, SR-27417A, SCH-37370, and WEB-2086 showed PAF antagonist activity, whereas pure antihistamines were inactive. The most potent PAF antagonist was SR-27417A, with a maximum effect of 56% and 80% at 1 and 10 mg/kg, respectively. Rupatadine and WEB-2086 antagonized PAF-induced wheal response, although they showed less maximum effect and shorter duration of action than SR-27417A. SCH-37370 exhibited only slight PAF antagonist activity at 10mg/kg. Overall, the histamine- and PAF-induced wheal model in dogs proved useful for independent evaluation of histamine and PAF antagonist properties of the tested compounds, as pure antagonists blocked the effect of only one of the mediators.

Rupatadine was the only one of the seven compounds studied that showed potent dual activity against PAF and histamine.

Protective effect of rupatadine fumarate in experimental conjunctivitis in guinea pigs.

Ferrando R, Giral M, Balsa MD, Merlos M, Garcia Rafanell J, Forn J. *Methods Find Exp Clin Pharmacol* 1996; 18 (Suppl B): 140. XX Congress of the Spanish Society of Pharmacology and the IV Spanish-French Meeting on Pharmacology. Granada (Spain), September 18-20 1996.

The topical antiallergic activity of the novel histamine (H) and PAF antagonist rupatadine fumarate (RF; UR-12592 fumarate) eyedrops was evaluated in comparison with loratidine (LOR) in a model of H-, PAF-or ovalbumin (OVA)-induced conjunctivitis in guinea pigs. From the results it was concluded that RF could be useful in the topical treatment of allergic conjunctivitis. (conference abstract). Conjunctivitis was induced by topical application of H (400 ug) or PAF (10 ug) in naive animals or OVA (140 ug) in actively sensitized guinea pigs. Drugs were administered as eye-drops (20 ul) 15 min before agonist or antigen provocation. Inflammation was scored (0-10 point scale) at 5, 15, 30, 60, 90, 120, and 150 min after induction. RF (0.001-0.01 % w/v) strongly and dose-dependently inhibited H-induced conjunctivitis, being about 20-fold more potent than LOR (IC50 values at 30 min were 0.0015 and 0.034% for RF and LOR, respectively). RF (0.05-0.2%) also inhibited PAF-and OVA-induced conjunctivitis, e.g. mean scores (at 30 min), PAF: 6.8 and 4.2 for control and 0.1% RF, respectively; OVA: 7.2 and 3.8. LOR, at the same concentrations, inhibited OVA-, but not PAF-induced conjunctivitis.

Pharmacokinetics and dose linearity of rupatadine fumarate in healthy volunteers.

Izquierdo I, Nieto C, Ramis J, Cooper M, Dewland P, Forn J. *Methods Find Exp Clin Pharmacol* 1997; 19 (Suppl A): 189. XXI Congress of the Spanish Society of Pharmacology. Barcelona (Spain), November 11-14 1997. Sponsored by: Spanish Society of Pharmacology (Sociedad Española de Farmacología).

The pharmacokinetics (PK) of single- and multiple dose rupatadine fumarate (RUP) and its effect on the inhibition of intradermal histamine induced cutaneous flares were examined in healthy male volunteers in 2 consecutive randomized, placebo (PL)-controlled, double blind studies. The terminal half-life beta was influenced by the different doses administered. Single and multiple doses of RUP were well tolerated and no serious adverse events were noted. RUP showed after once daily administration, a high and long acting antihistamine activity. (conference abstract). The single dose study was a randomized, double blind, 3-way crossover involving 8 subjects. Each subject received a single dose of 10, 20 and 40 mg RUP.

The multiple dose study was randomized, double blind, rising dose and PL controlled. 12 subjects received 20 and 40 mg, once daily for 7 days and only 3 subjects received PL. In both studies there were at least 14 drug free days between dose periods. Blood samples for determination of RUP were taken at different times on each study. Cutaneous flares were also induced by i.d. injection of histamine to obtain a concentration effect relationship. Dose linearity was demonstrated over the range 10-40 mg of RUP. The mean values of AUC_{0-infinity} were 8.68, 22.22 and 54.02 ng/ml/hr and mean values of C_{max} were 2.33, 5.83 and 14.68 ng/ml. Within the doses administered the individual values indicated a relatively high interindividual variation probably due to a varying degree of enterohepatic circulation. Steady state was reached on days 3-5. Both the percentage and duration of flare inhibition increased with dose. Mean inhibition of histamine reached a maximum of 69, 82 and 93% with 10, 20 and 40 mg after single dose, respectively. After multiple dose the inhibition of histamine flares rose rapidly after 1st dose and remained consistently high (70-90%) throughout the dosing period. Inhibitory effect remained high (more than 60%) until 48 and 96 hr after the last dose.

Rupatadine, a new potent, orally active dual antagonist of histamine and platelet activating factor (PAF).

Merlos M, Giral M, Balsa D, Ferrando R, Queralt M, Puigdemont A, Garcia Rafanell J, Forn J. *J Pharmacol Exp Ther* 1997; 280 (1): 114-21.

Rupatadine (UR-12592, 8-chloro-6, 11-dihydro-11-[1-[(5-methyl3-pyridinyl) methyl]-4-piperidinylidene]-5H-benzo[5,6]-cyclohepta[1,2b]pyridine) is a novel compound that inhibits both platelet-activating factor (PAF) and histamine (H₁) effects through its interaction with specific receptors (K_i(app) values against [3H]WEB-2086 binding to rabbit platelet membranes and [3H]-pyrilamine binding to guinea pig cerebellum membranes were 0.55 and 0.10 microM, respectively).

Rupatadine competitively inhibited histamine-induced guinea pig ileum contraction (pA₂ = 9.29 +/- 0.06) without affecting contraction induced by ACh, serotonin or leukotriene D₄ (LTD₄). It also competitively inhibited PAF-induced platelet aggregation in washed rabbit platelets (WRP) (pA₂ = 6.68 +/- 0.08) and in human platelet-rich plasma (HPRP) (IC₅₀ = 0.68 microM), while not affecting ADP- or arachidonic acid-induced platelet aggregation. Rupatadine blocked histamine- and PAF-induced effects in vivo, such as hypotension in rats (ID₅₀ = 1.4 and 0.44 mg/kg i.v., respectively) and bronchoconstriction in guinea pigs (ID₅₀ = 113 and 9.6 micrograms/kg i.v.). Moreover, it potently inhibited PAF-induced mortality in mice (ID₅₀ = 0.31 and 3.0 mg/kg i.v. and p.o., respectively) and endotoxin-induced mortality

in mice and rats (ID₅₀ = 1.6 and 0.66 mg/kg i.v.). Rupatadine's duration of action was long, as assessed by the histamine- and PAF-induced increase in vascular permeability test in dogs (42 and 34% inhibition at 26 h after 1 mg/kg p.o.).

Rupatadine at a dose of 100 mg/kg p.o. neither modified spontaneous motor activity nor prolonged barbiturate-sleeping time in mice, which indicates a lack of sedative effects. Overall, rupatadine combines histamine and PAF antagonist activities in vivo with high potency, the antihistamine properties being similar to or higher than those of loratadine, whereas rupatadine's PAF antagonist effects were near those of WEB-2066. Rupatadine is therefore a good candidate for further development in the treatment of allergic and inflammatory conditions in which both PAF and histamine are implicated.

Effects of rupatadine on cardiovascular profile in rats and guinea pigs. Comparison with other non-sedating antihistamines.

Giral M, Merlos M, Balsa D, Ferrando R, Garcia Rafanell J, Forn J. *Allergy 1997; 52 (Suppl 37): 44-5. EAACI '97 Annual Meeting. Rhodes (Greece), June 1-4 1997.*

The cardiovascular safety profile of i.v. infused rupatadine (RUP), a potent dual histamine and PAF antagonist, was evaluated in rats and guinea pigs and compared with that of other antihistamines. RUP and loratadine (LOR) produced minimal alterations in MABP and HR at the highest dose. Terfenadine (TER) provoked a fall in MABP and HR, with severe arrhythmias, and most animals died. No mortality was observed with when RUP or LOR. In guinea pigs, RUP (i.v. bolus) did not alter either ECG or haemodynamic parameters. LOR, however, produced a transient decrease followed by a prolonged increase in MABP, accompanied with a significant increase in HR. TER and astemizole (AST) decreased HR and MABP. From results obtained in guinea pigs it was suggested that RUP could have lower risk of inducing cardiovascular adverse effects than LOR. (conference abstract). The cardiovascular safety profile of rupatadine (RUP), a potent dual histamine and PAF antagonist, has been evaluated in rats and guinea pigs and compared with that of other antihistamines. Animals were anaesthetized and instrumental for the recording of mean arterial blood pressure (MABP) and ECG derived parameters such as heart rate (HR) and QT, PR and QRS intervals. RUP and loratadine (LOR) (3 - 30 mg/kg, intravenous infusion of 1 min) produced minimal alterations in MABP and HR at the highest dose. ECG parameters were not significantly modified. In contrast administration of 10 mg/kg terfenadine (TER) provoked a fall in MABP and HR, with severe arrhythmias, and most animals died within 4 min after administration. No mortality was observed when RUP or LOR were administered at doses up to 30 mg/kg. In guinea pigs, RUP 30 mg/kg (intravenous bolus) did not alter either ECG or haemodynamic parameters. LOR 30 mg/kg, however, produced a transient decrease followed by a prolonged increase in MABP, accompanied with a significant increase in HR. ECG intervals did not show any alteration. TER and astemizole (AST) 10 mg /kg induced marked changes in haemodynamic (decrease of HR and MABP) and ECG parameters: AST and TER increased PR (26% and 32% at 2 min, respectively) and AST increased QRS (32% at 2 min). AST and TER 15 mg /kg also produced QT prolongation and high mortality rate.

Inhibition of rat peritoneal mast cell exocytosis by rupatadine fumarate: a study with different secretagogues.

Merlos M, Balsa D, Giral M, Ferrando R, Garcia Rafanell J, Forn J. *Methods Find Exp Clin Pharmacol* 1997; 19 (Suppl A): 148. XXI Congress of the Spanish Society of Pharmacology. Barcelona (Spain), November 11-14 1997. Sponsored by: Spanish Society of Pharmacology.

The ability of rupatadine fumarate (RUP), an orally active dual antagonist of histamine (HA) and PAF, to inhibit rat mast cells (MC) exocytosis of inflammatory mediators induced by both IgE dependent and -independent stimuli, was evaluated in comparison with loratadine (LOR), a 2nd generation antihistamine. Both LOR and RUP inhibited HA and LTC₄ release from calcimycin (A-23187)-stimulated MC, but only RUP inhibited 48/80-induced HA release. LOR and RUP also inhibited ex vivo A-23187-induced HA release after p.o. dosing. In IgE- sensitized MC, both LOR and RUP inhibited antigen induced HA release. Effects were calcium dependent. Thus, RUP has in vitro antiallergic properties that are thought to be beyond its ability to block H₁ and PAF receptors. The mechanism is still unclear, but it is suggested that RUP may interfere with intracellular Ca²⁺ utilization (conference abstract). Peritoneal MC from male Sprague Dawley rats were isolated in Tyrode solution. MC were pre incubated in the absence or presence of products (0-10 min, 37 deg), then secretagogue (0.5 uM A-23187, 1 ug/ml compound 48/80 and 2/10 ug/ml anti DNP IgE/DNP albumin) was added and cells were further incubated (10-60 min, 37 deg). The released mediators were extracted and quantified spectrofluorimetrically (HA) or by a commercially available kit (LTC₄). In the in vitro experiments, RUP and LOR were similarly effective in inhibiting HA (55.5 and 50.2% at 10 uM, respectively) and LTC₄ (IC₅₀ = 5.6 and 5.8 uM) release from A-23187-triggered MC. In 48/80-stimulated MC, only RUP (18.0%) reduced HA release at 10 uM. Inhibitory behavior in the A-23187 and compound 48/80 assays varied depending on Ca²⁺ concentration in the medium. RUP (IC₅₀ = 73 uM) and LOR (IC₅₀ = 288 uM) also inhibited HA release from IgE sensitized MC after antigen exposure. In the ex vivo experiments, pretreatment with RUP and LOR (30 mg/kg, p.o.) similarly reduced A-23187-induced HA exocytosis (32.2 and 27.3%).

Rupatadine inhibits the eosinophil recruitment in BAL fluid of ovalbumin-sensitized guinea-pigs.

Merlos M, Giral M, Balsa D, Ferrando R, Garcia Rafanell J, Forn J. *J Allergy Clin Immunol* 1998; 101 (1 Pt.2): S218 AAAAI 54th Annual Meeting. Washington DC (USA), March 13-18 1998.

Female Dunkin-Hartley guinea pigs weighing 300-400 g were sensitized by administration of 5% OVA (2 ml, i.p., 2 ml, s.c.). After 25-27 days, animals were challenged with an aerosol of 0.5% OVA for 5 min. Adverse reactions showed by the animals (dyspnea, cyanosis, and bronchospasm) were recorded. Rupatadine (RUP), loratadine (LOR), dexamethasone (DEX) and cetirizine (CET) were administered (10 mg/kg, p.o.) 1 hr before challenge and compared with sham and vehicle (VEH) groups. Mortality was only observed in the VEH group (17%).

Rupatadine inhibited early symptoms and BAL eosinophil recruitment in a guinea pig model of allergic asthma. (conference abstract).

Inhibitory effects of rupatadine on mast cell histamine release and skin wheal development induced by *Ascaris suum* in hypersensitive dogs.

Queralt M, Brazis P, Merlos M, Puigdemont A. *Drug Dev Res* 1998; 44 (2-3): 49-55.

In sensitized dogs, p.o. rupatadine (RU, 8-chloro 6,11-dihydro 11-((5-methyl 3-pyridinyl) methyl) 4-piperidinylidene) 5H benzo(5,6) cyclohepta(1,2-b) pyridine fumarate, Uriach), a histamine and PAF antagonist, and p.o. loratadine (LO, Schering Plough), an H1 antagonist, but not p.o. SR-27417A (SR, Sanofi), a PAF antagonist, inhibited wheal induced by intradermal challenge with *Ascaris suum* extract (Greer). In vitro, histamine release from passively sensitized dog mast cells on challenge with antigen (Greer) was inhibited by RU and LO but not by SR. RU and LO were not cytotoxic in vitro; SR was. RU controls inflammatory reactions in dog skin; the effect may partly be due to modulation of mast cell degranulation, but not to PAF antagonism. 5 Spontaneously hypersensitive male Beagle dogs (14.2 kg) were fasted and given 10 ul 50 PNU/ml *A. suum* extract intradermally before and after 0.1, 1 or 10 mg/kg drug. *A. suum* extract induced a wheal, the area of which was maximally inhibited by 35%, 67% and 84%, respectively, by RU and 34%, 61% and 66%, respectively, by LO; the peak effect was reached at 2-4 hr for both drugs.

