Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rupatadine

Proprietary Product Name: Rupafin

Sponsor: iNova Pharmaceuticals (Australia) Pty Ltd

May 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Withdrawn
Date of Decision:	17 March 2011
Active ingredient(s):	Rupatadine fumarate
Product Name(s):	Rupafin
Sponsor's Name and Address:	iNova Pharmaceuticals (Australia) Pty Ltd 9-15 Chilvers Road Thornleigh NSW 2120
Dose form(s):	Tablet
Strength(s):	10 mg
Container(s):	Blister pack
Pack size(s):	Packs of 3 and 20
Approved Therapeutic use:	Not applicable
Route(s) of administration:	Oral
Dosage:	10 mg daily

Product Background

This AusPAR describes the evaluation of a submission by iNova Pharmaceuticals (Australia) Pty Ltd to register rupatadine (Rupafin), a new chemical entity. Rupafin is a second generation, long acting anti-allergic compound which displays strong antagonist activity towards both histamine H1-receptors and platelet-activating factor (PAF) receptors (dual activity). The PAF induces vasodilation and increased permeability which may be responsible for the appearance of rhinorrhoea and nasal congestion. PAF antagonism represents the likely mechanism behind the inhibition of eosinophil migration which has been suggested to be beneficial in the treatment of chronic urticaria. Rupafin inhibits the degranulation of mast cells induced by immunological and non-immunological stimuli, and inhibits the release of cytokines in human mast cells and monocytes. Some of the metabolites retain antihistaminic activity and may partially contribute to the overall efficacy of the drug. Rupafin exhibits greater affinity for peripheral H1-receptors than for central H1-receptors. It has little liposolubility resulting in minimal crossing of the blood-brain barrier. These properties account for the sponsor's claim of the observed lack of sedation. Rupatadine has some structural similarities to loratadine and desloratadine, both of which are registered in this country as S3 (non-prescription, pharmacist only) medicines.

The proposed indications are for the:

Symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in adults and adolescents (over 12 years of age).

The proposed dose is one tablet (10 mg) daily with or without food.

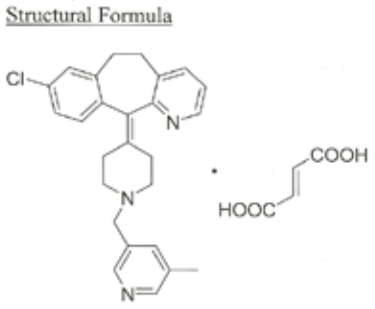
Regulatory Status

The product is marketed in a number of European countries, initially in Spain in March 2003 and then throughout much of the European Union (EU) including the United Kingdom in September 2009. It is also marketed in a number of countries in Central and South America and Africa. The indications include SAR, PAR and CIU. An application has not been submitted in Switzerland, Canada or the United States. An application was submitted in New Zealand on 29 October 2009.

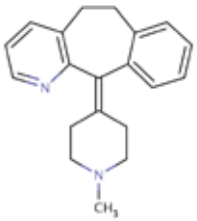
II. Quality Findings

Drug Substance (active ingredient)

Rupatadine displays activity towards both histamine H1 receptors and Platelet-Activation Factor (PAF) receptors. In this product it is presented as 12.8 mg of the rupatadine fumarate which is equivalent to 10 mg of rupatadine. It is similar to the registered anti-histamines azatadine, loratadine and desloratadine. In fact desloratadine is an active metabolite of rupatadine (and loratadine).



rupatadine fumarate



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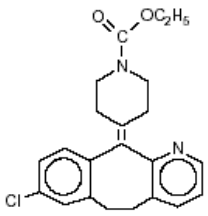
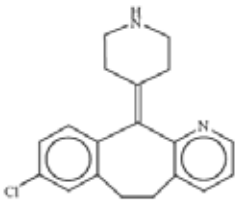


loratadine



desloratadine

Rupatadine fumarate is not naturally occurring and purely synthetic.[1] It is manufactured by a 3-step reaction scheme with many purification steps. It is achiral and the route of synthesis leads to a single polymorphic form of the anhydrous, non-solvated material. The final material precipitates as fine crystals and further micronisation is not necessary. The solubility decreases with increasing pH. The specification for rupatadine includes satisfactory limits for assay. Two of the synthetic impurities have proposed limits above the International Conference on Harmonisation (ICH) qualification threshold of 0.15% but these limits have been toxicologically qualified and/or justified.[2] Unspecified impurities

[1] Rupatadine fumarate will be referred to as rupatadine for the remainder of this AusPAR.
[2] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

are controlled to ICH levels. The residual solvents were controlled to tighter than ICH guidance.

Drug Product

The drug product is to be manufactured by J Uriach i Cia SA in Barcelona, Spain. Manufacture is by a typical wet granulation process.

The assay limits comply with the Therapeutic Goods Order 78 and allow for the change observed on storage. There are two specified degradants, the expiry limit for one of these degradants was supported with toxicological data and, as stated above, the limit for the other was accepted as it is a metabolite. Suitable release limits were set. Unspecified degradants are controlled to ICH limits.

The conditions for the dissolution test lacked discriminatory power in that 100% of the rupatadine is dissolved in 5 minutes. Data under other conditions indicated that sink conditions were not met, though in pH 4.5 the maximum dissolved was 90% showed sink conditions were almost met. Thus, the proposed dissolution test (which uses a medium relevant to normal gastric conditions) was accepted on the proviso that the limit be set at no less than (NLT) 85% in 15 minutes (with only 1 failure in 12 allowed) to ensure that the method is acting as an equivalent to a disintegration test. This was considered sufficient to ensure batch to batch (and tablet to tablet) consistency.

Stability data was provided to support the proposed shelf life of 3 years when stored below 25ºC in PVC/PVDC/Al blister packs. The storage condition 'protect from light' also applies.

Bioavailability

The formulation used in the Phase III efficacy studies was the same as proposed for supply in Australia.

Two bioavailability studies were provided. As well as rupatadine, the analytical methods also determined the concentrations of the active metabolites desloratadine (UR-12790, BCP) and either free UR-12788 (3-hydroxy desloratadine) or total (free and conjugated) UR-12788. The sponsor did not determine the levels of two other active metabolites UR-12767 (6-hydroxy desloratadine) and UR-12768 (5-hydroxy desloratadine). The sponsor argued that this was not required as they (like UR-12788) are both secondary metabolites, the relative activities are lower than rupatadine, UR-12790 and UR-12788 and that this would have required the collection of an unacceptable amount of blood. This was accepted in light of the fact that ICH guidance[3] states that 'bioequivalence should be based upon measured concentrations of the parent compound'.

The sponsor did not determine the absolute bioavailability of the tablets. It justified this based on the claim that a safe intravenous (IV) solution could not be prepared, a study performed against an oral solution is sufficient, and no adverse events have been observed since the overseas launch in 2003. This argument was brought to the attention of the Delegate.

UR/FC99/I-02

This study determined the relative bioavailability of the proposed 10 mg tablet to a 1 mg/mL compounded oral solution and a 1 mg/mL simple (extemporaneous) oral solution all at a dose of 10 mg. It was concluded that the bioavailability (area under the plasma concentration versus time curve - AUC) of rupatadine from the 10 mg tablet was

[3] CPMP/QWP/EWP/1401/98 Rev 1*Guideline on the Investigation of Bioavailability,* not yet adopted in Australia.

45% that of the simple oral solution (90% confidence interval (CI): 30-50%) and 58% that of the compounded oral solution. This suggests that the tablet is not ideally formulated. It was also noted that the AUC results after tablet administration were highly variable (coefficient of variability [CV] = 47%).

The sponsor put forward clinical arguments refuting the above suggestion. It stated that that the lower rupatadine absorption compared to an oral solution can be explained by a transitory saturation effect of the first pass metabolism, which does not affect the tablet formulation due to a non-immediate release of the active substance from tablets and to other factors such as gastrointestinal transit time, and, that the extent of total absorption is similar after administration of the two pharmaceutical forms as the results for the metabolites UR-12790 (BCP) and free UR-12788 (BCP-OH) were bioequivalent.

- In relation to a change in gastrointestinal transit time, this is supported by the results of this study where the formulated oral solution containing excipients that could have an effect on the intestinal transit time, had a lower rupatadine bioavailability compared to the simple oral solution.
- In relation to the first pass effect, this can only be true if the *in vivo* dissolution rate is slower than the *in vitro* dissolution rate which gives 100% dissolved in 0.1 M HCl in 5 minutes. This is plausible and seems to be borne out by the fact that the variability of the AUC of rupatadine after tablet administration is high and that the AUC rupatadine results for study UR/FC98/I-02 at a dose of 20 mg are 4-fold to 5-fold higher than the results of this study at a dose of 10 mg.