SR was ineffective. Dog skin mast cells were passively sensitized by incubation with 15% serum from *A. suum* sensitized dogs for 120 min. Drugs were incubated with cells for 10 min before 30 min challenge with 1 mg/ml *A. suum* antigen. Antigen alone maximally released 12.3% of mast cell histamine. 15 And 40 min incubation with RU or LO at 10 mM - 30 uM was not cytotoxic and showed no degranulating effects. SR 30 uM reduced cell viability to 65%. RU and LO dose dependently inhibited antigen induced histamine release; maximum effects were 83.3% and 66.7%, respectively, at 30 uM; RU was the more potent (IC50 5.3 vs. 19 uM). SR was ineffective.

Effects of rupatadine, a new dual antagonist of histamine and platelet-activating factor receptors, on human cardiac kv1.5 channels.

Caballero R, Valenzuela C, Longobardo M, Tamargo J, Delpon E. *Br J Pharmacol* 1999; 128 (5): 1071-81.

1. The effects of rupatadine, a new dual antagonist of both histamine H1 and platelet-activating factor receptors, were studied on human cloned hKv1.5 channels expressed in Ltk- cells using the whole-cell patch-clamp technique. 2. Rupatadine produced a use- and concentration-dependent block of hKv1.5 channels (KD=2.4+/-0.7 micronM) and slowed the deactivation of the tail currents, thus inducing the 'crossover' phenomenon. 3. Rupatadine-induced block was voltage-dependent increasing in the voltage range for channel opening suggesting an open channel interaction. At potentials positive to +10 mV the blockade decreased with a shallow voltage-dependence. Moreover, rupatadine also modified the voltage-dependence of hKv1.5 channel activation, which exhibited two components, the midpoint of the steeper component averaging -25. 2+/-2.7 mV. 4. When the intracellular K+ concentration ([K+]i) was lowered to 25% the voltage-dependent unblock observed at positive potentials was suppressed and the activation curve in the presence of rupatadine did not exhibit two components even when the midpoint of the activation curve was shifted to more negative potentials (-30. 3+/-1.3 mV). 5. On channels mutated on the residue R485 (R485Y) which is located on the external entryway of the pore the rupatadine-induced block did not decrease at potentials positive to +10 mV. In contrast, on V512M channels rupatadine reproduced all the features of the blockade observed on wild type channels. 6. All these results suggest that rupatadine blocks hKv1.5 channels binding to an external and to an internal binding site but only at concentrations much higher than therapeutic plasma levels in man. Efflux of K+ promotes the unbinding from the external site.

Furthermore, rupatadine binds to an internal site and dramatically modifies the voltage-dependence of channel opening.

In vitro inhibitory effect of rupatadine on histamine and TNF-alpha release from dispersed canine skin mast cells and the human mast cell line HMC-1.

Queralt M, Brazis P, Merlos M, de Mora F, Puigdemont A. *Inflamm Res* 2000; 49 (7) : 355-60.

Objective and design: To examine the inhibitory potential of rupatadine, a new H1-antihistamine and anti-PAF agent, on histamine and TNF-alpha release. Comparison with an H1-antihistamine (loratadine) and a PAF-antagonist (SR-27417A). **Material:** Dispersed canine skin mast cells were used to assess the effect of the drugs tested on FcepsilonRI-dependent and -independent histamine release; the human HMC-1 cell line was used to study TNF-alpha release. **Treatment and Methods:** Before stimulation mast cell populations were treated with increasing concentrations of rupatadine, loratadine and SR-27417A. Histamine and TNF-alpha release were measured following 15-30 min and 3 h activation, respectively. **Results:** The IC50 for rupatadine in A23187, concanavalin A and anti-IgE induced histamine release was 0.7+/-0.4 microM, 3.2+/-0.7 microM and 1.5+/-0.4 microM, respectively whereas for loratadine the IC50 was 2.1+/-0.9 microM, 4.0+/-1.3 M and 1.7+/-0.5 microM. SR-27417A exhibited no inhibitory effect. Rupatadine, loratadine and SR-27417A inhibited TNF-alpha release with IC50 2.0+/-0.9 microM, 2.1+/-1.1 M and 4.3+/-0.6 microM, respectively. **Conclusions:** Rupatadine and loratadine showed similar inhibitory effect on histamine and TNF-alpha release, whereas SR-27417A only exhibited inhibitory effect against TNF-alpha.

Effect of rupatadine on lymphocyte cytokine production

Barron S, Ramis I, Merlos M.

Allergy Clin Immunol Int: J World Allergy Org 2005; Suppl (1): 427 (Abs 1175) *World Allergy Congress: XIXth World Allergy Organization Congress – XXIVth Congress of the European Academy of Allergology and Clinical Immunology (EAACI). Munich (Germany), June 26 - July 1 2005.*

Background: Rupatadine is a new anti-histamine and anti-PAF drug used in the treatment of allergic rhinitis. Several studies have shown that rupatadine has additional anti-inflammatory properties besides the blockade of histamine and PAF receptor. Some second-generation antihistamines (anti-H1) inhibit cytokine production by lymphocytes. The aims of this study were to evaluate the inhibitory properties of rupatadine on human lymphocyte cytokine production using different activation models and to compare this effect with that of desloratadine. **Methods:** Lymphocytes were obtained from human peripheral blood with a ficoll gradient followed by a negative selection using MACS(r) immunomagnetic beads. Lymphocytes were activated with anti-CD3, anti-CD28 and IL-2 (activation A) or anti-CD3 and VCAM-1 (activation B). Anti-H1 were added 30 min before or simultaneously with activation. Supernatants were collected after 4 days of incubation and cytokine levels were measured by enzyme immunoassay technique.

Results: Pre-treatment with rupatadine followed by activation A inhibited IL-5, IL-6, GM-CSF and TNF-a production in a concentration-dependent manner between 10⁻⁷ and 10⁻⁵ M. Desloratadine showed a similar pattern of cytokine inhibition for IL-6, GM-CSF and TNF-a. Desloratadine, however, was not able to produce an inhibition of IL-5 higher than 30 % at any proved concentration, whereas the inhibition elicited by rupatadine reached 60% at 10⁻⁵

5M. In experiments where anti-H1 were added simultaneously with activation A, rupatadine was still able to inhibit TNF- α production; desloratadine, however, fail to do so. The inhibition of IL-5 production by rupatadine following activation B was significantly higher than that obtained with desloratadine. **Conclusion:** Rupatadine inhibits the production of lymphocyte inflammatory cytokines elicited by two different types of activation. Although desloratadine is also effective, rupatadine showed a better inhibitory profile, particularly on the production of Th2 cytokine IL-5 in all proved activation protocols.

This property may confer an advantage for rupatadine in the treatment of the allergic inflammation.

Antihistaminic effects of rupatadine and PKPD modelling.

Peña J, Carbó M, Solans A, Nadal T, Izquierdo I, Merlos M. *Eur J Drug Metab Pharmacokinet April/June 2008; 33 (2): 107-116.*

Rupatadine is a new oral antihistaminic agent used for the management of allergic inflammatory conditions, such as rhinitis and chronic urticaria. The aim of the present study was to develop a population pharmacokinetic/pharmacodynamics (PKPD) model for the description of the effect of rupatadine and one of its active metabolites, desloratadine, on the histamine-induced flare reaction and to predict the response to treatment after repeated administrations of rupatadine. Both rupatadine and desloratadine were characterized by two-compartmental kinetics.

For both compounds, covariates sex and weight had a significant effect on several parameters. The pharmacodynamics were described by an indirect model for the inhibition of flare formation that accounted for the contribution of both rupatadine and desloratadine to the antihistaminic effect. The final PKPD model adequately described the original data. The simulated response after repeated once-daily administrations of 10 mg rupatadine showed a significant and maintained antihistaminic effect over time, between two consecutive dosing intervals.

Rupatadine Inhibits Proinflammatory Mediator Secretion from Human Mast Cells Triggered by Different Stimuli.

Vasiadi M, Kalogeromitros D, Kempuraj D, Clemons A, Zhang B, Chliva C, Makris M, Wolfberg A, House M, Theoharides TC. *Int Arch Allergy Immunol 2009; 151(1):38-45.*

Background: Mast cells are involved in allergy and inflammation by secreting multiple mediators including histamine, cytokines and platelet-activating factor. Certain histamine 1 receptor antagonists have been reported to inhibit histamine secretion, but the effect on cytokine release from human mast cells triggered by allergic and other stimuli is not well known. We investigated the ability of rupatadine, a potent histamine 1 receptor antagonist that also blocks platelet-activating factor actions, to also inhibit mast cell mediator release.

Methods: Rupatadine (1-50 μ M) was used before stimulation by: (1) interleukin (IL)-1 to induce IL-6 from human leukemic mast cells (HMC-1 cells), (2) substance P for histamine, IL-8 and vascular endothelial growth factor release from LAD2 cells, and (3) IgE/anti-IgE for cytokine release from human cord blood-derived cultured mast cells. Mediators were measured in the supernatant fluid by ELISA or by Milliplex microbead arrays.

Results: Rupatadine (10-50 μ M) inhibited IL-6 release (80% at 50 μ M) from HMC-1 cells, whether added 10 min or 24 h prior to stimulation. Rupatadine (10-50 μ M for 10 min) inhibited IL-8 (80%), vascular endothelial growth factor (73%) and histamine (88%) release

from LAD2 cells, as well as IL-6, IL-8, IL-10, IL-13 and tumor necrosis factor release from human cord blood-derived cultured mast cells.

Conclusion: Rupatadine can inhibit histamine and cytokine secretion from human mast cells in response to allergic, immune and neuropeptide triggers. These actions endow rupatadine with unique properties in treating allergic inflammation, especially perennial rhinitis and idiopathic urticaria.

Efficacy and tolerability of rupatadine at four times the recommended dose against histamine and PAF induced flares responses and ex vivo platelet aggregation in healthy males.

Church MK *Br J Dermatol* 2010; 163(6): 1330-2

Background: European guidelines recommend increasing H1-antihistamine doses up to 4-fold in poorly responding urticaria patients. Objectives: To assess the efficacy and tolerability of high dose rupatadine (40 mg) against PAF and histamine-induced flare responses in human skin and to verify its anti-PAF activity by assessing its inhibition of PAF-induced platelet aggregation in the blood of subjects receiving 40 mg rupatadine. **Methods:** Flare study: six male volunteers received a single dose of 40 mg rupatadine. Flares were induced before dosing and up to 96 hours afterwards by intradermal PAF and histamine. Ex vivo study: four male volunteers received an oral dose of 40 mg rupatadine and blood samples taken 4 hours afterwards. Platelet aggregation was assessed in platelet-rich-plasma by incubation for 5 minutes with PAF. **Results:** Rupatadine 40 mg reached maximal plasma levels of 15.1 ± 4.4 ng/ml at one hour and its metabolite, desloratadine, 5.2 ± 0.9 ng/ml at two hours. Neither was detectable by 12 hours. Inhibition of histamine- and PAF-induced flares was significant within 2 hours, maximal at 6 hours ($87.8 \pm 3.1\%$ and $87.1 \pm 2.5\%$ inhibitions, $P < 0.0001$) and still statistically significant at 72 hours. Rupatadine 40 mg inhibited PAF-induced platelet aggregation ex vivo by $82 \pm 9\%$ ($P = 0.023$). A single oral dose of 40 mg rupatadine was well tolerated with mild transient somnolence being reported. **Conclusions:** A single dose of rupatadine at four times the recommended dose is well tolerated, highly effective for up to 72 hours against PAF- and histamine-induced dermal flares and has demonstrable PAF-receptor antagonism ex vivo.

Effect of Rupatadine on platelet-activating factor induced rhinitis in allergic rhinitis patients.

Muñoz R, Valero A, Giralt J, Izquierdo I, Doménech A, Bartra J, Picado C, Mulla J
Allergy 2011; 66, Suppl 94: 132 (Abs 290) XXX Cong Eur Acad Allergy Clin Immunol (EAACI), Istanbul, Turkey, 11-15 June 2011

Effects of Rupatadine on platelet activating factor (PAF) induced human mast cell degranulation compared with Desloratadine and Levocetirizine.

Muñoz Cano R, Torres Atencio I, Ainsua E, Martín Andorra M, Sánchez López J, Bartra J, Picado C, Valera Santiago A. *J Allergy Clin Immunol* 2012; 129, 2 Suppl : AB122 (465). *Am Acad Allergy Asthma Immunol (AAAAI) Annual Meeting 2012 Orlando, Florida, March 2-6, 2012, USA.*

Population pharmacokinetics of rupatadine in children 2-11 years of age with allergic rhinitis.

Izquierdo I, Estévez J, Doménech A, Valle A. *PAGE (Population Approach Group in Europe) Annual Meeting 2012, 5 - 8 June, Venice, Italy, Abstr 2615*

Clinical Efficacy

1. Adults

1.1. Allergic Rhinitis

A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H (1) receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis.

Saint Martin F, Dumur JP, Pérez I, Izquierdo I. *J Invest Allergol Clin Immunol* 2004; 14 (1): 34-40.

Background: The main objective of this randomized, double-blind, parallel-group, comparative study was to assess the efficacy and safety of rupatadine 10 mg (R10) and 20 mg (R20) administered once- daily for two weeks compared with those of loratadine 10 mg (L10) in the treatment of seasonal allergic rhinitis (SAR). **Methods:** A total of 339 SAR patients were randomized to receive R20 (111 patients), R10 (112 patients) or L10 (116 patients). The main efficacy variable was the mean total daily symptom score (mTDSS) based on the daily subjective assessment of the severity of rhinitis symptoms - rhinorrhea, sneezing, nasal itching, nasal obstruction, conjunctival itching, tearing and pharyngeal itching - recorded by patients. **Results:** The mTDSS was significantly lower in the groups treated with R20 (0.80 ± 0.46) and R10 (0.85 ± 0.52) than in the group treated with L10 (0.92 ± 0.51) by protocol analysis ($p=0.03$) but not by intention-to-treat analysis. The secondary variables used to assess efficacy (mDSS, DSSmax, CSS and TCSS) also showed significantly milder symptoms in patients treated with R20 and R10, particularly in sneezing and nasal itching. All treatments were well tolerated and no serious adverse events were recorded. Headache was the most frequent non-serious adverse event, and these did not show significant differences between treatments at similar dose levels. Somnolence was more frequent in R20 than in the other two groups. **Conclusions:** The present results suggest that rupatadine 10 mg a day may be a valuable and safe alternative for the symptomatic treatment of seasonal allergic rhinitis.

Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study.

Guadaño EM, Serra Batlles J, Meseguer J, Castillo JA, de Molina M, Valero A, Picado C. *Allergy* 2004; 59 (7): 766-71.

Background: The aim of this study is to establish the efficacy and safety of rupatadine vs ebastine and placebo in the treatment of seasonal allergic rhinitis (SAR). Rupatadine is a new second generation H1-antihistamine with once-daily dosing that may provide better control of symptoms than the currently used H1-receptor blockers because of its dual pharmacol. profile (anti-PAF and anti-H1). **Methods:** In a multicentre study, 250 patients with SAR were included in a double-blind, randomized, parallel-group and placebo-controlled study. Patients received either rupatadine 10 mg, ebastine 10 mg or placebo once daily for 2 wk. The main efficacy outcome was based on the patient's record of severity of nasal symptoms (sneezing, nasal itching, runny nose and nasal obstruction) and nonnasal symptoms (conjunctival itching, tearing and pharyngeal itching). The daily total symptom score (DTSS) was the mean of the DSS recorded for each of the seven symptoms assessed, and the mean DTSS (mDTSS) was the mean of the DTSS values for each study day. **Results:** Significant differences in mDTSS were detected between rupatadine and placebo (33% lower for rupatadine group; $P = 0.005$) after 2 wk of treatment. The TSS for rupatadine were 22%, lower than for ebastine, although the differences were not statistically significant. No serious adverse events were reported during the study period. **Conclusions:** Rupatadine 10 mg once daily was clearly superior to placebo in alleviating the symptoms of SAR over a 2-wk period. In comparison with ebastine, rupatadine shows a trend towards a better profile as regard several secondary efficacy variables.

Rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis: a randomised, double-blind parallel study.

Martinez Cocera C, De Molina M, Marti Guadaño E, Pola J, Conde J, Borja J, Pérez I, Arnaiz E, Izquierdo I. *J Investig Allergol Clin Immunol* 2005; 15 (1): 22-9.

This randomised, double-blind, parallel-group, multicentre clinical trial evaluated the efficacy and safety of rupatadine, a new antihistamine with antiplatelet-activating factor (PAF) activity, and cetirizine in the treatment of patients with seasonal allergic rhinitis (SAR). A total 249 patients were randomised to receive rupatadine 10 mg once daily (127 patients) or cetirizine 10 mg (122 patients) for two weeks. The main efficacy variable was the mean total daily symptom score (mTDSS) and was based on the daily subjective assessment of the severity of each rhinitis symptom—nasal (runny nose, sneezing, nasal itching and nasal obstruction) and non-nasal (conjunctival itching, tearing, and pharyngeal itching)—recorded by patients in their diaries. The mTDSS was 0.7 for both treatment groups (intention to treat analysis). In the investigator's global evaluation of efficacy at the seventh day, 93.3% and 83.7% patients in the rupatadine and cetirizine groups, respectively, showed some or great improvement ($p = 0.022$). In the per protocol analysis ($n = 181$), runny nose at the seventh day of treatment was absent or mild in 81.1% of patients in the rupatadine group and in 68.6% of patients in the cetirizine group ($p = 0.029$). In any case statistical significance was not maintained at the second week. Overall, all treatments were well tolerated. Adverse events (AEs) were similar in both treatment groups, i.e. headache, somnolence and fatigue/asthenia as the most often reported. Somnolence was reported in 9.6% and 8.5% of patients treated with rupatadine or cetirizine, respectively. The most reported AEs (67%) were mild in intensity. Our results suggest that rupatadine 10 mg may be a valuable and safe alternative for the symptomatic treatment of SAR.

Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna Challenge Chamber.

Stübner P, Horak F, Zieglmayer R, Arnaiz E, Leuratti C, Pérez I, Izquierdo I. *Ann Allergy Asthma Immunol* 2006; 96 (1): 37-44.

BACKGROUND: Rupatadine is a novel compound with potent dual antihistamine and platelet-activating factor antagonist activities and no sedative effects. **OBJECTIVE:** To evaluate the efficacy of rupatadine, 10 mg once daily, and placebo on allergen-induced symptoms (including nasal congestion), nasal airflow, nasal secretion, and subjective tolerability in response to grass pollen in a controlled allergen-exposure chamber. **Methods:** In a randomized, double-blind, placebo-controlled, crossover trial, 45 patients with a history of seasonal allergic rhinitis received rupatadine or placebo every morning for 8 days in 2 different periods separated by a 14-day washout interval. On day 8 of each crossover period, patients underwent a 6-hour allergen exposure in the Vienna Challenge Chamber, where a constant and homogeneous concentration of aeroallergens was maintained. Subjective and objective assessments were performed online during the exposure. **Results:** Subjective single and composite nasal and nonnasal symptoms were consistently less severe with rupatadine use than with placebo use starting from the first evaluation at 15 minutes to the end of the 6-hour Vienna Challenge Chamber challenge, with the most significant effects seen for nasal rhinorrhea, nasal itching, sneezing attacks, and total nasal symptoms ($P < .001$ for all). All the other symptoms (including nasal congestion, $P < \text{or} = .005$) were also significantly reduced with active treatment compared with placebo use. Mean secretion weights and overall feeling of complaint were significantly lower with rupatadine therapy than with placebo use ($P < \text{or} = .001$). Overall, rupatadine treatment was well tolerated. **Conclusion:** Rupatadine treatment is effective and well tolerated in patients with allergen-induced symptoms exposed to aeroallergens in a controlled exposure chamber.

A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis.

Fantin S, Maspero J, Bisbal C, Agache I, Donado E, Borja J, Mola O, Izquierdo I. *Allergy* 2008; 63 (7): 924-931.

Objective: To investigate the efficacy of rupatadine, in controlling symptoms of PER over a 12-week period. **Methods:** A randomized, double blind, parallel-group, placebo-controlled study was carried out in patients aged older than 12 years with PER. Main inclusion criteria were: instantaneous total symptom score (i6TSS) =45, nasal obstruction score =12, and overall assessment of PER =2 as moderate during the first visit. The primary efficacy endpoint was the 12-week average change from baseline of the patients' i6TSS. **Results:** In all, 736 patients were selected. Of them, 543 (73.8%) were randomized in three different groups: placebo ($n = 185$), cetirizine ($n = 175$) and rupatadine ($n = 183$). Rupatadine ($P = 0.008$) but not cetirizine ($P = 0.07$) statistically reduced the baseline i6TSS vs placebo (47.8%, 44.7% and 38.8%, respectively), after 12 weeks. Onset of action was observed at the first 24 h for both treatments (rupatadine vs placebo, $P = 0.013$; cetirizine vs placebo, $P = 0.015$). Furthermore, instantaneous total nasal symptoms score (iTNSS) (including nasal blockage) mean change from baseline showed a significant reduction with rupatadine 10 mg in comparison with placebo, along all treatment duration of 12 weeks. Study treatments were well tolerated. **Conclusion:** Rupatadine significantly relieves symptoms of PER, providing a rapid onset of action and maintains its effects over a long period of 12-weeks.

Rupatadine 10 and 20 mg are effective and safe in the treatment of perennial allergic rhinitis after 4 weeks of treatment: A randomized, double-blind, controlled trial with loratadine and placebo.

Kowalski ML, Jukiewicz D, Kruszewski-J, Nowak D, Zietkowski Z, Spicakova M, Vernerova E, Seberova E, Klenha K, Izquierdo I. *Therapy* 2009; 6(3): 417-25

Background and objectives: Allergic rhinitis is a global health concern of increasing prevalence that can impact quality of life and work and school performance of affected individuals. Antihistamines are recommended as the first-line treatment. This randomized, controlled trial aimed to investigate the effects of rupatadine in adult subjects with perennial allergic rhinitis. **Methods:** We randomly assigned 283 patients to receive placebo (n = 69), loratadine 10 mg (n = 70), rupatadine 10 mg (n = 73) or rupatadine 20 mg (n = 71). The study design was double blind and treatment was continued for 4 weeks. Subjective assessment of symptoms (reflective evaluation) was recorded by patients in a diary card. The primary end point was the percentage of days where the score of the most severe symptom was less than or equal to one (P_{dmax1}). Furthermore, the change from baseline in the severity of total symptom score and nasal symptom score were recorded, and the investigator and patient global assessments were evaluated. **Results:** All 283 patients were included in analyses (intention to treat); 265 (94%) patients completed the follow-up. Rupatadine 20 mg significantly improved the P_{dmax1} in comparison with placebo. Significant reductions from baseline in total symptom score were achieved with rupatadine 10 mg (-4.00), rupatadine 20 mg (-3.96) and loratadine (-3.94) compared with placebo (p < 0.01). Similarly, all three active treatments significantly reduced the nasal symptom score compared with placebo. No significant differences among groups in the incidence of overall adverse events were observed and no clinically significant QTc enlargements were detected. More patients receiving rupatadine complained of somnolence compared with loratadine. **Conclusion:** Once-daily rupatadine (10 and 20 mg) is an efficacious and safe treatment for the management of patients with perennial allergic rhinitis.

Reduction of Nasal Volume After Allergen-Induced Rhinitis in Patients Treated With Rupatadine: A Randomized, Cross-Over, Double-Blind, Placebo-Controlled Study.

Valero A, Serrano C, Bartrá J, Izquierdo I, Muñoz-Cano R, Mullol J, Picado C. *J Investig Allergol Clin Immunol* 2009; Vol. 19(6): 488-493.

OBJECTIVE: To measure the reduction in nasal obstruction using acoustic rhinometry in patients with allergic rhinitis treated with rupatadine. **Methods:** We performed a randomized, double-blind, cross-over, placebo-controlled clinical trial in asymptomatic patients with allergic rhinitis. Patients received rupatadine 10 mg or placebo once daily for 3 days, in 2 subsequent periods separated by a washout interval of 14 days. We performed a nasal allergen challenge during each period, and measured nasal volume using acoustic rhinometry and nasal nitric oxide (nNO) at baseline, and at 2 hours and 24 hours after the challenge. We also evaluated nasal symptoms (rhinorrhea, itching, obstruction, and sneezing), as well as total symptom score (T4SS) at the same time points as for the primary objective. **Results:** The study population comprised 30 outpatients with a mean (SD) age of 28 (10) years. Nasal airway blockage was significantly lower in the rupatadine group than in the placebo group (47%, P < .05) at 2 hours postchallenge. nNO in the rupatadine-treated patients remained unaltered, unlike in the placebo-treated group, where levels decreased at 2 hours. After treatment with rupatadine, patients showed a lower decrease in the mean total symptoms score at 2 hours (3.6 [2.6]) compared with placebo (3.9 [2.9]), although these differences did not achieve statistical significance. Overall, rupatadine was well tolerated and no serious or unexpected adverse events were observed. **Conclusions:** Rupatadine

10 mg can reduce nasal obstruction assessed by objective measures and is well tolerated in patients with allergic rhinitis.

ESTUDO FUTURA: Avaliação da eficácia e segurança do fumarato de rupatadina no tratamento da rinite alérgica persistente.

Olavo de Godoy Mion, Regis A. Campos, Martti Antila, Priscila Bogar Rapoport, Nelson Rosario João Ferreira de Mello Junior, Roberto Eustáquio Santos Guimarães, Marcos Mocellin, Giovanni Di Gesu, Dirceu Solé, Luc Wexler, João Ferreira de Mello, Fábio Morato Castro, Maria Letícia Chavarria. *Braz J Otorhinolaryngol* 2009; 75(5): 673-9.

Allergic rhinitis affects 10-30% of the population, negatively impacting one's quality of life and productivity. It has been associated with sinusitis, otitis media, sleep disorders, and asthma. Rupatadine is a second generation antihistamine with increased affinity to histamine receptor H1; it is also a potent PAF (platelet-activating factor) antagonist. It starts acting quite quickly, offers long lasting effect, and reduces the chronic effects of rhinitis. **AIM:** This study aims to assess the efficacy and safety of rupatadine in the treatment of persistent allergic rhinitis. **MATERIALS AND METHOD:** this is a multi-centric open prospective study. This study included 241 patients from 13 centers in Brazil and was held between October of 2004 and August of 2005. Signs and symptoms of rhinitis and tolerance to medication were analyzed after one and two weeks of treatment. **Results:** reduction on general scores from 8.65 to 3.21 on week 2 ($p < 0.001$). All signs and symptoms improved significantly in the first day of treatment ($p < 0.001$), except for nasal congestion and secretion, which improved from the second day of treatment ($p < 0.001$). Adverse events occurred in 19.9% of the cases, 27.7% on week 1. **Conclusion:** rupatadine effectively controls persistent allergic rhinitis; it is safe and presents low incidence of side effects.

Rupatadine and levocetirizine for seasonal allergic rhinitis: a comparative study of efficacy and safety.

Maiti R, Rahman J, Jaida J, Allala U, Palani A. *Arch Otolaryngol Head Neck Surg* 2010; 136(8):796-800.

OBJECTIVE: To determine the better agent among rupatadine fumarate and levocetirizine dihydrochloride for seasonal allergic rhinitis. Although treating and ensuring a decent quality of life to patients is challenging, an increasing understanding of pathomechanisms has revealed the potentiality of new-generation antihistamines in the treatment of seasonal allergic rhinitis. **DESIGN:** A 2-week, single-center, randomized, open, parallel group comparative clinical study between rupatadine and levocetirizine in patients with seasonal allergic rhinitis. **SETTING:** A tertiary care center. **PATIENTS:** Following inclusion and exclusion criteria, 60 patients were assigned to either the rupatadine or levocetirizine group. **INTERVENTIONS:** Two-week treatment with rupatadine or levocetirizine. **MAIN OUTCOME MEASURES:** After 2 weeks, all postdrug symptoms were listed, baseline laboratory investigations (total and differential leukocyte count and IgE level) were repeated, and clinical improvement was assessed in terms of change in Total Nasal Symptom Score, Rhinoconjunctivitis Quality of Life Questionnaire score, and laboratory parameters. **Results:** Differential count ($P = .01$) and absolute eosinophil count ($P = .009$) was significantly lowered by both drugs, but rupatadine was found to be superior. In the rupatadine group there was a significantly higher reduction ($P = .004$) in IgE level and Total Nasal Symptom Score ($P < .001$) compared with the levocetirizine group. There was a decrease of 18.08% ($P = .02$) in Rhinoconjunctivitis Quality of Life Questionnaire score in the rupatadine group, which was

significantly greater compared with the levocetirizine group. Incidence of adverse effects was less in the rupatadine group compared with the levocetirizine group. **Conclusion:** Rupatadine is a better choice for seasonal allergic rhinitis compared with levocetirizine because of its better efficacy and safety profile.