Whether the low bioavailability of the tablet is due to poor formulation or the inherent pharmacokinetics of rupatadine, the results mean that there is the potential for a two-fold batch to batch (and tablet to tablet) variability in the bioavailability of rupatadine from the tablets. This was brought to the attention of the Delegate.

In relation to the metabolites, the UR-12790 (BCP) and free UR-12788 (BCP-OH) responses after tablet administration were bioequivalent to the responses after administration of the simple oral solution.

UR/FC98/I-02

This study determined the effect of food (high fat breakfast) on the proposed 10 mg tablet at a dose of 20 mg. The point estimates indicate that food does not have a significant effect on the bioavailability (AUC) of rupatadine, but the 90% CI are broad and bioequivalence of the two treatments has not been proven. The AUC results after tablet administration were highly variable (CV = 64%). These facts were brought to the attention of the Delegate.

In relation to the metabolites, similar results were obtained for the UR-12790 (BCP), but those for total UR-12788 (BCP-OH) indicate equivalence. However the behaviour of the metabolites is less likely to reflect any differences and consequently most emphasis should been placed on evaluation of data from the active ingredient.

Advisory Committee Considerations

Initial Consideration

Details of this submission were presented at a meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

The PSC was unable to recommend approval for registration on pharmaceutic and biopharmaceutic grounds of the application due to the deficiencies in the data provided in support of the application which make it difficult to fully characterise the drug product.

The PSC endorsed all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic issues. In addition, the Committee considered that the sponsor should be asked to:

- Provide data on content uniformity for the tablets used in bioavailability Studies UR/FC99/1-02 and UR/FC98/1-02.
- Discuss the observations that the half-life is lower for the tablet formulation compared to the oral solution formulations and the clearance (CL/F) is higher (Study UR/FC99/1-02).
- Provide a justification for not determining the levels of the UR-12766 and UR-12767 (the other two active metabolites) in the subject plasma samples given that these account for 20% and 16% respectively of the total systemic exposure to rupatadine.

These issues were raised and the responses to the later two points (which are clinical in nature) were referred to the Delegate and were also referred back to PSC.

- The Committee did not accept the sponsor's explanation for the low bioavailability of rupatadine from the tablet formulation compared to the oral solutions observed in Study UR/FC99/1-02. The PSC agreed that the most likely reason for this is poor tablet formulation.

The response was referred to the Delegate and was also referred back to PSC.

- The Committee considered the sponsor's justification for not providing an absolute bioavailability data unacceptable. The PSC agreed that the sponsor should be asked to conduct an absolute bioavailability study. The PSC believed this was very relevant given that rupatadine is extensively metabolised pre-systemically, has the potential for interactions and enterohepatic recirculation and the results obtained from Study UR/FC99/1-02.

The response was referred to the Delegate and was also referred back to PSC.

- The PSC agreed that the dissolution test method used is non-discriminatory and therefore provides no confidence that the process can distinguish between acceptable and unacceptable tablet batches.

Further data were provided and it was accepted that the dissolution test method, though not ideal, was acceptable after the limit had been tightened from NLT 85% in 30 minutes to NLT 85% in 15 minutes.

- The Committee noted that there was an increase in the time to maximal plasma concentration (C_{max}) and AUC in the elderly and after erythromycin dosing compared to healthy volunteers.
- The PSC agreed that the potential for cardiac side effects should be drawn to the attention of the Delegate and the ACPM.
- The Committee raised safety concerns about the proposed trade name for this product given its closeness to the already registered Rifabutin, Rifadan and Butafen.

The sponsor put forward extensive clinical arguments as to why the tradename of Rupafin should be accepted and these were brought to the attention of the Delegate.

- The PSC agreed to review this application again when responses to the outstanding issues are available and before it is presented for consideration by the ACPM.

Further Consideration

The PSC reviewed additional data and comments provided by the sponsor and the TGA.

The PSC agreed that the main issues of concern raised at its previous meeting had not been resolved. In particular, the Committee reiterated that:

- The pharmacokinetic profile of rupatadine has not been adequately defined.
- There was insufficient information to determine if the low rupatadine bioavailability was due to unusual pharmacokinetics or poor formulation.

The PSC agreed that to further understand the pharmacokinetic profile of rupatadine, the sponsor should provide an absolute bioavailability study and a steady state bioavailability study versus an oral solution.

The Committee also considered that a clinical dose ranging study enveloping the proposed dose of 10 mg could have been helpful to characterise the product.

The PSC therefore concluded that the nature of the outstanding biopharmaceutic issues would preclude approval of this application.

Quality Summary and Conclusions

There were no objections to the registration of this product with respect to pharmaceutical chemistry and quality control.

With respect to bioavailability:

- The formulation proposed for supply in Australia is the same as that used in the Phase III efficacy studies.
- No absolute bioavailability study was provided, but the company argue that: a safe IV solution could not be prepared; a study performed against an oral solution is sufficient; and no adverse events have been observed since overseas launch in 2003.

The bioavailability of rupatadine from the proposed tablet is only 45% that of a simple (extemporaneous) oral solution. Therefore there is a potential batch to batch (and even tablet to tablet) variability in the bioavailability from the tablets.

- This may be due to poor tablet formulation, however, the sponsor has put forward plausible argument that this is pharmacokinetic in nature, that it is due to a transitory saturation effect of the first pass metabolism, which does not affect the tablet formulation due to a non-immediate release of the active substance from tablets, and to other factors such as gastrointestinal transit time.
- The sponsor also argues that the overall activity is from rupatadine and four active metabolites, that two of the metabolites show bioequivalence between the tablets and the oral solution (the other two are present in lesser amounts and were not investigated).
- The Delegate was asked to note that this variation could lead to as much as two-fold increase in bioavailability and to consider whether such variability precludes the registration of the product.

III. Nonclinical Findings

Introduction

The general quality of the submitted studies was high. All studies on single- and repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity, and most of the safety pharmacology studies, were Good Laboratory Practice (GLP) compliant. The few safety related studies not performed under GLP were conducted in established laboratories and adequately documented.

Pharmacology

Primary pharmacodynamics

Rationale and mechanism of action (in vitro studies)

Rupatadine is characterised as a non-sedating H_1 anti-histamine and platelet-activating factor (PAF) receptor antagonist. Roles for histamine and PAF in the pathophysiology of allergic rhinitis and chronic idiopathic urticaria are reported in the literature.

Receptor binding experiments

Binding of rupatadine to histamine H_1 receptors isolated from the guinea-pig cerebellum and lung was demonstrated by inhibition of ^{3}H-mepyramine binding; equilibrium inhibition constant (affinity) [K_i] values were 26–256 nM in the various experiments. Binding was time-dependent and pseudo-irreversible. Rupatadine was ~7.5 and 10-times more potent than the structurally-related anti-histamines loratadine and fexofenadine. H_1 receptor occupation by rupatadine in guinea-pig cerebellum and lung after oral (PO) dosing was relatively rapid (with maximum binding evident at 2–4 hours post-dose) and dose-dependent; low or no binding was seen at 48 hours post-dose.

Rupatadine was shown to bind to PAF receptors isolated from rabbit platelets and guinea-pig macrophages and lung in a reversible, non-competitive fashion (K_i values, 551–7200 nM; ~4–5-times more potent than loratadine). Rupatadine binding to human forms of the receptors was not investigated.

Functional assays

Rupatadine inhibited chemically and immunologically induced histamine release from mast cells from the rat and dog and from a human mast cell line (HMC-1); median inhibitory concentration (IC_{50}) values were 3–7 μM, and similar to those observed for loratadine. The drug was shown to inhibit histamine-induced contraction of the guinea-pig ileum in a concentration-related manner, with an IC_{50} of 44 nM.

PAF-induced platelet aggregation was inhibited by rupatadine in a concentration-related manner in platelet-rich plasma from rabbits (IC_{50} values, 2.9–4.6 μM), washed rabbit platelets (IC_{50}, 0.2 μM) and dog whole blood (IC_{50}, 0.3 μM). Consistent with specific antagonism of PAF activity, rupatadine (200 μM) had little effect on arachidonic acid- or adenosine diphosphate (ADP)-induced platelet aggregation. Rupatadine was ~30-fold more potent than loratadine. Rupatadine inhibited PAF-induced chemotaxis of human neutrophils by 13–107% over 0.01–30 μM. Other H_1 receptor antagonists (ceterizine, fexofenadine, mizolastine and loratadine) showed limited inhibition of PAF-induced neutrophil chemotaxis in comparison (2–43% compared with 86% inhibition at 10 μM). Some inhibition of leukotriene B_4-induced chemotaxis by rupatadine was also observed (39–55% inhibition at the same concentration range) but this was not significantly greater than with the other H_1 receptor antagonists.