Rupatadine 10 mg in adolescent and adult symptom relief of perennial allergic rhinitis.

Molina M, Pinto E, Cister A, Alamar Martínez R, Montero J, García González JJ, Serra J, De La Torre F, Izquierdo I *Therapy* 2010; 7 (4): 429-436

Background & objectives: This randomized, double-blind clinical trial assessed the efficacy and safety of rupatadine 10 mg administered once-daily for 4 weeks compared with placebo and ebastine 10 mg in the management of symptoms of perennial allergic rhinitis (PAR).

Methods: We randomly assigned 223 patients to receive placebo (n = 73), ebastine 10 mg (n = 79) or rupatadine 10 mg (n = 71). The efficacy and safety population analysis included 219 patients. The efficacy assessment was based on patients reflective assessment of the severity of symptoms in a diary card. Symptoms of allergic rhinitis included rhinorrhea, sneezing, nasal itching, nasal obstruction and ocular itching. The main variable of efficacy was the percentage of days where the score of the most severe symptom was less than or equal to one (Pdmax1). Furthermore, the change from baseline in the severity of total symptom score (5TSS) and nasal symptom score (4TNSS) were measured, as well as investigators and patients global assessment of efficacy. **Results:** Pdmax1 was nonsignificantly lower for rupatadine 10 mg (49%) and ebastine 10 mg (51%) than for placebo (42%) at the end of the study period. Both 5TSS and 4TNSS were significantly improved for rupatadine 10 mg users compared with placebo (p = 0.019 and p = 0.025, respectively). No significant differences were seen between active treatments. All treatments were similarly safe and well tolerated, with headache (33%) and somnolence (17%) as the most often reported adverse events in all treatment groups. **Conclusions:** Symptomatic relief of PAR symptoms with rupatadine 10 mg was rapidly and effectively attained. A 4-week treatment of patients suffering from PAR with rupatadine 10 mg is as effective and well tolerated as ebastine 10 mg.

Rupatadine improves nasal symptoms, airflow and inflammation in patients with persistent allergic rhinitis: a pilot study.

Ciprandi G, Cirillo I. *J Biol Regul Homeost Agents* 2010, 24 (2): 177-83.

Nasal obstruction is the main symptom in patients with allergic rhinitis and may be measured by rhinomanometry. Rupatadine is a new antihistamine with potential antiallergic activities. The aim of this pilot study is to evaluate nasal symptoms, nasal airflow and nasal mediators in patients with persistent allergic rhinitis, before and after treatment with rupatadine. Twenty patients with persistent allergic rhinitis were evaluated, 15 males and 5 females (mean age 35 +/- 9.1 years), all of whom received rupatadine (10 mg/daily) for 3 weeks. Nasal and ocular symptoms (measured by VAS), rhinomanometry, and nasal mediators (ECP and tryptase) were assessed in all subjects before and after treatment. Rupatadine treatment induced significant symptom relief (both nasal and ocular, respectively p=0.005 and p =0.0004), including obstruction (p=0.0015) and significant increase of nasal airflow (p=0.0025). Moreover, there was a significant difference of nasal mediators. In **conclusion**, this pilot study demonstrates the effectiveness of rupatadine treatment in: i) improving nasal and ocular symptoms, ii) increasing nasal airflow, iii) exerting antiallergic activity in patients

with persistent allergic rhinitis. These positive results could explain the effectiveness of rupatadine in the treatment of persistent allergic rhinitis, as reported in a previous study. Further controlled studies need to be conducted to confirm these preliminary findings.

Rupatadine Improves Nasal Symptoms, Quality of Life (ESPRINT-15), and Severity in a Subanalysis of a Cohort of Spanish Allergic Rhinitis Patients.

Valero A, Izquierdo I, Giralt J, Bartra J, del Cuvillo A, Mullol J *J Investig Allergol Clin Immunol* 2011; 21(3): 229-235

Background: According to current guidelines, new second-generation oral H1-antihistamines, as well as intranasal corticosteroids (ICSs), are recommended for the treatment of allergic rhinitis (AR) in adults and children. Objective: To assess changes in AR severity, in addition to nasal symptoms and health-related quality of life (HRQoL), after 4 weeks of treatment with rupatadine in a cohort of AR patients. **Methods:** A subanalysis of a longitudinal, observational, prospective, multicenter Spanish study was carried out in spring-summer 2007. Enrolled patients had a clinical diagnosis of AR of at least 2 years' evolution, a total nasal symptom score (TNSS) of at least 5, and had not received antihistamines in the previous week or ICSs in the previous 2 weeks. HRQoL (ESPRINT-15 questionnaire), disease severity (using both the original and modified Allergic Rhinitis and its Impact on Asthma [ARIA] classifications), and nasal symptoms (TNSS) were measured at baseline and after 4 weeks of rupatadine treatment. **Results:** Data from a cohort of 360 patients treated with rupatadine were analyzed (57.2% women, 42.5% with intermittent AR, 36.4% with asthma, and 61.7% with conjunctivitis). After 4 weeks of treatment, the patients showed a significantly lower mean (SD) TNSS (8.2 [1.9] vs 3.1 [2.1], $P < .001$), a significant improvement in HRQoL (3.0 [1.2] vs 1.0 [0.9], $P < .001$) and significantly reduced AR severity ($P < .0001$). **Conclusions:** In addition to an improvement in nasal symptoms and HRQoL, rupatadine reduced AR severity after 4 weeks of treatment.

Morning and evening efficacy evaluation of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis: a randomized, double-blind, placebo-controlled trial.

Marmouz F, Giralt J, Izquierdo I, Rupatadine investigator's group *J Asthma Allergy* 2011;4 : 27-35

Background: A circadian rhythm of symptoms has been reported in allergic rhinitis (AR). Severity of all major symptoms of AR, including runny nose, sneezing, and nasal congestion, is typically at its peak in the morning. The objective of this study was to explore the efficacy of the antihistamine and platelet activating factor (PAF) antagonist rupatadine in the morning and evening and to evaluate whether rupatadine provides effective symptom relief throughout the 24-hour dosing interval. **Methods:** A total of 308 patients ≥ 18 years of age with PAR was randomly assigned to once-daily rupatadine 10 mg, rupatadine 20 mg, or cetirizine 10 mg for 4 weeks in a placebo-controlled, double-blind study. The main outcome was the morning/evening reflective total symptom score (5TSS) over the treatment period. Secondary endpoints included morning/evening reflective nasal total symptom score (4NTSS), individual symptoms, P_{dmax1} as percentage of days with daily severest symptom score #1, and subject/investigator evaluation of therapeutic response. **Results:** All active groups were significantly more effective than placebo in improving morning and evening evaluations of 5TSS ($P < 0.001$) and 4NTSS ($P < 0.001$) at 2 or 4 weeks. At morning evaluation, there was a significant reduction from baseline for 5TSS with rupatadine 10 mg

(-36.8%, $P < 0.01$) and 20 mg (-46.3%, $P < 0.01$) compared with placebo. Similarly, 4NTSS was reduced significantly more with rupatadine 10 mg (-34%, $P < 0.05$) and 20 mg (-41%, $P < 0.01$) compared with placebo. In the cetirizine 10 mg group, the reduction was -32.7% and -32.2% for 5TSS and 4NTSS, respectively, but this reduction was not significant compared with placebo. The percentage reduction was greater at evening than at morning evaluation. 5TSS reduction with rupatadine 10 mg (-40.7%, $P < 0.05$) and 20 mg (-49.9%, $P < 0.01$) and cetirizine 10 mg (-40.1%, $P < 0.05$) was significantly better than with placebo. 4NTSS values for active groups were also significantly improved versus placebo. When individual symptoms were assessed, statistically significant differences for rhinorrhea ($P < 0.01$), nasal itching ($P < 0.01$), and sneezing ($P < 0.01$) were shown in all active groups compared with placebo at morning and evening evaluations. P_{dmax1} index was significantly improved for all active groups and the overall efficacy assessed by patients or investigators showed a significant improvement ($P < 0.01$) versus placebo at 2 and 4 weeks. The incidence of somnolence was significantly greater in all active groups versus placebo. **Conclusion:** The sustained 24-hour action of rupatadine 10 mg provides an effective control of morning and evening symptoms in patients with PAR treated for up to 4 weeks.

Morning and evening efficacy evaluation of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis: a randomized, double-blind, placebo-controlled trial [Corrigendum].

Marmouz F, Giralt J, Izquierdo I. *Journal of Asthma and Allergy*. 2011;4:27–35.

A direct comparison of efficacy between desloratadine and rupatadine in seasonal allergic rhinoconjunctivitis: a randomized, double-blind, placebo-controlled study.

Lukat KF, Rivas P, Roger A, Kowalski ML, Botzen U, Wessel F, Sanquer F, Agache I, Izquierdo I. *J Asthma Allergy* 2013; 6: 31-9

Background: H1-antihistamines are recommended as the first-line symptomatic treatment of allergic rhinitis. The objective of this study was to evaluate the effects of rupatadine (RUP) versus desloratadine (DES) in subjects with seasonal allergic rhinitis (SAR). **Method:** To assess the efficacy and safety of RUP in SAR in comparison with placebo (PL) and DES. A randomized, double-blind, multicenter, international, and PL-controlled study was carried out. The main selection criteria included SAR patients over 12 years old with a positive prick test to a relevant seasonal allergen for the geographic area. Symptomatic patients at screening with a nasal symptom sum score of ≥ 6 points (nasal discharge, nasal obstruction, sneezing, and nasal pruritus), a non-nasal score of ≥ 3 points (ocular pruritus, ocular redness, and tearing eyes), and a rhinorrhea score of ≥ 2 points with laboratory test results and electrocardiography within acceptable limits were included in the study. Change from baseline in the total symptom-score (T7SS) over the 4-week treatment period (reflective evaluation) was considered the primary efficacy variable. Secondary efficacy measures included total nasal symptom score (T4NSS) and conjunctival symptom score (T3NNSS), both of which are reflective and instantaneous evaluations. Furthermore questions related to quality of life (eg, sleep disturbances or impairment of daily activities) have also been evaluated. Safety was assessed according to adverse events reported, as well as laboratory and electrocardiography controls. **Results:** A total of 379 patients were randomized, of which 356 were included and allocated to PL ($n = 122$), RUP ($n = 117$), or DES ($n = 117$). Mean change of T7SS over the 4-week treatment period was significantly reduced in the RUP (-46.1%, $P = 0.03$) and DES (-48.9%, $P = 0.01$) groups, compared with PL. Similarly,

RUP and DES were comparable and significantly superior to PL for all secondary endpoints, including nasal and conjunctival symptoms and patients' and investigator's overall clinical opinions. Symptom score evaluation (both reflective and instantaneous evaluations) throughout the treatment period showed a progressive and maintained significant improvement with both treatments at day 7 ($P = 0.01$), day 14 ($P = 0.007$), and day 21 ($P = 0.01$) in comparison with PL. Adverse events were scarce and were similar in both treatment groups. Electrocardiography (QTc) and lab test results did not show any relevant findings. **Conclusion:** RUP is a very good choice for SAR due to its contribution to the improvement of nasal (including obstruction) and non-nasal symptoms to a similar degree as DES.

Platelet-activating factor nasal challenge induces nasal congestion and reduces nasal volume in both healthy volunteers and allergic rhinitis patients.

Rosa Muñoz-Cano, M.D., Antonio Valero, M.D., Ph.D., Jordi Roca-Ferrer, Ph.D., Joan Bartra, M.D., Ph.D., Jaime Sanchez-Lopez, M.D., Joaquim Mullaol, M.D., Ph.D., and Cesar Picado, M.D., Ph.D. *Am J Rhinol Allergy* 27, e48–e52, 2013.

Background: Platelet-activating factor (PAF) is a lipid mediator produced by most inflammatory cells. Clinical and experimental findings suggest that PAF participates in allergic rhinitis (AR) pathogenesis. The aim was to assess the PAF ability to induce clinical response in nasal airway after local stimulation. **Method:** Ten nonatopic healthy volunteers (HVs) and 10 AR patients out of pollen season were enrolled. PAF increasing concentrations (100, 200, and 400 nM) were instilled into both nasal cavities (0, 30, and 60 minutes, respectively). Nasal symptoms (congestion, rhinorrhea, sneezing, itching, and total 4 symptom score and nasal volume between the 2nd and 5th cm (Vol2–5) using acoustic rhinometry (AcR), were assessed at -30, 0, 30, 60, 90, 120, and 240 minutes. **Result:** PAF increased individual and total nasal symptom score in both HVs and seasonal AR (SAR) patients from 30 to 120 minutes (maximum score at 120', $p < 0.05$). Nasal obstruction was the most relevant and lasting nasal symptom. PAF also induced a significant reduction of Vol2–5 at 90' (27%), 120' (38.7%), and 240' (36.4%). No differences in the response to PAF nasal challenge were observed between HVs and SAR subjects in either clinical symptoms or AcR. **Conclusion:** This is the first description of PAF effects on human nasal mucosa using a cumulative dose schedule and evaluated by both nasal symptoms and AcR. Nasal provocation with PAF showed long-lasting effects on nasal symptoms and nasal obstruction in HVs and in patients with SAR. Nasal challenge may be a useful tool to investigate the role of PAF in AR and the potential role of anti-PAF drugs.

Evaluation of nasal symptoms induced by platelet activating factor, after nasal challenge in both healthy and allergic rhinitis subjects pretreated with rupatadine, levocetirizine or placebo in a cross-over study design.

Rosa Muñoz-Cano, Antonio Valero, Ignacio Izquierdo, Jaume Sánchez-López, Alejandro Doménech, Joan Bartra, Joaquim Mullaol and Cesar Picado *Muñoz-Cano et al. Allergy, Asthma & Clinical Immunology* 2013, 9:43

Background: Platelet-activating factor (PAF) is produced by most inflammatory cells and it is involved in inflammatory and allergic reactions. We aimed to assess the anti-PAF effects of rupatadine and levocetirizine in the upper airways. **Findings:** Healthy volunteers (HV, $N = 10$) and seasonal allergic rhinitis (SAR, $N = 10$) asymptomatic patients were treated out of the pollen season with either rupatadine 20 mg, levocetirizine 10 mg, or placebo once a day

during 5 days prior to the PAF nasal challenge. Total 4-nasal symptom score (T4SS) and nasal patency (Vol2-5, by acoustic rhinometry) were assessed from 0 to 240 minutes after a repeated PAF challenge. In SAR patients but not in HV, both rupatadine and levocetirizine showed a trend to decrease PAF-induced T4SS from 60 to 120 minutes. Rupatadine but not levocetirizine caused a significant reduction ($p < 0.05$) of T4SS area under the curve compared to placebo. Rupatadine and levocetirizine caused no significant changes on nasal patency compared to placebo. **Conclusions:** These results suggest that both rupatadine and levocetirizine showed a tendency decrease toward nasal symptoms, but only rupatadine significantly reduces the overall nasal symptoms (AUC) induced by PAF in SAR patients.