Efficacy

In vivo, dose-related inhibition of histamine- and PAF-induced skin wheal in rats and dogs and paw oedema in rats was shown following PO administration of rupatadine. Inhibition of *Ascaris suum* extract-induced skin wheal was shown in dogs. Maximum effects on skin wheal were usually observed 4–6 hours post-dose and efficacy against histamine-induced lesions was generally slightly greater than that of PAF-induced lesions. The lowest doses tested in the studies were efficacious and associated with exposure levels below (rats) or close to (dogs) exposure in humans at the recommended clinical dose.

Rupatadine was also shown to inhibit histamine and PAF induced conjunctivitis in guinea pigs (PO or topical ocular administration), mortality induced by PAF, *E. coli* endotoxin and Compound 48/80 (an agent that induces degranulation of mast cells) in mice (PO or IV administration) and endotoxin induced mortality and histamine induced hypotension in rats (IV administration).

Several *in vivo* studies investigated the effects of rupatadine on allergic pathways. Rupatadine inhibited type I hypersensitivity reactions in models of passive cutaneous anaphylaxis in rats (median infective dose (ID_{50}), 0.97 mg/kg PO) and active anaphylactic shock in mice (ID_{50}, 4.76 mg/kg PO). Estimated exposure was 4-fold (rats) and 2-fold (mice) the anticipated clinical exposure. Topical ocular treatment inhibited the development of allergic conjunctivitis in guinea pigs in a dose-related manner. A single PO dose (10 mg/kg) significantly reduced signs present in the immediate phase (bronchospasm, dyspnoea and cyanosis) and the delayed response (eosinophil recruitment to the lung) in a guinea-pig model of allergic asthma.

Pharmacological activity of metabolites

Several metabolites of rupatadine were shown to also possess significant H_1 anti-histamine activity, namely desloratadine (which is registered in its own right), 3-hydroxy-desloratadine (3-OH-DL), 5-hydroxy-desloratadine (5-OH-DL) and 6-hydroxy-desloratadine (6-OH-DL). *In vitro* binding and functional assays indicated 1.2–2-times higher potency for desloratadine compared with rupatadine and lower relative potency (1.7–3.8-times) for the others. PAF receptor antagonist activity (measured as inhibition of PAF-inducted platelet aggregation in rabbit platelet-rich plasma) of these metabolites was ~8–14-times weaker compared with rupatadine. Inhibition of histamine and PAF induced paw oedema was observed following PO administration of the metabolites in rats, with the effect of the most potent (desloratadine) only modestly weaker compared with rupatadine.

Pharmacodynamic and pharmacokinetic data indicate that desloratadine and (to a lesser extent) 3-OH-DL may contribute to efficacy in patients.

Secondary pharmacodynamics

No significant analgesic effect was observed for rupatadine (≤100 mg/kg PO) in models of acute pain in mice (acetic acid writhing test) or rats (tail flick assay); relative exposure based on maximal plasma concentration (C_{max}) is estimated to be ~300–380. Results in the mouse study, though, were confounded by a possible vehicle effect.

Safety pharmacology

Safety pharmacology studies investigated effects on the central nervous system (CNS), cardiovascular system, respiratory system, renal system and gastrointestinal (GI) tract and potential anti-cholinergic activity. Except where indicated, animal:human exposure comparisons in this section are based on plasma C_{max} values for rupatadine and its active metabolite desloratadine.

CNS effects

Transient clinical signs (piloerection, hunched posture and decreased motor activity at 1–4 hours post-dose) were observed at low incidence in mice treated with rupatadine PO, mostly at 100 mg/kg. A dose-related increase in the incidence of leptazol-induced clonic convulsions (and decrease in time to onset) was seen in mice at doses ≥10 mg/kg PO (estimated relative exposure, ≥38) but there was no treatment-related effect on the incidence of leptazol-induced tonic convulsions (≤100 mg/kg PO). Barbiturate- and ethanol-induced sleeping times were increased in mice at 100 mg/kg PO rupatadine (estimated relative exposure, ≥380). Sedative effects were observed for up to 8 hours post-dose in monkeys, including yawning at ≥10 mg/kg PO and increased passivity and decreased motor activity and response to pinching at 90 mg/kg PO (estimated relative exposure based on body surface area-adjusted doses, ≥14). Somnolence is noted as a common adverse reaction in the draft Product Information document.

Cardiovascular and respiratory effects

Rupatadine produced concentration-dependent inhibition of hERG K^+ channel tail currents (IC_{50}, 8.1 μM) and weaker inhibition of outward currents (IC_{50}, >10 μM); the IC_{50} values are >740-times the clinical C_{max}. There was no effect on action potentials in canine Purkinje fibres under physiological conditions, although action potential duration was significantly increased with rupatadine at 10 μM with simulation of bradycardia and under hypokalaemic conditions.

Heart rate was increased in anaesthetised guinea pigs (by ~20% for 30 minutes post-dose at 30 mg/kg IV) and dogs (by ≤28% for 2 hours post-dose at 20 mg/kg IV) but was decreased in anaesthetised rats (by ≤29% for 10 minutes post-dose at 30 mg/kg IV). Changes in heart rate were accompanied by reduced blood pressure in rats (5 minutes) and dogs (60 minutes). Dogs also showed increased tidal volume and femoral flow rate at ≥2 mg/kg IV (estimated relative exposure, ≥69), and increased left ventricular pressure, respiratory rate and respiratory minute volume at 20 mg/kg/day IV (estimated relative exposure, ≥690), for up to 10 minutes after dosing. There were no effects on electrocardiogram (ECG) in anaesthetised dogs at doses ≤20 mg/kg IV. Slight prolongation of the QTc interval was observed in rats at 30 mg/kg IV for 10 minutes post-dose; it is noted though that statistical significance was not attained, the margin of exposure in very high (≥72) and the rat is poor model for effects on the human ECG. Rupatadine did not increase ketoconazole-induced QT prolongation in the guinea pig.

Rupatadine (≤100 mg/kg PO) had no effect on bleeding time in mice or on clotting factors in rabbits.

Effect on renal function

A transient reduction in urinary output and electrolyte excretion for 3 hours post-dose was observed following a single high dose of rupatadine in rats (100 mg/kg PO), which was followed by an increase in both parameters for 3–24 hours post-dose. Chronic administration of rupatadine in the repeat-dose toxicity studies was associated with increased urinary volume in rats (≥3 mg/kg/day PO), while urinalysis parameters were unaffected in the studies in dogs (≤40 mg/kg/day PO).

Gastrointestinal effects

Rupatadine inhibited gastrointestinal transit by about 40% in rats at 100 mg/kg PO; there was no effect at 10 mg/kg PO (estimated relative exposure, ≥43). The finding is consistent with the drug's pharmacology and the involvement of PAF and histamine in GI motility.

Anticholinergic effects

Rupatadine significantly inhibited acetylcholine- and histamine-induced contractions of the guinea-pig ileum *in vitro* (by 48% and 66%, respectively) at 20 μg/mL but not at 2 μg/mL (~350-times the clinical C_{max}); barium-induced contractions were unaffected.

In an *in vivo* study of central anti-cholinergic effects, rupatadine (≤300 mg/kg PO) had no effect on physostigmine induced mortality in mice. Peripheral anti-cholinergic effects were observed in a study in dogs, with decreased pupillary reflex, decreased conjunctival and nasal humidity and a low incidence of miosis seen at 40 mg/kg PO, for ≤48 hours post-dose. No effects were observed at doses ≤7 mg/kg (estimated relative exposure, ≥290). Together, the results suggest no significant anti-cholinergic effects for rupatadine at clinical doses.