Rupatadine relieves allergic rhinitis: a prospective observational study.

Ph. Eloy, L. Tobback and J. Imschoot *B-ENT, 2015, 11, 11-18*

Background: Allergic rhinitis has reached epidemic levels for years in Belgium and substantially impacts the quality of life of patients. Observational, non-interventional studies can provide valuable data, supplementing findings from double blind trials, on the true value of a drug therapy in daily practice. Rupatadine is a new, second-generation, selective oral H1-antihistamine. The primary objective of this study was to evaluate the evolution of quality of life in patients treated with rupatadine in clinical practice. The impact of rupatadine on the severity of allergic rhinitis symptoms, the subject's evaluation of the treatment, and the safety of rupatadine were also evaluated. **Methods:** This prospective, non-interventional, observational, multicenter study included 2,838 adults aged over 18 years. The diagnosis of moderate to severe allergic rhinitis was confirmed. Patients were assessed with validated scales at baseline and after 6 weeks of treatment with rupatadine (10 mg, once daily). **Results:** All outcome parameters improved significantly: mini-rhinoconjunctivitis quality of life questionnaire (mini-RQLQ, $p < 0.001$), total 5-symptom score (T5SS) severity ($p < 0.001$), visual analog scale (VAS) of symptom severity ($p < 0.001$), and the allergic rhinitis and its impact on asthma (ARIA) severity classification ($p < 0.001$). Compliance was very good in 72.2% of patients, and only a few minor adverse effects were reported. The therapeutic responses, evaluated by the patients, were complete relief in 21% and strong relief in 62%. **Conclusion:** This study, which included a wide cohort of allergic-rhinitis patients, confirmed the clinical benefit of rupatadine when prescribed in clinical practice, even for the most severe symptoms, including nasal congestion.

1.2. Urticaria

Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study.

Gimenez Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, Poop G, Donado E, Pérez I, Izquierdo I, Arnaiz E. *Allergy* 2007; 62 (5): 539-546.

Background: Chronic urticaria is one of the most common and disturbing cutaneous condition. The treatment of chronic idiopathic urticaria (CIU) is still a challenge. Antihistamines are recommended as first-line treatment. Rupatadine is a new potent non-sedative anti-H1. Objective: To study rupertadine efficacy and safety for moderate to severe CIU treatment. **Methods:** This randomized, double-blind, placebo-controlled, parallel-group, multicentre, study was designed to assess primarily mean pruritus score (MPS) reduction with rupertadine, 10 and 20 mg, administered once daily for 4 weeks. Three hundred and thirty-three patients with active episodes of moderate-to-severe CIU were included. **Results:** A 57.5% ($P < 0.005$) and 63.3% ($P = 0.0001$) significant MPS reduction from baseline, was observed at week 4 with 10 and 20 mg rupertadine, respectively, compared with placebo (44.9%). Both doses of rupertadine were not significantly different at any time point, with respect to their effects on pruritus severity, number of wheals and total symptoms scores. Rupertadine 10 mg had an overall better adverse event profile. **Conclusion:** Rupertadine 10 mg is a fast, long-acting, efficacious and safe treatment option for the management of patients with moderate-to-severe CIU.

Once-daily rupertadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study.

Dubertret L, Zalupca L, Cristodoulo T, Benea V, Medina I, Fantin S, Lahfa M, Pérez I, Izquierdo I, Arnaiz E. *Eur J Dermatol* 2007; 17 (3): 223-228.

This randomised, double-blind, placebo-controlled, parallel-group, international, dose-ranging study investigated the effect of treatment with rupertadine 5, 10 and 20 mg once daily for 4 weeks on symptoms and interference with daily activities and sleep in 12-65 years-old patients with moderate-to-severe chronic idiopathic urticaria (CIU). Rupertadine 10 and 20 mg significantly reduced pruritus severity by 62.05% and 71.87% respectively, from baseline, over a period of 4 weeks compared to reduction with placebo by 46.59% ($p < 0.05$). Linear trends were noted for reductions in mean number of wheals and interference with daily activities and sleep with rupertadine 10 and 20 mg over the 4-week treatment period. The two most frequently reported AEs were somnolence (2.90% for placebo, 4.29% for 5 mg-, 5.41% for 10 mg- and 21.43% for 20 mg-rupertadine-treated group) and headache (4.35% for placebo, 2.86% for 5 mg-, 4.05% for 10 mg- and 4.29% for 20 mg-rupertadine-treated group). These findings suggest that rupertadine 10 and 20 mg is a fast-acting, efficacious and safe treatment for the management of patients with moderate-to-severe CIU. Rupertadine decreased pruritus severity, in a dose- and time-dependent manner.

Fast onset of action of Rupatadine 10- and 20 mg in the reduction of pruritus in patients suffering from chronic urticaria.

Giménez Arnau A, Ianosi S, Kaszuba A, Zalupca L, Cristodoulo T, Pérez I, Arnaiz E 16th Congress of the European Academy of Dermatology and Venereology (EADV). Vienna (Austria), May 16-20 2007.

Aims: To evaluate at which time point did rupatadine 10 and 20 mg effectively relieves pruritus following the first dose, in the treatment of moderate to severe Chronic Urticaria or Chronic Idiopathic Urticaria (CIU). **Methods:** The pooled data from two randomised, double-blind, placebo-controlled, 4-week multicentre studies were used for this analyses. The first was a dose-ranging study comparing the efficacy and safety of rupatadine 5mg, 10mg and 20 mg once daily in 248 CIU patients randomised to one of the active arms or placebo. The second study compared the efficacy of rupatadine 10 mg and 20mg once daily with placebo in 334 CIU patients. Patients were included in the studies if they had CIU, i.e. pruritus, episodes of hives of characteristic wheal and flare appearance, occurring regularly (at least three times a week for a period of at least 6 weeks during the previous 3 months), without an identifiable aethiology. **Results:** A 37.8% ($p < 0.01$) and 42.17% ($p < 0.001$) significant percentarges pruritus score reduction from baseline, was observed after 12 hours drug intake) with 10 and 20 mg rupatadine respectively compared with placebo (24.32%). A clear difference between 10- and 20 mg versus placebo was observed (39.74% and $p < 0.01$; 45.32 and $p < 0.001$, respectively) after 24h treatment, showing that rupatadine, at both dosages effectively relieved CIU symptoms after the first dosage. This effect was maintained after 7 days of treatment and throughout the study period (4-weeks). **Conclusion:** Rupatadine 10- and 20 mg shows a very fast onset of action in reducing pruritus in patients with an active episode of CIU.

Fast onset of action of rupatadine in the reduction of pruritus in patients suffering from chronic urticaria : pooled analysis

Gimenez-Arnau A; Donado E; Arnaiz E; Pérez I; Izquierdo I *Allergy* 2007; 62 Suppl 83:306 Abstract 848 XXVI Congress of the European Academy of Allergology and Clinical Immunology (EAACI 2007). Göteborg (Sweden), June 9-13 2007.

Rationale: The roles of histamine and PAF (platelet activating factor) as important and complementary mediators involved in the skin of patients with atopic dermatis and chronic urticaria. It seems reasonable that a dual-blochage of histamine and PAF receptors may provide special advantage over other classic antihistamines. **Aims:** To evaluate at which time point did rupatadine 10- and 20 mg, a new histamine H1 receptor and PAF antagonist, in the treatment of moderate to severe Chronic Idiopathic Urticaria (CIU). **Methods:** The pooled data from two randomised, double-blind, placebo-controlled, 4-week multicentre studies were used for this analyses. The first was a dose-ranging study comparing the efficacy and safety of rupatadine 5-, 10- and 20 mg once daily or placebo in 248 CIU patients. The second study compared the efficacy of rupatadine 10- and 20mg once daily with placebo in 334 CIU patients. In both trials, patients were included if they had CIU, i.e. pruritus, episodes of hives of characteristic wheal and flare appearance, occurring regularly (at least three times a week for a period of at least 6 weeks during the previous 3 months), without an identifiable aethiology. **Results:** A 37.8% ($p < 0.01$) and 42. 2% ($p < 0.001$) significant percentarges pruritus score reduction from baseline, was observed after 12 hours drug intake) with 10- and 20 mg rupatadine respectively compared with placebo (24.3%). A clear difference between 10- and 20 mg versus placebo was observed (39.7% and $p < 0.01$; 45.3 and $p < 0.001$, respectively) after 24h treatment, showing that rupatadine, at both dosages effectively relieved CIU symptoms after the first dosage. This effect was maintained after 7

days of treatment and throughout the study period (4-weeks). **Conclusion:** Rupatadine shows a very fast onset of action after first administration in reducing pruritus in patients with an active episode of moderate/severe CIU.

The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo- controlled treatment with rupatadine 10 and 20 mg.

Giménez-Arnau A, Izquierdo I, Maurer M. *J Eur Acad Dermatol Venereol* 2009; 23(9): 1088-91

Background According to the EAACI/GA(2)LEN/EDF guidelines for urticaria management, modern non-sedating H1-antihistamines are the first-line symptomatic treatment for chronic urticaria. Two previous randomized clinical trials demonstrated rupatadine efficacy and safety in chronic urticaria treatment. However, a responder analysis to identify clinically meaningful differences in patients with chronic urticaria has not yet been performed. **Methods** This analysis includes the pooled data from two randomized, double-blind, placebo-controlled, multicenter studies in which chronic urticaria patients were treated with rupatadine at different doses. Responder rates were defined as the percentage of patients after 4 weeks of treatment who exhibited a reduction of symptoms by at least 50% or 75% as compared to baseline. The variables analysed were as follows: Mean Pruritus Score (MPS), Mean Number of Wheals (MNW), and Mean Urticaria Activity Score (UAS). **Results** A total of 538 patients were included. This responder analysis, using different response levels, shows that the efficacy of rupatadine 10 mg and 20 mg is significantly better as compared to placebo in the treatment of chronic urticaria patients. Notably, treatment with rupatadine 20 mg daily resulted in a higher percentage of patients with response of 75% symptom reduction or better than rupatadine 10 mg. **Conclusion** Our results support the use of higher than standard doses of non sedating antihistamines in chronic urticaria. We strongly recommend performing and reporting responder analyses for established and new drugs used by patients with chronic urticaria.

Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria.

Metz M, Scholz E, Ferran M, Izquierdo I, Giménez-Arnau A, Maurer M. *Ann Allergy Asthma Immunol* 2010; 104: 86–92.

Background: Patients with acquired cold urticaria (ACU) show itchy wheals during cold exposure. This disturbing condition involves histamine and platelet-activating factor in its pathogenesis. Rupatadine is a dual antagonist of both histamine and platelet-activating factor. **OBJECTIVE:** To assess rupatadine efficacy in preventing reactions to cold challenge in patients with ACU. **Methods:** A crossover, randomized, double-blind, placebo-controlled study in which 21 patients with ACU received rupatadine, 20 mg/d, or placebo for 1 week each is presented. The main outcome was the critical stimulation time threshold (CSTT) determined by ice cube challenge. Secondary outcomes included CSTT and the critical temperature threshold assessed by a cold provocation device (TempTest 3.0), as well as scores for wheal reactions, pruritus, burning sensations, and subjective complaints after cold challenge. **Results:** After rupatadine treatment, 11 (52%) of 21 patients exhibited a complete response (ie, no urticaria lesions after ice cube provocation). A significant improvement in CSTT compared with placebo was observed after ice cube and TempTest 3.0 challenge ($P = .03$ and $P = .004$, respectively). A significant reduction of critical temperature threshold (P

< .001) and reduced scores for cold provocation-induced wheal reactions ($P = .01$), pruritus ($P = .005$), burning sensation ($P = .03$), and subjective complaints ($P = .03$) after rupatadine treatment were also found. Mild fatigue ($n = 4$), somnolence ($n = 1$), and moderate headache ($n = 1$) were reported during active treatment. **Conclusion:** Rupatadine, 20 mg/d, shows high efficacy and is well tolerated in the treatment of ACU symptoms.

Rupatadine and levocetirizine in chronic idiopathic urticaria: a comparative study of efficacy and safety.

Maiti R, Jaida J, Raghavendra B, Goud P, Ahmed I, Palani A. *J Drugs Dermatol*. 2011 Dec 1;10(12):1444-50.

Background: Chronic Idiopathic Urticaria is difficult to treat due to its persistent debilitating symptoms. New generation anti-histaminics are first line treatment for this condition. The aim of this study is to compare efficacy and safety of rupatadine and levocetirizine in chronic idiopathic urticaria. **Methods:** A randomized, single blinded, single-centred, parallel group outdoor based clinical study was conducted in 70 patients of CIU to compare the two drugs. After initial clinical assessment and baseline investigations, rupatadine was prescribed to 35 patients and levocetirizine to another 35 patients for 4 weeks. At follow-up, the patients were re-evaluated and then compared using different statistical tools. Main outcome measures were DC eosinophil, Absolute Eosinophil Count (AEC), serum IgE, Total Symptom Score, Aeries Quality of Life Questionnaire score, and Global efficacy score. **Results:** Rupatadine significantly improved patients' clinical condition including symptom score from baseline to day 28. In rupatadine group, there was 27.9 percent decrease ($P=0.027$) in DC eosinophil, 35.6 percent decrease ($P=0.036$) in AEC, 15.3 percent decrease ($P=0.024$) in serum IgE, 28.2 percent decrease ($P=0.02$) in Total Symptom Scoring, and 27.3 percent decrease ($P=0.006$) in Aeries Quality of Life Questionnaire score. Global efficacy score of rupatadine was found to be significantly greater ($P=0.009$) than levocetirizine. The overall incidence of adverse drug reactions was also found to be less in rupatadine group. **Conclusion:** Rupatadine is a better choice in CIU in comparison to levocetirizine due to better efficacy and safety profile.