Pharmacokinetics

Absorption and plasma kinetics

Rupatadine was rapidly absorbed following PO administration in all nonclinical species (mouse, rat and dog) and in humans, with C_{max} reached within 1 hour of dosing. Plasma half-lives for the unchanged drug were short in the laboratory animal species (<1 hour; compared with ~5–9 hours in humans at the recommended clinical dose), with rapid metabolism evident (based on the time to maximal plasma concentration [T_{max}] values for desloratadine). Exposure (plasma AUC) to desloratadine was usually greater than to the parent compound following PO administration (≥13-fold in mice and ≤5-fold in rats and dogs). Desloratadine:rupatadine AUC ratios were markedly higher with PO compared with IV administration in rats and to a lesser extent in dogs, indicating a first-pass effect. Plasma AUCs for rupatadine and especially desloratadine were greater than dose-proportional, except for rupatadine in the rat, where dose-proportional exposure was seen. Sex differences in exposure were seen in rodents with dietary administration (that is, higher exposure to desloratadine in male compared with female mice, and higher exposure to rupatadine and lower exposure to desloratadine in male compared with female rats) although such differences were not apparent in rats with gavage administration. There was evidence for modest accumulation of rupatadine and more substantial accumulation of desloratadine with repeated dosing in rats and dogs. The bioavailability of rupatadine following PO dosing was variable, ranging from 15–52% in rats and 52–64% in dogs. Enzyme induction was evident with continued treatment at high doses, with decreased exposure to rupatadine observed in rats at 120 mg/kg/day in a 13-week study and decreased exposure to a metabolite precursor to desloratadine (UR-12605) observed in dogs at 20 mg/kg/day in a 26-week study.

Distribution

Plasma protein binding by rupatadine was high, ranging from 98–99% in rats, dogs and humans. Radioactivity was rapidly and widely distributed in rats following a single PO dose of ^{3}H-rupatadine. Outside of the GI tract, the liver had the highest level of radioactivity, with peak levels 80-times greater than the C_{max} in blood in Sprague Dawley rats. High levels of radioactivity were also seen in the lungs and kidneys (tissue:blood C_{max}, ~3.5). Penetration across the blood-brain barrier was limited in the study in Sprague Dawley rats (peak levels of radioactivity being ~7-times lower than blood), though more significant in a study in LH rats (tissue:blood C_{max}, 0.55). Radioactivity declined significantly in most tissues by 24 hours post-dose. Melanin binding was evident as a slower decline in radioactivity from pigmented compared with non-pigmented skin, and as higher levels and slower decline in radioactivity in the eyes of pigmented (LH) vs non-pigmented (Sprague Dawley) rats. Consistent with extensive tissue distribution and high

plasma protein binding, the volume of distribution of rupatadine following IV dosing was high (about 7 L/kg in rats and 3 L/kg in dogs).

Metabolism

Metabolism of rupatadine was studied *in vitro* and *in vivo* in rats, dogs and humans, and was found to principally involve hydroxylation of the methyl group in the pyridine ring (generating UR-12338) with subsequent oxidation to acid (UR-12605) and then further hydroxylation at various positions and dealkylation of the tertiary amine (generating desloratadine, 3-, 5-, and/or 6-hydroxy-desloratadine and other metabolites). Cytochrome P450 (CYP)3A4 was identified as the P450 isoform chiefly responsible for the metabolism of rupatadine in *in vitro* experiments, with CYP2C19 and 2D6 also potentially involved. The pattern of metabolism was comparable across species except with regard to the formation of 3-hydroxy-desloratadine (3-OH-DL) and its glucuronide. These were major circulating metabolites in humans, but were found only at low levels in rat plasma and were not observed in dogs. To compensate for this, 3-OH-DL was directly administered in a number of single-dose toxicity studies in mice and rats and in a repeat-dose toxicity study in rats.

Excretion

The major route of excretion following PO and IV dosing in rats and dogs and PO dosing in humans was the faeces (up to 87%, 74% and 61% of the administered dose in the respective species). Faecal and especially urinary excretion was principally in the form of metabolites. Significant biliary excretion was demonstrated in rats (16% of an oral dose was recovered in bile and 74% of an IV dose).

Pharmacokinetic drug interactions

Rupatadine was shown to be able to inhibit CYP3A4 (IC_{50}, 0.66 μM), CYP2C19 (IC_{50}, 2.73 μM) and CYP2D6 (IC_{50}, 0.5–4.68 μM) in human liver microsomes *in vitro*. Weak inhibition of CYP2E1 activity was also observed (<7% at 5 μM). These concentrations are >100-times higher than the clinical C_{max}; inhibition of the CYPs at therapeutic concentrations is therefore not expected.

Relative exposure

Exposure to rupatadine and desloratadine (plasma AUC from time zero to 24 hours [$AUC_{0-24\,h}$]) in animal toxicity studies that included toxicokinetic data is compared with that of humans at the recommended clinical dose in Table 1. Relative exposure to 3-OH-DL in a repeat-dose toxicity study in rats in which the metabolite was directly administered has also been calculated. Where single exposure ratios are reported in the text, this refers to relative exposure for rupatadine and relative exposure to desloratadine in higher.

Table 1: Relative exposure to rupatadine and metabolites in PO toxicity studies

Study no.	Species	Treatment period	Dose (mg/kg/day)	Sex	Analyte[#]	AUC_{0-24h} (ng·h/mL)	Exposure ratios[a]
Repeat-dose toxicity studies							
UHS/13/95 [CIN/048/95]	Rat	13 weeks	3, 30, 120	M/F	Rupatadine	298, 2725, 8512	16, 146, 455
					Desloratadine	386, 9761, 42915	14, 346, 1522
UHS/12/95 [CIN/049/95]	Dog	13 weeks	1.25, 7, 40	M/F	Rupatadine	329, 2835, 14606	18, 152, 781
					Desloratadine	816, 8036, 55332	29, 285, 1962
UHS/35/C [CIN/127/97]		26 weeks	1, 5, 20	M/F	Rupatadine	241, 1890, 6752	13, 101, 361
					Desloratadine	755, 5258, 25353	27, 186, 899
Supportive data for carcinogenicity studies [dietary administration]							
RCC650428	Mouse	4 weeks	6, 25, 100	M	Rupatadine	4.0, 60, 332	0.2, 3, 18
					Desloratadine	709, 4353, 33119	25, 154, 1174
				F	Rupatadine	<LOQ, 17, 299	NA, 0.9, 16
					Desloratadine	164, 2586, 19993	6, 92, 709
RCC650441	Rat	4 weeks	2.5, 10, 40	M	Rupatadine	35, 285, 1944	2, 15, 104
					Desloratadine	15, 588, 4390	0.5, 21, 156
				F	Rupatadine	24, 245, 1490	1.3, 13, 80
					Desloratadine	148, 1360, 10221	5, 48, 362
Studies in pregnant animals							
UHS0040	Rabbit	12 days[b]	5, 25, 100	F	Rupatadine	15.1, 181, 931	0.8, 10, 50
					Desloratadine	13.3, 206, 1880	0.5, 7, 67
Studies with 3-OH-DL administration							
CIN/255/00	Rat	28 days	3, 30, 120	M	3-OH-DL	72, 339, 5554	3, 15, 245
				F		49, 785, 3275	2, 35, 144
Pharmacokinetics in humans							
IC012 RUP/1/04	Human	5 days	10 mg/day	M/F	Rupatadine	18.7[c]	NA
					Desloratadine	28.2	NA
					3-OH-DL	22.7	NA

[#]AUC values for rupatadine are expressed in terms of the fumarate salt for animals and humans;

[a]Calculated as animal:human AUC_{0-24h};

[b]Between Gestation Day (GD) 6–18;

[c]Equivalent to 14.6 ng·h/mL rupatadine base;

NA = not applicable.

Toxicology

Acute toxicity

The acute toxicity of rupatadine was investigated following single PO and intraperitoneal (IP) doses in mice and rats. Animals of both sexes were used and the post-dose observation period was of appropriate duration (14 days). Administration of a 2000 mg/kg PO dose resulted in mortality soon after in both species (generally 1–4 hours post-dose) due to cardiorespiratory difficulties. Heart and lung congestion were identified at necropsy. Maximum non-lethal doses were 500 mg/kg PO and 50–200 mg/kg IP in mice, and 50 mg/kg IP in rats. A maximum non-lethal dose by the PO route was not established in the rat due to the use of just a single dose-level.

Repeat-dose toxicity

Studies of up to 26 weeks duration by the PO route were conducted in rats and dogs. A limited dietary study of 4 weeks duration was also conducted in mice. The rat and dog studies were appropriately designed although at 6 months the duration of the pivotal study in the non-rodent species is shorter than the 9 months recommended under the relevant TGA-approved EU guideline current at the time of the evaluation.[4] However, considering the absence of a progression in toxicity with treatment for 13 compared with 26 weeks in dogs and the nature of the findings in the 6-month study, this is considered acceptable.

The major targets for rupatadine toxicity were the liver, kidney, lungs and male and female reproductive tissues, with effects also noted in the heart, lymphoid tissues, skeletal muscle, adrenal gland, pancreas, thyroid, parathyroid, tongue and GI tract. The drug was better tolerated in dogs compared with rats.

Hepatic changes

An increase in the incidence of coagulative necrosis was observed in the 18-month mouse carcinogenicity study at dietary doses ≥25 mg/kg/day (relative exposure based on AUC, ≥0.9 for rupatadine and ≥92 for desloratadine; ≥9-times the recommended clinical dose on a body surface area basis). Centrilobular hypertrophy was observed in rats with treatment at ≥30 mg/kg/day in the 26-week study and at ≥2.5 mg/kg/day via the diet in the 2-year carcinogenicity study (relative exposure, ≥1.3 for rupatadine and ≥0.5 for desloratadine; >1.8-times the human dose on a body surface area basis) and is considered an adaptive change rather than a toxic effect. Additional microscopic liver findings in rats comprised vacuolation of hepatocytes at 120 mg/kg/day in the 13- and 26-week studies (relative exposure, ≥455) and an increased incidence of fatty change in males rats at all doses in the carcinogenicity study (relative exposure, ≥2 for rupatadine and ≥0.5 for desloratadine). In contrast, evidence of hepatic effects in dogs was limited to slight increases in serum alkaline phosphates (ALP) and alanine transaminase (ALT) (without statistical significance) in the 13-week study at 40 mg/kg/day (relative exposure, ≥781). The pivotal dog study establishes a No Observed Effect Level (NOEL) for liver toxicity of 20 mg/kg/day (relative exposure, ≥361). Based on the nature of the liver changes, the confinement of the significant effects to rodents, and consideration of the dose and exposure multiples, their relevance to humans is considered likely to be low.

[4] EMEA, Committee for Proprietary Medicinal Products (CPMP), May 1999. ICH Topic S4. Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing), CPMP/ICH/300/95.

Renal toxicity

Foamy vacuolation of the inner cortical tubules and outer medullary tubules of the kidney was observed at 120 mg/kg/day in the 26-week study in rats (relative exposure, ≥455). This finding was associated with increased blood urea nitrogen and creatinine levels. Increased urinary volume was also observed in the study. In dogs, an increase in the incidence and severity of cortical/medullary scarring of the kidney occurred at 40 mg/kg/day PO in the 13-week study, with accompanying cortical mineralisation and an increase in blood urea nitrogen levels. The NOELs for renal toxicity in the pivotal rat and dog studies are 30 and 20 mg/kg/day. Exposure at these doses is a very large multiple of the clinical exposure (≥146 for rats and ≥361 for dogs), and the observed renal effects are considered unlikely to be of clinical significance.

Cardiopulmonary effects

Eosinophilic alveolar material and foamy alveolar macrophages were observed in the lungs of all female and most male rats at 120 mg/kg/day in the 26-week study (relative exposure, ≥455); this led to laboured breathing/poor condition and necessitated euthanasia in some cases. Inflammatory cell infiltration in the lung was also evident at this dose level, and abnormal contents of the trachea were noted in some animals at necropsy. An increased incidence of lung congestion was reported at ≥30 mg/kg/day in the 13-week rat study as well as in the mouse carcinogenicity study at ≥40 mg/kg/day. Increased alveolar histiocytosis was also seen in the rat carcinogenicity study at 40 mg/kg/day (relative exposure, ≥80). Histopathological changes in the heart (myocyte degeneration, vacuolation and fibrosis) were also observed at 120 mg/kg/day in the 26-week rat study, and are considered to be related to the lung changes described above. NOELs for cardiopulmonary toxicity are 30 mg/kg/day in the rat and 20 mg/kg/day in the dog (relative exposure, ≥146 [rat] and ≥361 [dog]).

Effects on reproductive tissues

Atrophy of seminiferous tubules of the testes, with absent or reduced spermatozoa in the epididymides were observed at the highest dose in the 26-week study in rats (120 mg/kg/day; exceeding the maximum tolerated dose). In female rats, cystic corpora lutea and/or hypertrophic luteal cells of the ovary and hypertrophic/vacuolated epithelium and myometrial macrophages of the uterus were frequently observed at the same dose in this study. These findings are consistent with the reduced male and female fertility at the same dose level observed in a fertility study in rats (discussed further under *Reproductive toxicity* below). Hypertrophy and hyperplasia of corpora lutea were also seen at all doses in the carcinogenicity study in mice. PAF is recognised to be involved in oocyte maturation and ovulation (reviewed by Tiemann [2008]).[5] No treatment-related effects on reproductive tissues were observed in dogs. NOELs for effects on male and female reproductive tissues are 30 mg/kg/day in the rat (relative exposure, ≥146) and 20 mg/kg/day in the dog (relative exposure, ≥361).

Effects on lymphoid tissues

An increased incidence of atrophy of the thymus occurred at 120 mg/kg/day in the 26-week study in rats (relative exposure, ≥455), and increased incidence and severity of involution of the thymus occurred in male dogs treated at 40 mg/kg/day for 13 weeks (relative exposure, ≥781). These dose levels exceeded the maximum tolerated doses in the two species (suppression of body weight gain was in the order of 20–70%), and the findings are consistent with non-specific toxicity/stress. Histiocytosis and/or macrophage

[5] Tiemann U. The role of platelet-activating factor in the mammalian female reproductive tract. Reprod Domest Anim 2008; 43: 647–555.

infiltration of lymph nodes and/or spleen occurred at 120 mg/kg/day, and at 30 mg/kg/day in a few cases, in the 26-week study in rats. Increased white blood cell (WBC) counts and neutrophils and decreased lymphocytes and eosinophils were observed in the pivotal rat study, consistent with the effects on lymphoid tissues and inflammatory changes in the lung. Lymphoid atrophy and histiocytosis in the spleen and bone marrow atrophy were increased in incidence in mice at the high-dose level (≥40 mg/kg/day) in the carcinogenicity study. There were no effects on lymphoid tissues in the pivotal dog study (≤20 mg/kg/day; relative exposure, ≥361).

Other toxicities

A number of additional effects were noted with treatment at the high-dose level (120 mg/kg/day) in the 26-week study in rats. Skeletal muscle atrophy was observed in several female animals, occurring in the context of a marked reduction in body weight gain. This was not also seen in males however, even though the effect on body weight gain was more marked. Adrenal cortical hypertrophy was common in both sexes, and is consistent with non-specific toxicity with treatment at a dose beyond that maximally tolerated. Pancreatic islet cell vacuolation was observed in males only, and there was thyroid follicular cell hypertrophy in males and parathyroid cell hypertrophy in females. The effects on the thyroid may reflect hormonal disturbances due to effects on the liver (altering clearance). NOELs for these are 30 mg/kg/day in the rat (relative exposure, ≥146) and 20 mg/kg/day in the dog (relative exposure, ≥361). In the rat carcinogenicity study, a modest increase in focal hyperplasia of the parathyroid was observed in males at 40 mg/kg/day (relative exposure, ≥104) but not at 10 mg/kg/day (relative exposure, ≥15).

Unsettled behaviour (hyperactivity, vocalisation, aggression, scratching/biting of cage) and other clinical signs (including tremors, excessive salivation and panting and rapid breathing) were observed at ≥5 mg/kg/day in the pivotal dog study. Hyperactivity and vocalisation were also seen at 1 mg/kg/day, but to a much more limited extent. These signs were transient and presumed to be pharmacologically mediated. Relative exposure at the Lowest Observable Effect Level (LOEL) is large (≥13).

Treatment with rupatadine via the diet in the mouse carcinogenicity study was associated with constipation (at ≥6 mg/kg/day), inflammation and/or dilation of the colon and rectum, and epithelial and basal cell hyperplasia in the stomach (≥25 mg/kg/day), and hyperkeratosis in the stomach and tongue (≥40 mg/kg/day). These findings are attributable to rupatadine's PAF- and H_1-receptor antagonist activity, causing inhibition of PAF and histamine mediated GI motility and disrupting PAF's role as an inhibitor of keratinocyte proliferation and differentiation (Shimada *et al.*, 1998).[6] There were no analogous findings in rats or dogs.