Temperature Thresholds in Assessment of the Clinical Course of Acquired Cold Contact Urticaria: A Prospective Observational One year Study

M. Estela MARTINEZ-ESCALA, Laia CURTO-BARREDO, Lluïsa CARNERO, Ramon M. PUJOL and Ana M. GIMENEZ-ARNAU *Acta Derm Venereol* 2015; 95: 278–282

Cold contact urticaria is the second most common subtype of physical urticaria. Cold stimulation standardized tests are mandatory to confirm the diagnosis. The aim of this study is to define the utility of determining thresholds (critical time and temperature) in assessment of the clinical course of typical acquired cold contact urticaria. Nineteen adult patients (10 women and 9 men; mean age 45 years) were included in the study and the diagnosis was confirmed with the ice-cube test and TempTest® 3.0. Patients were treated continuously for one year with 20 mg/day rupatadine (anti-H1). Thresholds measurements were made before and after treatment. Improvements in temperature and critical time thresholds were found in the study sample, demonstrating the efficacy of continuous treatment with rupatadine. In most cases association with a clinical improvement was found. We propose an algorithm for the management of acquired cold contact urticaria based on these results

1.3. Others – Allergy by mosquito bites

Treatment of mosquito-bite allergy with rupatadine.

Karppinen A, Brummer Korvenkontio H, Reunala T. *Allergy* 2008; 63 (Suppl 88): 82 (Abs184). XXVIIth Congress of the European Academy of Allergology and Clinical Immunology (EAACI). Barcelona (Spain), June 7-11 2008.

This double-blind, placebo-controlled, crossover study was performed with rupatadine and matched placebo in 30 mosquito-bite-sensitive adults. Rupatadine reduced the size of bite reaction and the accompanying pruritus. There was no difference in the adverse events under rupatadine and placebo. This study in mosquito-bite-sensitive adults shows that prophylactically given rupatadine is an effective treatment for the mosquito-bite whealing and accompanying pruritus. (conference abstract: 27th Congress of the European Academy of Allergology and Clinical Immunology, Barcelona, Spain, 07/06/2008-11 /06/2008).

Methods: A double-blind, placebo-controlled, crossover study was performed with rupatadine 10 mg and matched placebo in 30 mosquito-bite-sensitive adults (mean age 37 yr). The subjects had suffered from harmful mosquito bite reactions for a mean of 15 yr. Either rupatadine or placebo was taken at 8.00 hr for 4 days, followed by a 5-day washout period and then alternative treatment was given for 4 days. On day 3, in both drug periods, the subjects received 2 *Aedes aegypti* mosquito-bites on the forearm. The size of 2 15-mm bite lesions and intensity of accompanying pruritus were measured. **Results:** 26 Subjects were analyzed for the efficacy. The size of the 15-mm bite reaction was under placebo 106 sq.mm and rupatadine 55 sq.mm. This decrease (48%) was significant. The accompanying pruritus decreased from 60 (VAS; median) under placebo to 47.5 under rupatadine, which also was a significant difference. There was no significant difference in the adverse events under rupatadine and placebo.

Rupatadine 10 mg in the treatment of immediate mosquito-bite allergy.

Karppinen A, Brummer-Korvenkontio H, Reunala T, Izquierdo I. *J Eur Acad Dermatol Venereol.* 2012 Jul;26(7):919-22.

Background People frequently experience wealing and delayed papules from mosquito bites. Wealing is mediated by antiserum IgE antibodies and histamine. Rupatadine is a new antihistamine effective in allergic rhinitis and urticaria, but the effect on mosquito-bite allergy is not known. **Objective?** To determine the effectiveness of rupatadine in immediate mosquito-bite allergy-confirmed adult patients. **Methods** A double-blind, placebo-controlled, cross-over study was performed with rupatadine 10mg and matched placebo in 30 mosquito-bite-sensitive adults. The mean age was 37years and the subjects had suffered from harmful mosquito bites for a mean of 15 years. Either rupatadine or placebo was taken at 08:00 am for 4 days, followed by a 5 day wash out period and then alternative treatment was given for 4?days. On day 3, in both drug periods the subjects received two *Aedes aegypti* mosquito-bites on the forearm. The size of lesions and intensity of pruritus [visual analogue scale (VAS)] were measured after 15 min bite reaction. **Results** Twenty-six subjects were analysed for efficacy. The size of the 15 min bite reaction under placebo was of 106 mm (2) and under rupatadine, of 55 mm(2) . This is a significant decrease (48%; P = 0.0003). The accompanying pruritus decreased from 60 (VAS; median) under placebo to 47.5 under rupatadine, which also is a significant (P = 0.019) difference. There was no significant (P = 0.263) difference in adverse events under rupatadine and placebo. **Conclusion** The present placebo-controlled study in mosquito-bite-sensitive adults shows that rupatadine 10 mg prophylactically given is an effective treatment for the mosquito-bite wealing and skin pruritus.

2. Children

2.1. Allergic Rhinitis

Rupatadine in children aged 6-11 years with allergic rhinitis: a proof of concept evaluation by a 4 weeks treatment follow-up study. Rupatadine oral solution, in children aged 6-11 with allergic rhinitis: a proof of concept evaluation and 4 weeks treatment follow-up efficacy and safety study.

Izquierdo I, Cranswick N, McCreanor J, Antonijoan R, Gich I, Barbanoj MJ. *Pediatr Allergy Immunol* 2009; 20 (Suppl. 20): 2. Abstracts of the EAACI Pediatric Allergy and Asthma Meeting. Venice (Italy), November 12-14 2009. 3 – Poster Symposium.

Rupatadine oral solution in children with persistent allergic rhinitis: A randomized, double-blind, placebo-controlled study.

Potter P, Maspero JF, Vermeulen J, Barkai L, Németh I, Baillieu RA, Garde JM, Giralt J, Doménech A, Izquierdo I, Nieto A. *Pediatr Allergy Immunol*. 2013; 24(3) 144-50.

Background: Allergic rhinitis (AR) is one of the most common chronic diseases in childhood. No large, multicentre clinical trials in children with persistent allergic rhinitis (PER) have previously been performed. Rupatadine, a newer second-generation antihistamine, effective and safe in adults, is a promising treatment for children with AR. The aim of the present study was to evaluate the efficacy and safety of a new rupertadine oral solution in children aged 6-11 yr with PER. **Methods:** A multicenter, randomized, double-blind, placebo-controlled study was carried out worldwide. Patients between 6 and 11 yr with a diagnosis of PER according to ARIA criteria were randomized to receive either rupertadine oral solution (1 mg/ml) or placebo over 6 wk. The primary efficacy end-point was the change from baseline of the total nasal symptoms score (T4SS) after 4 wk of treatment. **Results:** A total of 360 patients were randomized to rupertadine (n = 180) or placebo (n = 180) treatment. Rupertadine showed statistically significant differences vs. placebo for the T4SS reduction both at 4 (-2.5 ± 1.9 vs. -3.1 ± 2.1 ; $p = 0.018$) and 6 wk (-2.7 ± 1.9 vs. -3.3 ± 2.1 ; $p = 0.048$). Rupertadine also showed a statistically better improvement in the children's quality of life compared with placebo. Adverse reactions were rare and non-serious in both treatment groups. No QTc or laboratory test abnormalities were reported. **Conclusions:** Rupertadine oral solution (1 mg/ml) was significantly more effective than placebo in reducing nasal symptoms at 4 and 6 wk and was well tolerated overall. This is the first large clinical report on the efficacy of an H1 receptor antagonist in children with PER in both symptoms and quality of life.

2.2. Urticaria

Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2–11 years.

Paul Potter, Essack Mitha, László Barkai, Györgyi Mezei, Eva Santamaría, Iñaki Izquierdo, Marcus Maurer. *Pediatric Allergy and Immunology* 27 (2016) 55–61 2015 John Wiley & Sons A/S.

Background: Recommendations in current guidelines for the treatment of chronic spontaneous urticaria (CSU) in infants and children are mostly based on extrapolation of data obtained in adults. This study reports the efficacy and safety of rupatadine, a modern H1 and PAF antagonist recently authorized in Europe for children with allergic rhinitis and CSU. **Methods:** A double-blind, randomized, parallel-group, multicentre, placebo-controlled compared study to desloratadine was carried out in children aged 2–11 years with CSU, with or without angio-edema. Patients received either rupatadine (1 mg/ml), or desloratadine (0.5 mg/ml) or placebo once daily over 6 weeks. A modified 7-day cumulative Urticaria Activity Score (UAS7) was employed as the primary end-point. **Results:** The absolute change of UAS7 at 42 days showed statistically significant differences between active treatments vs. placebo (-5.5 ± 7.5 placebo, -11.8 ± 8.7 rupatadine and -10.6 ± 9.6 desloratadine; $p < 0.001$) and without differences between antihistamines compounds. There was a 55.8% decrease for rupatadine followed by desloratadine (-48.4%) and placebo (-30.3%). Rupatadine but not desloratadine was statistically superior to placebo in reduction of pruritus (-57%). Active treatments also showed a statistically better improvement in children's quality of life compared to placebo. Adverse events were uncommon and non-serious in both active groups. **Conclusion:** Rupatadine is effective and well tolerated in the relief of urticaria symptoms, improving quality of life over 6 weeks in children with CSU. This is the first study using a modified UAS to assess severity and efficacy outcome in CSU in children.

Clinical Safety

1. General

Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain.

Valero A, de la Torre F, Castillo JA, Rivas P, del Cuvillo A, Antepará I, Borja J, Donado E, Mola O, Izquierdo I *Drug Saf* 2009; 32(1): 33-42

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 (EMA) 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 Bazett 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.

2. Cardiac Safety

Cardiac safety of rupatadine according to the new ICH guideline: a "thorough QT/QTc study".

Donado E, García O, Pérez I, Barbanoj MJ, Antonijoan R, Peña J, Solans A, Izquierdo I, Morganroth J. *XXV Congress of the European Academy of Allergology and Clinical Immunology (EAACI 2006). Vienna (Austria), June 10-14 2006. Abstract Book: 216 (Abs 760).*

Background: A delay in cardiac repolarization, measured by a prolongation of QTc interval, increases the risk of torsade de pointes, an arrhythmia that can degenerate into a fatal ventricular fibrillation, as reported previously by some antihistamines such as terfenadine or astemizole. Objective: We aimed to evaluate the effects of rupatadine, a new once-daily non-sedating H1-antihistamine with platelet activating factor (PAF) antagonist activity, on the QTc interval, according to the recommendations of EMEA and ICH Guidelines (ICH E14): a "Thorough QT/QTc study" **Methods:** This randomized, blinded (volunteers and ECG analysis), parallel, placebo and moxifloxacin controlled clinical trial was conducted in 160 healthy volunteers (gender balanced) randomized in four treatment groups: rupatadine therapeutic dose: 10mg/day or suprathreshold dose: 100mg/day (RU 100), placebo or moxifloxacin 400 mg/day. RU was dosed to steady state. A centralized ECG lab was used to evaluate the ECG digital data: 3 ECGs around each of 13 scheduled time points, after single dose and again after steady state. The primary analysis was based on individual subject corrected QT (QTc) prolongation. Treatment effects (change from baseline) were assessed using the largest time-matched mean difference on QTc between the drug and placebo. Per ICH E14, the study was considered negative if the upper bound of the 95% one sided confidence interval for the largest time-matched mean effect of the drug on the QTc excludes 10 ms. Outlier analyses were performed to complete the cardiac safety profile of rupatadine. **Results:** The validity of the trial was demonstrated by the fact that moxifloxacin, the positive control group, demonstrated the expected change in QTc duration. The ECG data for rupatadine at both 10 and 100 mg showed no signal of any effects on the ECG. There was no gender effect, pharmacodynamic-kinetic relationship of rupatadine and main metabolites, or imbalance in outliers, which also confirmed the lack of any signal of RU especially on QTc duration. No serious or unexpected adverse events were recorded. **Conclusions:** This thorough ECG trial has demonstrated that rupatadine, up to 10 times therapeutic dose, does not have any proarrhythmic potential and hence raises no cardiac safety concerns for this novel antihistamine.

Heart Rhythm Disturbances Associated With Rupatadine: A Case Series From the Spanish and Portuguese Pharmacovigilance Systems.

Carvajal A, Macias D, Salado I, Sainz M, Ortega S, Campo C, Garcia del Pozo J, Martin Arias L, Velasco A, Gonçalves S, Pombal R, Carmona R. *Clin Pharmacol Ther* 2009; 85(5): 481-4.

We searched the Spanish and Portuguese pharmacovigilance databases for spontaneous case reports of heart rhythm disturbances associated with rupatadine and other new H1 antihistamines. Five cases were found involving patients treated with rupatadine (13.9% of all reports relating to this drug). In all five cases, the reaction started after exposure and resolved when the drug was discontinued. In two cases, rupatadine was the only medication being taken by the patient, and no other condition that could explain the heart rhythm disturbances was diagnosed. The reporting odds ratio was 3.2 (95% confidence interval,

1.0-10.5). The reporting rate was 2 cases per 100,000 patients treated per year (95% confidence interval, 0.4-6.0). These results suggest a causal relationship between rupatadine and heart rhythm disturbances.

No cardiac effects of therapeutic and suprathapeutic doses of rupatadine: results from a 'thorough QT/QTc study' performed according to ICH guidelines.

Donado E, Izquierdo I, Pérez I, García O, Antonijoan RM, Gich I, Solans A, Peña J, Morganroth J, Barbanoj MJ. Br J Clin Pharmacol 2010; 69(4):401-10.

AIMS: To evaluate the effects of therapeutic and suprathapeutic doses of rupatadine on cardiac repolarization in line with a 'thorough QT/QTc study' protocol performed according to International Conference on Harmonization guidelines. **Methods:** This was a randomized (gender-balanced), parallel-group study involving 160 healthy volunteers. Rupatadine, 10 and 100 mg day⁻¹, and placebo were administered single-blind for 5 days, whilst moxifloxacin 400 mg day⁻¹ was given on days 1 and 5 in open-label fashion. ECGs were recorded over a 23-h period by continuous Holter monitoring at baseline and on treatment days 1 and 5. Three 10-s ECG samples were downloaded at regular intervals and were analysed independently. The primary analysis of QTc was based on individually corrected QT (QTcI). Treatment effects on QTcI were assessed using the largest time-matched mean difference between the drug and placebo (baseline-subtracted) for the QTcI interval. A negative 'thorough QT/QTc study' is one where the main variable is around < or =5 ms, with a one-sided 95% confidence interval that excludes an effect >10 ms. **Results:** The validity of the trial was confirmed by the fact that the moxifloxacin-positive control group produced the expected change in QTcI duration (around 5 ms). The ECG data for rupatadine at both 10 and 100 mg showed no signal effects on the ECG, after neither single nor repeated administration. Furthermore, no pharmacokinetic/pharmacodynamic relationship, gender effects or clinically relevant changes in ECG waveform outliers were observed. No deaths or serious or unexpected adverse events were reported. **Conclusions:** This 'thorough QT/QTc study' confirmed previous experience with rupatadine and demonstrated that it had no proarrhythmic potential and raised no concerns regarding its cardiac safety.