Genotoxicity

The potential genotoxicity of rupatadine was investigated *in vitro* in bacterial reverse mutation assays, a forward mutation test in mammalian cells and a chromosomal aberration assay in human lymphocytes, and *in vivo* in a mouse bone marrow micronucleus test. A suitable set of *S. typhimurium* and *E. coli* strains was used in the assays for bacterial gene mutation. Concentrations/doses used were appropriate (limited by cytotoxicity, solubility or mortality) except in the *in vitro* assay for clastogenicity where the highest concentrations tested produced slightly less suppression of the mitotic index

[6] Shimada A, Ota Y, Sugiyama Y, Sato S, Kume K, Shimizu T, Inoue S. *In situ* expression of platelet-activating factor (PAF)-receptor gene in rat skin and effects of PAF on proliferation and differentiation of cultured human keratinocytes. J Invest Dermatol 1998; 110: 889–893.

than is specified in the TGA-adopted EU guideline (that is, ≤43% compared with >50%.[7] This is not considered to have significantly compromised the validity of the study though and even if it was discarded, the package of studies still meets the standard battery of tests recommended in the TGA-adopted EU guideline. All of the assays were validated with appropriate positive controls and returned negative results for the drug.

Carcinogenicity

The carcinogenic potential of rupatadine, administered via the diet, was investigated in an 18 month study in mice and a 2 year study in rats. Study design was in accordance with recommendations in the TGE-adopted EU guidance on carcinogenic potential.[8] Suitable dose levels were selected in both studies, based on dose-limiting constipation and resultant mortality in mice and the extent of reductions in body weight gain at the high-dose level in rats. Toxicokinetic data were obtained up to Week 4 concurrently in rats and at the same dosage levels in a separate 4 week study in mice. Use of these data to support the carcinogenicity studies is not ideal but is considered acceptable.

There was no treatment-related increase in the incidence of neoplastic lesions in mice. NOELs for carcinogenicity are 40 mg/kg/day in males and 60 mg/kg/day in females, with relative exposure (based on extrapolation of AUC) estimated to be 6 for rupatadine in both sexes and 358 (males) and 323 (females) for desloratadine. In rats, thyroid follicular cell adenoma was increased in males at 40 mg/kg/day (relative exposure, ≥104), associated with follicular cell hypertrophy (seen at ≥10 mg/kg/day; relative exposure, ≥15). There was no increase in follicular cell carcinoma. These findings likely result from hepatic enzyme induction increasing thyroid hormone clearance, leading to increased TSH secretion and prolonged stimulation of the thyroid. NOELs for carcinogenicity in rats are 10 mg/kg/day in males and 40 mg/kg/day in females (relative exposure, ≥15 and ≥80 in the respective sexes). Based on the likely mechanism, the apparent species specificity for thyroid effects (that is, their absence in mice and dogs) and the high exposure margins, the increase in thyroid follicular cell adenoma observed in rats is not considered to indicate that rupatadine poses a particular carcinogenic hazard to patients.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages, and comprised a combined fertility/embryofetal development study, an early embryonic development study and a pre-/postnatal development study in rats, and an embryofetal development study in rabbits. The studies all involved administration by the clinical route (PO) and were generally adequate, although toxicokinetic data were only obtained in the study in rabbits. Litter incidences of fetal findings were not fully reported in one relevant study. The potential for placental transfer of rupatadine or excretion in milk was not directly investigated.

Male fertility was significantly reduced in the rat at 120 mg/kg/day (relative exposure, ≥455), associated with decreases in sperm velocity, motility and concentration, and consistent with the microscopic changes in the male reproductive tract seen at this dose in the 26-week repeat-dose toxicity study. Relative exposure at the NOEL for effects on male fertility (25 mg/kg/day) is estimated to be ≥122. In females, fertility was reduced, normal oestrus cycling disrupted and the time to mating increased at all doses tested (≥5

[7] pp. 51 - 62 of the Rules Governing Medicinal Products in the European Union - EudraLex - Medicinal products for human use, 1998 Edition: Volume 3B - Safety and the Environment - 3BS6A. Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.

[8] EMEA, Committee for Proprietary Medicinal Products (CPMP), 25 July 2002. Note for Guidance on Carcinogenic Potential, CPMP/SWP/2877/00.

mg/kg/day; relative exposure, ≥27 for rupatadine and ≥23 for desloratadine). The ovary and uterus had been identified as target organs for rupatadine toxicity in the 26-week general toxicity study in rats. No NOEL was established for effects on female fertility, although it was noted that effects at the lowest dose were relatively modest and the exposure margin was high.

Treatment at 120 mg/kg/day in the rat fertility/embryofetal development study was associated with decreased number of implantations, increased pre- and post-implantation loss and decreased live litter size. This dose was maternotoxic (based on suppression of maternal body weight gain during gestation) although the findings are also consistent with a role for PAF in implantation (Tiemann, 2008).[5] A dose-related increase in the incidence of incomplete ossification of the interparietal bone and decreased fetal bodyweight was evident at all doses (≥5 mg/kg/day; relative exposure, ≥27 for rupatadine and ≥23 for desloratadine). An increase in the incidence of runted fetuses was observed at 25 and 120 mg/kg/day, and enlarged or dilated ventricles of the brain at all doses; these abnormalities exceeded historical control levels, but the relationship to treatment is unclear as there was no dose-response and the cases occurred in single litters. No treatment-related effects on embryofetal development were evident in rabbits (≤100 mg/kg/day; relative exposure, ≥50).

In the pre-/postnatal study in rats, treatment with rupatadine at 120 mg/kg/day (relative exposure, ≥455) was associated with difficulties in delivering, ranging from signs of excessive straining to prolonged, incomplete or halted parturition, frequently necessitating euthanasia. This may reflect PAF receptor antagonism by rupatadine; PAF is involved in parturition (Tiemann, 2008).[5] Still births were markedly increased at this dose, and pup survival (particularly between post natal day [PND] 1–4) was decreased (probably due to reduced maternal care). The offspring of dams treated at 120 mg/kg/day had decreased birth weights and showed reduced postnatal body weight gain (during lactation in both sexes and also post-weaning in males) and developmental delays (ear opening and acquisition of righting reflexes and startle responses). Slight effects on these developmental parameters were also observed at 25 mg/kg/day (relative exposure, ≥122). There were no apparent treatment-related effects on the sexual development or reproductive performance of male or female offspring, although a dose-related reduction in the number of corpora lutea and implantations was observed, with a resulting reduction in the number of live embryos, at ≥25 mg/kg/day. Relative exposure at the NOEL for postnatal development in the rat (5 mg/kg/day) is estimated to be 27 for rupatadine and 23 for desloratadine.

Pregnancy classification

The sponsor had proposed Pregnancy Category B2 for rupatadine. For category B2, available animal data should "show no evidence of an increased occurrence of fetal damage". Given that adverse fetal effects were seen in rats, the product should instead be placed in Category B3.

Use in children

Rupatadine is not indicated for use in children who are under 12 years of age. No specific studies in juvenile animals were submitted.

Local tolerance

No local tolerance studies were submitted. This is acceptable for an orally administered drug.

Toxicity of 3-hydroxy-desloratadine

Specific studies were conducted with 3-OH-DL, as this was a major metabolite in humans, but was not detected or was detected only at very low levels in rats and dogs. *In vitro* cardiovascular safety studies indicated weaker effects for 3-OH-DL and its glucuronide on hERG K^+ channels compared with rupatadine. 3-OH-DL showed no inhibition of channel currents at 1 μM, and only slight inhibition of tail current (23%) was observed with its glucuronide at 10 μM. Action potential duration was slightly increased in canine Purkinje fibres under bradycardic and hypokalaemic conditions with 3-OH-DL at 10 μM; only a slight effect was observed with 3-OH-DL-glucuronide. Single-dose toxicity studies with 3-OH-DL, administered by the PO and IV routes, were conducted in mice and rats. 3-OH-DL resulted in mortality in mice but not rats at 2000 mg/kg PO, due to cardio-respiratory difficulties. 3-OH-DL was generally well-tolerated following PO administration to rats for 4 weeks (≤120 mg/kg/day). Renal tubular vacuolisation was observed at ≥30 mg/kg/day in males (relative exposure, 15–245) but not at 3 mg/kg/day (relative exposure, 3) and not in females. 3-OH-DL and its glucuronide were not genotoxic in bacterial reverse mutation assays. Taken together, these data indicate that the human metabolite 3-OH-DL and its glucuronide do not present a significant toxicological concern beyond that of rupatadine itself. Furthermore, it should be noted that these two compounds are also metabolites of the registered agents loratadine and desloratadine.

Nonclinical Summary and Conclusions

Rupatadine acts as an antagonist of histamine H_1- and platelet-activating factor (PAF) receptors. Receptor binding experiments indicated pseudo-irreversible binding to the histamine H_1-receptor and non-competitive binding to the PAF receptor. Inhibition of histamine release from mast cells, histamine induced contraction of the guinea pig ileum, and PAF induced platelet aggregation and neutrophil chemotaxis was demonstrated *in vitro*. *In vivo*, PO administration of rupatadine inhibited histamine and PAF mediated effects in various animal models, including skin wheal and paw oedema induced by the two agents in rats and/or dogs (with efficacious doses associated with exposure levels below or close to that in humans at the recommended clinical dose), histamine induced conjunctivitis in guinea pigs and PAF induced mortality in mice, as well as in rodent models of active and passive anaphylaxis.