3. CNS Effects

Central and peripheral evaluation of rupatadine, a new antihistamine/platelet activating factor antagonist, at different doses in healthy volunteers.

Barbanoj MJ, Garcia-Gea C, Morte A, Izquierdo I, Pérez I, Jane F. *Neuropsychobiology*. 2004; 50 (4): 311-21.

AIMS: To assess peripheral anti-H1 and central nervous system (CNS) activity of single increasing doses of rupatidine fumarate (RU), a new antihistamine/platelet-activating factor antagonist compound, in comparison with hydroxyzine and placebo. **Methods:** Eighteen healthy young subjects of both sexes took part in a crossover, randomised, double-blind, placebo-controlled study. Treatments tested were: RU 10, 20, 40 and 80 mg and hydroxyzine 25 mg, as a positive standard. Before and several times after drug intake, peripheral anti-H1 activity was appraised by the skin reactivity to intradermal injection of histamine. CNS effects were also obtained by objective tests of psychomotor performance and subjective mood scales. **Results:** All active treatments showed a significant reduction of the wheal and flare reaction in relation to placebo, RU displaying a potent dose-dependent inhibition pattern. The global nonparametric Friedman test to changes from placebo in 15 objective variables from psychomotor performance showed a significant impairment of similar magnitude after hydroxyzine 25 mg ($p = 0.01$) and RU 80 mg ($p = 0.02$), but this was slower in development and recovery after the latter. After RU 40 mg, a smaller impairment was also obtained ($p = 0.04$). Activity ($p = 0.01$) and drowsiness ($p = 0.02$) scales showed significant changes, the subjects feeling less active and more drowsy after all active treatments. **Conclusion:** RU presents a potent dose-dependent peripheral anti-H1 activity, displaying psychomotor impairment activity only at the highest dose (80 mg), while therapeutically relevant lower doses (10 and 20 mg) were similar to placebo.

Evaluation of the cognitive, psychomotor and pharmacokinetic profiles of rupatadine, hydroxyzine and cetirizine, in combination with alcohol, in healthy volunteers.

Barbanoj MJ, Garcia-Gea C, Antonijoan R, Izquierdo I, Donado E, Pérez I, Solans A, Jane F. *Hum Psychopharmacol Clin Exp* 2006; 21 (1): 13-26.

INTRODUCTION: The Central Nervous System (CNS) impairment induced by moderate alcohol (ALC) ingestion may be enhanced if other drugs are taken simultaneously. Rupatadine (RUP) is a new H (1)-antihistamine which also inhibits platelet activating factor (PAF) release in inflammatory reactions. **OBJECTIVE:** The main aim of the study was to assess the effects of ALC 0.8 g/Kg on RUP (10 mg and 20 mg) CNS effects. An evaluation of alcohol and RUP pharmacokinetics was also attained. **Methods:** Eighteen healthy young volunteers of both sexes participated in a phase I, randomised, crossover, double-blind, placebo-controlled study. At 2-week intervals they received six treatments: (a) placebo (PLA), (b) ALC alone and ALC in combination with: (c) hydroxyzine 25 mg (HYD), (d) cetirizine 10 mg (CET), (e) RUP 10 mg or (f) RUP 20 mg. At baseline and several times thereafter, seven psychomotor performance tests (finger tapping, fine motoric skills, nystagmus, temporal estimation, critical-flicker-fusion frequency, 'd2' cancellation, simple reaction) and eleven subjective self-reports (drunkenness, sleepiness, alertness, clumsiness, anger, inattentiveness, efficiency, happiness, hostility, interest and extraversion) were carried out. Two-way (treatment, time) ANOVAs for repeated measures to each variable together with a multivariate non-parametric approach were applied. Plasma concentrations of alcohol, and of RUP and its metabolites, were quantified by validated immunofluorescence and LC/MS/MS methods, respectively. Plasma-time curves for all

compounds were analysed by means of model-independent methods. **Results:** The combination of alcohol with HYD, CET and RUP 20 mg produced more cognitive and psychomotor impairment as compared to alcohol alone, being the combination of alcohol and HYD the one which induced the greatest deterioration. The combination of alcohol and RUP 10 mg could not be differentiated from ALC alone. Subjective self-reports reflect effects on metacognition after the combination of alcohol with HYD and CET i.e. the increased objective impairment observed was not subjectively perceived by the subjects. No significant differences were obtained when comparing alcohol plasma concentrations assessed after the treatments evaluated. RUP showed a lineal kinetic relationship after 10 and 20 mg with a higher exposition to both metabolites assayed. **Conclusions:** Present results showed that single oral doses of rupatadine 10 mg in combination with alcohol do not produce more cognitive and psychomotor impairment than alcohol alone. Higher doses of rupatadine, in combination with alcohol, may induce cognitive and psychomotor deterioration as hydroxyzine and cetirizine at therapeutic doses.

Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers.

Vuurman E, Theunissen E, van Oers A, van Leeuwen C, Jolles J. *Hum Psychopharmacol Clin Exp* 2007; 22 (5): 289-97. 27

Introduction: Rupatadine fumarate is a potent, selective, histamine H(1)-receptor antagonist and PAF inhibitor with demonstrated efficacy for the relief of allergic rhinitis. Rupatadine does not easily cross the blood-brain barrier and is believed to be non-sedating at therapeutic doses. Consequently, rupatadine should show no impairment on car driving. **OBJECTIVE:** This study compared the acute effects of rupatadine, relative to placebo and hydroxyzine (as an active control), on healthy subjects' driving performance. **Methods:** Twenty subjects received a single dose of rupatadine 10 mg, hydroxyzine 50 mg, or placebo in each period of this randomized, double-blind, three-way crossover study. Two hours postdosing, subjects operated a specially instrumented vehicle in tests designed to measure their driving ability. Before and after the driving tests ratings of sedation were recorded. **Results:** There was no significant difference between rupatadine and placebo in the primary outcome variable: standard deviation of lateral position (SDLP); however, hydroxyzine treatment significantly increased SDLP ($p < 0.001$ for both comparisons). Objective (Stanford sleepiness scale) and subjective sedation ratings (Visual Analogue Scales) showed similar results: subjects reported negative effects after hydroxyzine but not after rupatadine. **Conclusion:** Rupatadine 10 mg is not sedating and does not impair driving performance.

Rupatadine does not potentiate the depressant CNS effects of lorazepam: randomized, double-blind, crossover, repeated dose, placebo-controlled study (p).

García-Gea C, Ballester MR, Martínez J, Antonijoan RM, Donado E, Izquierdo I, Barbanoj MJ *Br J Clin Pharmacol* 2010 ,69(6): 663-74.

Although one defining characteristic of second generation H-1-antihistamines is their lack of CNS effects, it has been proved that some compounds of this group are not devoid of such effects. There is evidence that second generation H-1-antihistamine compounds without relevant CNS effects at therapeutic doses could increase the behavioural impairment produced by sedating drugs when both are taken concomitantly. The evaluation of possible drug interactions is crucial, especially when both compounds could

have CNS effects, due to the possible consequences at the patient safety level. **WHAT THIS STUDY ADDS** The study demonstrates the lack of CNS effects after repeated administration at therapeutic doses of the unique second generation H-1-antihistamine with anti-PAF activity. The study demonstrates the lack of interaction between repeated administration of rupatadine 10 mg and a single oral dose of lorazepam 2 mg. The study presents a useful design to evaluate the interaction between two compounds saving time and the exposure of the volunteers to medication. **AIM** The main objective was to assess whether benzodiazepine intake when rupatadine plasma concentrations were at steady-state would increase the CNS depressant effects. Rupatadine is a new H-1-antihistamine which also inhibits platelet activating factor (PAF) release and has been shown to be clinically effective at doses of 10 mg. **Methods** Sixteen healthy young volunteers took part in a crossover, randomized, double-blind, placebo controlled trial comprising two experimental periods (repeated administration for 7 days of rupatadine 10 mg or placebo as single oral daily doses, separated by a washout of 14 days). On days 5 and 7, according to a fully balanced design, a single oral dose of lorazepam 2 mg or placebo was added. CNS effects were evaluated on these days by seven objective tests of psychomotor performance and eight subjective visual analogue scales (VAS) at pre-dose and several times after drug intake. Four treatment conditions were evaluated: placebo, rupatadine 10 mg, lorazepam 2 mg and rupatadine 10 mg + lorazepam 2 mg. **Results** Significant CNS effects, either impairment of psychomotor performance or subjective sedation, were observed when lorazepam was administered, either alone or in combination with steady state concentrations of rupatadine. No significant differences were found between these two conditions. In addition, rupatadine was not different from placebo. All treatments were well tolerated. **Conclusion** Repeated doses of rupatadine (10 mg orally) did not enhance the CNS depressant effects of lorazepam (2 mg orally, single dose) either in objective psychomotor tasks or in subjective evaluations.

4. Drug Interactions

Influence of food on the oral bioavailability of rupatadine tablets in healthy volunteers: a single-dose, randomized, open-label, two-way crossover study.

Solans A, Carbó M, Peña J, Nadal T, Izquierdo I, Merlos M. *Clin Ther* 2007; 29 (5): 900-8.

BACKGROUND: Rupatadine is an oral active antihistamine for the management of diseases with allergic inflammatory conditions, such as perennial and seasonal rhinitis and chronic idiopathic urticaria. Oral rupatadine has been approved for the treatment of allergic rhinitis and chronic urticaria in adults and adolescents in several European countries. **OBJECTIVE:** The purpose of this study was to describe the effect of the concomitant intake of food on the pharmacokinetic profile and bioavailability of a single dose of rupatadine. **Methods:** This was a single-dose, randomized, open-label, 2-way crossover study in which healthy male and female volunteers received a single, 20-mg oral dose of rupatadine under fed and fasting conditions. Blood samples were collected and plasma concentrations of rupatadine and its active metabolites desloratadine and 3-hydroxydesloratadine were determined by liquid chromatography tandem mass spectrometry. Tolerability was based on the recording of adverse events (AEs), physical examinations, electrocardiograms, and laboratory tolerability tests immediately before each treatment period and at the final visit of the study. **Results:** Twenty-four volunteers (12 males; mean [SD] age, 25.4 [5.3] years [range, 18-34 years]; mean [SD] weight, 71.2 [4.3] kg [range, 64-77 kg]; 12 females; mean [SD] age, 26.8 [6.5] years [range, 18-38 years]; mean [SD] weight, 58.4 [6.8] kg, [range 50-

69 kg]) were enrolled and randomized with equal distribution of sex. A significant increase in AUC from drug administration to the final quantifiable sample (AUC(0-t)) and AUC from drug administration to infinity (AUC(0-infinity)) values of rupatadine was seen under fed conditions without affecting C(max). The ratios (90% CI) of the mean log-transformed AUC(0-t) and AUC(0-infinity) for rupatadine revealed a significant increase in AUC(0-t) (ratio 131%; 90% CI, 111%-154%) and AUC(0-infinity) (ratio 133%; 90% CI, 113%-156%), whereas C(max) remained unaltered (ratio 97%; 90% CI, 80%-116%). Plasma concentration-time profiles of desloratadine and 3-hydroxydesloratadine were similar with and without food, and no differences were seen for AUC(0-t), AUC(0-infinity), or C(max). Seven (28%) subjects reported ≥ 1 AE. All AEs were mild, resolved spontaneously, and did not affect the outcome of the study. **Conclusions:** The results of this study indicate that concomitant intake of food with a single 20-mg oral dose of rupatadine exhibits a significant increase in rupatadine bioavailability. Despite the absence of bioequivalence, the drug was well tolerated under fed and fasting conditions, and no major changes in severity and/or prevalence of AEs were reported.

Pharmacokinetic and safety profile of rupatadine when coadministered with azithromycin at steady-state levels: a randomized, open-label, two-way, crossover, Phase I study.

Solans A, Izquierdo I, Donado E, Antonijoan R, Peña J, Nadal T, Carbo M, Merlos M, Barbanoj M. *Clin Ther* 2008; 30 (9): 1639-50.

Background: Rupatadine is an oral active antihistamine and platelet-activating factor antagonist indicated for the management of allergic rhinitis and chronic urticaria in Europe. **OBJECTIVE:** The purpose of this study was to describe the effect of the concomitant administration of azithromycin and rupatadine on the pharmacokinetics of rupatadine and its metabolites after repeated doses. **Methods:** This was a multiple-dose, randomized, open-label, 2-way, crossover, Phase I study in which healthy male and female volunteers received rupatadine 10 mg once a day for 6 days either alone or with azithromycin 500 mg on day 2 and 250 mg from day 3 to day 6. Treatments were administered after a fasting period of 10 hours with 240 mL of water, and fasting conditions were kept until 3 hours postmedication. A washout period of at least 21 days between the 2 active periods was observed. Blood samples were collected and plasma concentrations of rupatadine and its metabolites desloratadine and 3-hydroxydesloratadine were determined by liquid chromatography tandem mass spectrometry. Tolerability was based on the recording of adverse events (AEs), physical examination, electrocardiograms, and laboratory screen controls at baseline and the final study visit. **Results:** Twenty-four healthy volunteers (15 males, 9 females; mean (SD) age, 25.67 (5.58) years; weight, 65.96 (8.57) kg) completed the study. Except for maximum observed concentration during a dosing interval (C_{max, ss}) of 3-hydroxydesloratadine, on average, there were no statistically significant differences in mean plasma concentrations in any of the main pharmacokinetic parameters of rupatadine, desloratadine, and 3-hydroxydesloratadine when administered in combination with azithromycin or alone. The C_{max, ss} ratio was 111 (90% CI, 91-136) and area under the plasma concentration-time curve during a dosing interval (AUC_{0-tau}) ratio had a value of 103 (90% CI, 91-117). The corresponding ratios for the rupatadine metabolites were 109 (90% CI, 100-120) for C_{max, ss} and 103 (90% CI, 96-110) for AUC_{0-tau} for desloratadine and 109 (90% CI, 103-115) for C_{max, ss} and 104 (90% CI, 100-108) for AUC_{0-tau} for 3-hydroxydesloratadine. Point estimates for C_{max, ss} ratios using paired data were 111% for rupatadine, 109% for desloratadine, and 109% for 3-hydroxydesloratadine. The 90% CIs were included in the interval 80% to 125% for desloratadine and 3-hydroxydesloratadine,

whereas 90% CI for rupatadine was shifted to the right of the interval used for comparing bioavailability of the drugs. A total of 5 subjects reported 9 AEs; 5 of these were thought to be related to the drug administration and all were categorized as mild or moderate. The reported AEs were somnolence (1/24 in the rupatadine group and 1 /24 in the rupatadine plus azithromycin group), diarrhea (1/24 in the rupatadine plus azithromycin group), and gastric discomfort (2/24 in the rupatadine plus azithromycin group). Four AEs were considered not to be related (2 episodes of headache, 1 anemia, 1 cheilitis). All were resolved spontaneously. No serious AEs were reported. **Conclusions:** The results of this study in these healthy volunteers found no significant differences in pharmacokinetic parameters other than C_{max}, ss of 3-hydroxydesloratadine between rupatadine 10 mg administered alone or with azithromycin 500 mg on day 2 and 250 mg from day 3 to day 6. The administration of rupatadine compared with rupatadine plus azithromycin met the regulatory definition of bioequivalence in terms of exposure and rate parameters; however, C_{max}, ss of rupatadine was outside the conventional confidence interval.

Review Articles

Rupatadine: A new selective histamine H (1) receptor and platelet-activating factor (PAF) antagonist. A review of pharmacological profile and clinical management of allergic rhinitis.

Izquierdo I, Merlos M, Garcia-Rafanell J. *Drugs Today* 2003; 39 (6): 451-68.

Rupatadine is a new agent for the management of diseases with allergic inflammatory conditions, such as seasonal and perennial rhinitis. The pharmacological profile of rupatadine offers particular benefits in terms of a strong antagonist activity towards both histamine H(1) receptors and platelet-activating factor (PAF) receptors. Rupatadine has a rapid onset of action, and its long-lasting effect (> 24 h) permits once-daily dosing. Rupatadine should not be used in combination with the cytochrome P450 inhibitors, such as erythromycin or ketoconazole, due to an increase in AUC and C_{max} for rupatadine, although no clinically relevant adverse events have been reported. In addition, rupatadine, at the recommended dose of 10 mg, has been shown to be free of sedative effects and not to cause significant changes in the corrected QT interval in special populations, including the elderly, nor when coadministered with erythromycin or ketoconazole. Preclinical data have also shown that rupatadine and its main active metabolites did not interfere with cloned human HERG channel and did not affect in vitro isolated dog Purkinje fibers at concentrations at least 2000 times greater than those obtained with therapeutic doses in humans. Rupatadine is clinically effective in relieving symptoms in patients with seasonal and perennial allergic rhinitis. Newly published data on its efficacy and safety suggest that this compound may improve the nasal and non-nasal symptoms in comparison to other currently available second generation H(1) receptor antihistamines.

Rupatadine: pharmacological profile and its use in the treatment of allergic disorders.

Picado C. *Expert Opin Pharmacother* 2006; 7 (14): 1989-2001.

Rupatadine is a once-daily, non-sedating, selective and long-acting new drug with a strong antagonist activity towards both histamine H1 receptors and platelet-activating factor receptors. The use of rupatadine is indicated in adult and adolescent patients (> 12 years of age) suffering from intermittent and persistent allergic rhinitis and chronic idiopathic urticaria. In the treatment of these diseases, rupatadine is at least as effective as ebastine, cetirizine, loratadine and desloratadine. A very good safety profile of rupatadine has been evidenced in various studies, including a long-term (1-yr) safety study. Rupatadine does not present drug-drug interactions with azithromycin, fluoxetine and lorazepam, but should not be administered concomitantly with known CYP3A4 inhibitors.

Rupatadine: a review of its use in the management of allergic disorders.

Keam SJ, Plosker GL. *Drugs*. 2007; 67 (3): 457-74.

Rupatadine (Rupafin((R)), Rinialer((R)), Rupax((R)), Alergoliber((R))) is a selective oral histamine H(1)-receptor antagonist that has also been shown to have platelet-activating factor (PAF) antagonist activity in vitro. It is indicated for use in seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in patients aged ≥ 12 years. Clinical trials show that rupatadine is an effective and generally well tolerated treatment for allergic rhinitis and CIU. It has a rapid onset of action and a prolonged duration of activity. Importantly, it has no significant effect on cognition, psychomotor function or the cardiovascular system. Once-daily rupatadine significantly improves allergic rhinitis symptoms in patients with SAR, PAR or persistent allergic rhinitis (PER) compared with placebo, and provides similar symptom control to that of loratadine, desloratadine, cetirizine or ebastine. In patients with CIU, longer-term use of rupatadine improves CIU symptoms to a greater extent than placebo. It is as well tolerated as other commonly used second-generation H(1)-receptor antagonists. Thus, the introduction of rupatadine extends the range of oral agents available for the treatment of allergic disorders, including allergic rhinitis and CIU.

Rupatadine in allergic rhinitis and chronic urticaria.

Mullol J, Bousquet J, Bachert C, Canonica WG, Gimenez-Arnau A, Kowalski ML, Martí-Guadaño E, Maurer M, Picado C, Scadding G, Van Cauwenberge P. *Allergy* 2008; 63 (Suppl. 87): 5-28.

Histamine is the primary mediator involved the pathophysiology of allergic rhinitis and chronic urticaria, and this explains the prominent role that histamine H1-receptor antagonists have in the treatment of these disorders. However, histamine is clearly not the only mediator involved in the inflammatory cascade. There is an emerging view that drugs which can inhibit a broader range of inflammatory processes may prove to be more effective in providing symptomatic relief in both allergic rhinitis and chronic urticaria. This is an important consideration of the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative which provides a scientific basis for defining what are the desirable properties of an ideal antihistamine. In this review of rupatadine, a newer dual inhibitor of histamine H1- and PAF-receptors, we evaluate the evidence for a mechanism of action which includes anti-inflammatory effects in addition to a powerful inhibition of H1- and PAF-receptors. We assess this in relation to the clinical efficacy (particularly the speed of onset of action) and safety of rupatadine, and importantly its longer term utility in everyday life. In clinical trials,

rupatadine has been shown to be an effective and well-tolerated treatment for allergic rhinitis and chronic idiopathic urticaria (CIU). It has a fast onset of action, producing rapid symptomatic relief, and it also has an extended duration of clinical activity which allows once-daily administration. In comparative clinical trials rupertadine was shown to be at least as effective as drugs such as loratadine, cetirizine, desloratadine and ebastine in reducing allergic symptoms in adult/adolescent patients with seasonal, perennial or persistent allergic rhinitis. Importantly, rupertadine demonstrated no adverse cardiovascular effects in preclinical or extensive clinical testing, nor negative significant effects on cognition or psychomotor performance (including a practical driving study). It improved the overall well-being of patients with allergic rhinitis or CIU based on findings from quality of life questionnaires and patient global rating scores in clinical trials. Thus, rupertadine is a recently introduced dual inhibitor of histamine H1- and PAF-receptors, which has been shown to be an effective and generally well-tolerated treatment for allergic rhinitis and chronic urticaria. It possesses a broader profile of anti-inflammatory properties inhibiting both inflammatory cells and a range of mediators involved in the early- and late-phase inflammatory response, but the clinical relevance of these effects remain to be clarified.

Pharmacological profile, efficacy and safety of rupertadine in allergic rhinitis.

Katiyar S, Prakash S. *Prim Care Respir J* 2009; 18(2): 57-68.

Allergic rhinitis (AR) is a disease with high prevalence. In AR, exposure to airborne allergens elicits an allergic response which involves epithelial accumulation of effector cells - e.g. mast cells and basophils - and subsequent inflammation. During the early response in AR, histamine has been found to be the most abundant mediator and it is associated with many symptoms of this disease mediated through the histamine H1 receptor. Therefore, anti-histamines have a role to play in the management of AR. However, the available antihistamines have certain well-known side effects like sedation and potential pro-arrhythmic effects owing to their interactions with other drugs, as well as having poor or no effect on platelet activating factor (PAF) which also plays an important role in AR. This article is a qualitative systematic literature review on the pharmacological profile of rupertadine in order to evaluate its safety and efficacy in AR as compared to other anti-histamines. Rupertadine is a once-daily non-sedative, selective, long-acting H1 anti-histamine with antagonistic PAF effects through its interaction with specific receptors. Rupertadine significantly improves nasal symptoms in patients with AR. It has a good safety profile and is devoid of arrhythmogenic effects. These properties make rupertadine a suitable first line anti-histamine for the treatment of AR.

Rupertadine for the treatment of allergic rhinitis and urticaria.

Metz M, Maurer M. *Expert Rev Clin Immunol* 2011; 7(1):15-20.

Allergies are a widespread group of diseases of civilization and most patients are still undertreated. Since histamine is considered to be the most important mediator in allergies such as allergic rhinitis and urticaria, the most commonly used drugs to treat these disorders are antihistamines acting on the histamine 1 (H1) receptor. The currently available antihistamines, however, have significant differences in their effects and safety profiles. Furthermore, the Allergic Rhinitis and its Impact on Asthma initiative calls for additional desirable properties of antihistamines. Here, we review the profile of rupertadine, a new dual platelet-activating factor and H1-receptor antagonist that fulfils these criteria and therefore offers an excellent option for the treatment of allergic diseases.

Rupatadine: a novel second-generation antihistamine.

Grzelewska-Rzymowska I, Górski P *Post Dermatol Alergol* 2011, 28(6): 480–488

Histamine is the primary mediator involved in the pathogenesis of allergic rhinitis and chronic idiopathic urticaria. Platelet-activating factor (PAF) is also a mediator which plays a key role in the allergic reaction. Rupatadine is a novel antihistamine of the second generation approved recently in Europe for the treatment of allergic rhinitis and chronic idiopathic urticaria in patients aged \geq 12 years. Rupatadine shows both antihistamine and anti-PAF effects because it presents hybrid molecule. One unit of this molecule has high affinity to H1 receptor, and the second one blocks the receptor for PAF. Relative potency of rupatadine is much higher than that of other second generation antihistamines. Rupatadine also has anti-allergic and anti-inflammatory activity. The drug blocked the release of histamine from mast cells and other proinflammatory cytokines such as IL-5, IL-6, IL-8, TNF- α and GM-CSF from activating human lymphocytes. It also blocked in vitro chemotaxis of human eosinophils to eotaxin, and neutrophils to PAF and LTB₄. Anti-allergic and anti-inflammatory activity of rupatadine **results** from blocking NF κ B. Clinical trials have indicated that rupatadine is significantly more effective than placebo and equally effective as other antihistamines of the second generation. Rupatadine is well tolerated, and side effects are mild and moderate, the most common ones were headache and somnolence. The drug is safe, not cardiotoxic, does not impair psychomotor or cognitive activity.

Positioning of antihistamines in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.

Mullol J *Clin Exp Allergy Rev* 2012, 12:17-26

Allergic rhinitis (AR) is a major health problem with high and ever-increasing prevalence worldwide. At least one-fifth of adults in industrialized countries are estimated to have AR, defined as nasal and eye symptoms that are sufficiently severe to have a substantial negative impact on the quality of life (QoL). The former classification of AR comprised seasonal AR (SAR) and perennial AR (PAR), which did not adequately reflect the presentation and clinical course of the disease. The Allergic Rhinitis and its Impact on Asthma (ARIA) classification is based on the duration of symptoms and the disease severity. Both intermittent AR (IAR: symptoms \leq 4 days/week or \leq 4 consecutive weeks) and persistent AR (PER: symptoms $>$ 4 days/week and $>$ 4 consecutive weeks) may be mild, moderate, or severe based on the QoL impairment (sleep, daily activities/leisure, work productivity/ school performance) and bothersome symptoms. Despite its disabling effects, AR remains a condition where affected individuals do not seek appropriate treatment, are undertreated and do not adhere well to treatment, which all lead to low disease control and high societal costs. The four pillars of AR treatment are allergen and pollutant avoidance, patient education, pharmacotherapy and allergen-specific immunotherapy. Oral antihistamines, together with intranasal corticosteroids and leucotriene antagonists, constitute important pharmacological options for the treatment of AR at all levels of severity. New second generation antihistamines are H1-receptor antagonists with high efficacy (rapid onset of action for AR symptoms, sometimes even on nasal congestion, improvement of QoL and additional anti-allergic effects) and safety (low sedation rates). Although new antihistamines have been studied and approved for SAR and PAR, only some of them have been reported to show efficacy and safety for treatment of AR under the ARIA classification: levocetirizine (high efficacy) and rupatadine (dual antihistamine and anti-PAF effects) for PER, and desloratadine (high safety) for both IAR and PER.

Rupatadine for allergic rhinoconjunctivitis: metanalysis of randomised, double-blind, placebo-controlled studies.

Compalati E, Anthi R, Braido F, Canonica GW *XXXI Cong Eur Acad Allergy Clin Immunol (EAACI), Geneva, Switzerland, 16-20 June 2012 (Abtr 862)*

Rupatadine (Rupafin), symptomatic treatment of allergic rhinitis and urticaria in adults and adolescents

Bijl D. *Geneesmiddelenbulletin 2012, 46(3) 29-31*

Update on rupatadine in the management of allergic disorders

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In a review of rupatadine published in 2008, the primary focus was on its role as an antihistamine, with a thorough evaluation of its pharmacology and interaction with histamine H1-receptors. At the time, however, evidence was already emerging of a broader mechanism of action for rupatadine involving other mediators implicated in the inflammatory cascade. Over the past few years, the role of platelet-activating factor (PAF) as a potent mediator involved in the hypersensitivity-type allergic reaction has gained greater recognition. Rupatadine has dual affinity for histamine H1-receptors and PAF receptors. In view of the Allergic Rhinitis and its Impact on Asthma group's call for oral antihistamines to exhibit additive anti-allergic/anti-inflammatory properties, further exploration of rupatadine's anti-PAF effects was a logical step forward. New studies have demonstrated that rupatadine inhibits PAF effects in nasal airways and produces a greater reduction in nasal symptoms than levocetirizine. A metaanalysis involving more than 2500 patients has consolidated the clinical evidence for rupatadine in allergic rhinoconjunctivitis in adults and children (level of evidence Ia, recommendation A). Other recent advances include observational studies of rupatadine in everyday clinical practice situations and approval of a new formulation (1 mg/ml oral solution) for use in children. In this reappraisal, we revisit some key properties and pivotal clinical studies of rupatadine and examine new clinical data in more detail including studies that measured healthrelated quality of life and studies that investigated the efficacy and safety of rupatadine in other indications such as acquired cold urticaria, mosquito bite allergy and mastocytosis.