Several metabolites of rupatadine also demonstrated significant H_1 anti-histamine activity. The most potent of these was desloratadine, which was up to twice as potent as rupatadine *in vitro*, and is registered in its own right.

These primary pharmacology studies, showing histamine H_1 and receptor antagonist activity for rupatadine, and inhibition of histamine and PAF mediated effects in various animal models at clinically relevant doses, support the drug's use for the proposed indications.

Secondary pharmacodynamic studies indicated no significant analgesic activity for rupatadine. No receptor screen was conducted.

Safety pharmacology studies identified sedation and other slight CNS effects in mice and monkeys, mostly at relatively high doses. Entry into the CNS was seen to be limited in rats. The potential for sedation in patients can be better assessed from the clinical data set. Slight cardiovascular effects (changes in blood pressure and heart rate) were observed in anaesthetised rats, guinea pigs and dogs following IV dosing at large relative exposure levels. The drug only weakly inhibits the hERG K^+ channel, and there were no effects on QT interval in dogs at exposures several hundred-fold greater than the clinical C_{max}. Rupatadine inhibited gastrointestinal transit and displayed anti-cholinergic activity, but only at concentrations very much larger than the clinical C_{max}.

Pharmacokinetic studies indicated rapid absorption of rupatadine following oral administration in all species (mouse, rat, dog and human). Rapid metabolism was evident, and exposure to desloratadine was generally greater than to rupatadine. Modest accumulation of rupatadine and more substantial accumulation of desloratadine were seen with repeat dosing in rats and dogs. Tissue distribution in rats was rapid and extensive; of relevance to the potential for sedation, distribution to the brain was limited. Plasma protein binding by rupatadine was high (98–99%) in rats, dogs and humans.

Rupatadine metabolism involved hydroxylation, oxidation and N-dealkylation to form a complex mix of products. Metabolism of rupatadine was primarily catalysed by CYP3A4, with some involvement of CYP2C19 and CYP2D6. The pattern of metabolism was comparable across species apart from the formation of 3-hydroxy-desloratadine (3-OH-DL) and its glucuronide, which were major circulating metabolites in humans but present at only low levels in rats and not detected in dogs. The faeces were the major route of excretion in all species. Urinary and faecal excretion was principally in the form of metabolites. Rupatadine inhibited human CYPs 3A4, 2C19 and 2D6 at high concentrations (>100-times the clinical C_{max}).

Pivotal repeat-dose toxicity studies were conducted by the PO route in rats and dogs (26 weeks). The major targets for rupatadine toxicity were the liver, kidney, lungs, male and female reproductive tissues. Effects were also noted in the heart, lymphoid tissues, skeletal muscle, adrenal gland, pancreas, thyroid, parathyroid, tongue and GI tract. Effects were less pronounced in dogs compared with rats.

Findings in the toxicity studies were often consistent with adaptive changes, exaggerated pharmacology or non-specific toxicity. Based on their nature, likely mechanism, and the existence of large margins of exposure at the NOELs (or LOELs), they are considered unlikely to be of clinical significance.

Genotoxicity studies comprised *in vitro* gene mutation assays in bacterial and mammalian cells, an *in vitro* human chromosomal aberration assay and an *in vivo* test for clastogenicity in mice. Negative results were returned in all.

Carcinogenicity studies involved dietary administration to mice (18 months) and rats (2 years). Treatment did not increase tumour incidence in mice or female rats. In male rats, thyroid follicular cell adenoma was increased at 40 mg/kg/day (relative exposure, >100). This was associated with thyroid follicular cell hypertrophy, and is likely to be secondary to thyroid hormone disruption due to hepatic enzyme induction.

Rupatadine is not genotoxic and was not carcinogenic in mice. The positive finding in the rat carcinogenicity study is not considered to indicate that rupatadine poses a particular carcinogenic hazard to patients based on consideration on the likely (indirect) mechanism, the species specificity for thyroid effects, and the existence of a large exposure multiple (15 in males, 80 in females) at the NOEL.

Reproductive toxicity studies in rats revealed decreased fertility in males (associated with reductions in sperm count, velocity and motility and seminiferous tubule atrophy) and also females (with abnormal oestrus, cystic corpora lutea and changes to the ovary and uterus observed). Treatment with rupatadine was also associated with reduced numbers of implantations and increased pre- and post-implantation loss in rats (at a maternotoxic dose). Embryofetal development was impaired in rats, with delays in ossification and decreased fetal weights observed (including in the absence of maternotoxicity). Embryofetal development was not affected in the rabbit. Difficulties in delivering and increased stillbirths were observed in treated rats. Decreased survival and postnatal bodyweight gain, developmental delays and impairment of female fertility were observed in the offspring.

Findings of decreased male fertility, embryofetal lethality, difficulties in delivering, stillbirths, delayed postnatal development, and impaired fertility of the female offspring in treated rats were only encountered at very high doses and exposure multiples for rupatadine at the NOELs are large (≥27). No NOELs were established for impairment of female fertility, delayed fetal ossification and decreased fetal weight in the rat. However, relative exposure to rupatadine at the LOEL for these effects was large (27), and the fetal effects were not also observed in the rabbit (at higher exposure levels). The possibility for such effects in patients treated with Rupafin seems limited but cannot be entirely discounted from the available data.

There were no nonclinical objections to the registration of Rupafin for the proposed indications.

IV. Clinical Findings

Introduction

The sponsor submitted reports of 11 pharmacokinetic studies, 9 pharmacodynamic studies (of which 4 focused on efficacy aspects and 5 on safety) and 16 efficacy and safety studies (of which in the opinion of the evaluator, three could be considered pivotal).

Pharmacokinetics

Introduction

Eleven pharmacokinetic studies were presented. Studies in patients with renal or hepatic impairment were lacking. Single and multiple dose pharmacokinetic studies have been done in normal subjects. The effects of food (including grapefruit juice) and interactions with other drugs metabolised by CYP3A4 were studied.

In general, it was not clear which of the studies used a rupatadine product identical to that now proposed for registration. This was clarified in the sponsor's response to the clinical evaluation report. Most of the studies used the formulation proposed for marketing.

Absorption

Absolute bioavailability has not been established, but a study using ^{14}C-rupatadine fumarate (URC 023/993407) showed that > 99% of an oral solution was absorbed (in that < 1% was excreted as unchanged drug).

The relative bioavailability of rupatadine 10 mg tablets (having the same formulation as that specified for the subject of this application) and an extemporaneous oral solution was measured in Study UR/FC99/I-02. This study was summarised in Section II. This was an open, randomised, single dose, three-period crossover relative bioavailability study conducted in Spain in 1999. Twelve subjects completed the study. Rupatadine fumarate appears to be rapidly absorbed after oral administration, with C_{max} following single dosage at about 2.2 µg/L, and T_{max} about 0.75-1.0 hour.

Influence of food

Study UR/FC98/I-02 was a comparative study of the single-dose pharmacokinetics in fasting and fed subjects. This study was also summarised in Section II. This was an open, randomised, single dose, two-period crossover in 25 normal subjects conducted in France in 1998. From the results, it appears that for the rupatadine product used in the study, food slows absorption.

Elimination

Excretion

Study URC023/993407 was an open, single dose study involving 6 normal men conducted in the UK in 1997. The results indicated that 96% of the dose was excreted within 168 hours (35% in urine and 61% in faeces), mostly as inactive metabolites (UR-12335 in urine). Elimination half-life following multiple daily rupatadine dosage at 10 mg/day (from Study UR/FC99/I-01) was approximately 6-8 hours for rupatadine; and 27-33 hours and 35-41 hours, respectively, for the active metabolites UR-12790 and UR-12788. Inter-subject variability was high.

Metabolism

In the radioactivity study URC023/993407, plasma concentrations of rupatadine and metabolites were determined using LC-tandem mass spectrometry methods. Some mean data are tabulated in Table 2.

Table 2: Plasma concentrations of rupatadine and metabolites

Analyte	C_{max}	Median T_{max} (h)	AUC_{0-t}
Radioactivity	189[1]	1.75	4333.6
Rupatadine	23.3 ng/mL	0.75	100.7
BCP (desloratadine)	6.71 ng/mL	1.5	81.0
UR-12788 (BCP-OH)	2.92 ng/mL	5	61.2
UR-12335	66.1 ng/mL	8	1553.3

[1]Units: ng equivalents/mL

Of the metabolites listed above, BCP and BCP-OH are pharmacologically active.

In vitro studies had shown the major role of CYP3A4 in rupatadine metabolism, and the results of studies IC03RUP/I/02 (effect of grapefruit juice), UR/FC98/I-04 (effect of erythromycin), and UR/FC98/I-03 (effect of ketoconazole) were consistent with this.

Dose proportionality

Dose proportionality was not easy to assess from the information available. In Study RD 477/20996, a randomised, double-blind, single dose, three-period crossover study conducted with 8 normal men in the UK in 1995 and Study RD 477/20997, a double-blind, rising multiple dose study conducted in 15 normal men in the UK in 1995, approximate dose proportionality was observed between 10 mg and 40 mg single doses, but the product used may not have been that for which registration is sought.

Special populations

A small study (UR/FC99/I-01) was done comparing pharmacokinetics and young and old healthy subjects. This was an open-label, multiple dose, parallel group study involving two groups of 12 normal subjects conducted in France in 1999. Small to moderate increases in levels of drug and metabolites were measured in the elderly group compared with the young group but the evaluator agreed with the sponsor that there is no need on pharmacokinetic grounds to recommend a dose reduction in the elderly.

Interactions

Studies were conducted on the possible pharmacokinetic interaction between rupatadine and drugs or specific foods which may have an inhibitory effect on CYP3A4: grapefruit juice (Study IC03RUP/I/02), erythromycin (Study UR/FC98/I-04), ketoconazole (Study

UR/FC98/I-03), and fluoxetine (Study IC09RUP/1/04). The question of an interaction with azithromycin (Study IC08RUP/1/03) was also studied.

Study IC03RUP/I/02

This was an open, randomised, single dose, two-period crossover study involving 24 randomised normal subjects conducted in Spain in 2003. Subjects were required to fast for ≥ 10 hours before dosing and for ≥ 4 hours after dosing except for consumption of the required grapefruit juice. Those assigned to grapefruit juice received 240 mL 100% grapefruit juice three times daily for 2 days before drug administration, 240 mL with the drug at 8 am, and 240 mL at 30 minutes and 90 minutes post-dose. Grapefruit juice was otherwise prohibited to all subjects from 10 days pre-treatment until the end of the study period. Consumption of grapefruit juice resulted in a marked increase in rupatadine C_{max} and AUC.

Study UR/FC98/I-04

This was an open-label, multiple dose, randomised, three-period, crossover in 28 normal subjects conducted in France in 1998 investigating the pharmacokinetic interaction with erythromycin. Increased concentrations of rupatadine occurred with co-administration, probably resulting from inhibition of CYP 3A4 during hepatic first pass.

Study UR/FC98/I-03

This was a multiple dose study of the pharmacokinetic interaction with ketoconazole. Increased concentrations of rupatadine occurred with co-administration, probably resulting from inhibition of CYP 3A4 during hepatic first pass.

Study IC09RUP/1/04

This was a multiple-dose study of the pharmacokinetic interaction with fluoxetine. The results indicated that if the two drugs were co-administered, dosage adjustment was unlikely to be necessary.

Study IC08RUP/1/03

This was an open-label, multiple dose, randomised, two-period crossover study involving 24 normal subjects conducted in Spain in 2004 investigating a possible pharmacokinetic interaction with azithromycin, motivated by concern (based on its structure) that azithromycin might interact with rupatadine through an effect on glycoprotein P. The results indicated that if the two drugs were co-administered, dosage adjustment was unlikely to be necessary.

Evaluator's overall conclusions on pharmacokinetics

An adequate account of pharmacokinetics has been presented. The main gap in data results from absence of an intravenous preparation and the result of this is absence of values for absolute bioavailability and volume of distribution.

Pharmacodynamics

Introduction

Studies of pharmacodynamics were done

- to elucidate efficacy
  - the pharmacodynamic components of Studies RD 477/20996 and RD 477/20997 (described above); and
  - Studies RD 477/20680, RD 477/21289, IC04RUP/II/02, UR/FC96/IB-02; and

- to obtain safety data
    - Studies UR/FC96/I-01, UR/FC97/I-01 and IC014RUP/1/05 (CNS effects);
    - IC012RUP/1/04 (QTc); and
    - DM02RUP/IV/04 (driving).

Studies relating to efficacy

Study RD 477/20996, pharmacodynamic component

Flare was induced by intradermal injection of histamine into the subscapular region 24, 20 and 16 hours pre-dose, and 1, 2, 4, 6, 12, 24, 48, 72 and 96 hours post-dose. Percentage inhibition of flare was shown to be greatest with the 40 mg dose at 12 hours (93.3%) while the 20 mg dose also had its greatest inhibitory effect at 12 hours (81.8%) and for the 10 mg dose the effect was greatest at 24 hours (68.7%).

Study RD 477/20997, pharmacodynamic component

Flare was induced as in Study RD 477/20996. This study also demonstrated significant inhibition of flare with inhibition greater for the 40 mg dose than the 20 mg dose.

Study RD 477/20680

This was a double-blind, placebo-controlled, rising single dose, three-group, three-period crossover pharmacodynamic and tolerance study. It was conducted with 19 normal men in the UK in 1995.

Study RD 477/21289

This was an open, rising single dose, two-period study of the inhibition of PAF induced platelet aggregation by rupatadine. It was conducted with 4 normal men in the UK in 1996.

Study IC04RUP/II/02

This was a multiple dose, randomised, double-blind, placebo-controlled, two-period crossover study of the effect of rupatadine on the physiologic response to aeroallergen exposure, assessed by challenge testing in a Vienna Challenge Chamber. It was conducted with 45 patients in Austria.

Study UR/FC96/IB-02

This was a single dose, double-blind, randomised, placebo-controlled, four-period crossover study of the effect of a single dose of rupatadine on response to a nasal challenge test with specific antigen. It was conducted with 23 patients in Spain in 1997.

Studies relating to safety

Study UR/FC96/I-01

This was a single dose, randomised, double-blind, six-period crossover study of the central and peripheral effects and tolerability of single doses of rupatadine. It was conducted with 21 normal subjects in Spain in 1997.

Study UR/FC97/I-01

This was a single dose, randomised, double-blind, six-period crossover study conducted with 20 normal subjects in Spain in 1998. The primary objective of this study was to assess the effects of rupatadine on the central effects of alcohol when administered simultaneously.

Selected results were as follows:

Pharmacokinetics

No effect of rupatadine was shown on the time course of plasma alcohol levels.

Electroencephalogram (EEG)

Recordings were made at 1, 2, 4, 6, 8 and 10 hours after each treatment, and analysed by a large number of techniques. Treatment C (alcohol alone) caused the greatest changes, maximal at about 1 hour. The changes caused by this treatment were generally statistically greater than the changes caused by each of the other treatments.

Tapping test (number of taps per second)

All the active treatments (A, B, C, D and E) showed significant impairment.

Fine motor skill test (placing dots in rectangles)

This test was inconclusive.

Nystagmus

This occurred significantly earlier with the active treatments.

Perception of time progression

This test was inconclusive.

Simple reaction time

All the active treatments (A, B, C, D and E) showed significant impairment. The greatest impairment was observed following treatment E (hydroxyzine plus alcohol).

Evaluator Comment

> There appears to be a pharmacodynamic interaction between rupatadine and alcohol, but this study provides little useful information. The objective was broadly stated, the number and variety of tests done was large, multiple statistical analyses were used, and the number of subjects was relatively small, so there was potential for over interpretation of data. In addition to this, the study was structured to assess the effect of rupatadine on alcohol treatment, rather than the effect of alcohol on rupatadine treatment.

Study IC012RUP/1/04

This was a randomised, placebo and active control, parallel study with blinded subjects and evaluators and unblinded investigators. It was designed to provide an assessment of the effect of rupatadine on the QTc interval of the standard ECG. It was conducted with 168 healthy subjects in Spain in 2005. The trial fulfils the requirements for a "thorough QT/QTc Study" as defined in the TGA-adopted EU guideline.[9] The size of the study, the population studied (which excluded males with QTc >430 milliseconds (msec) and females with QTc >450 msec), extent of challenge with rupatadine and use of both placebo and positive controls were all appropriate. Measurement of drug and metabolite concentrations showed that peak levels were achieved in the groups specified after multiple dosing (Table 3).

[9] EMEA. ICH E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, 25 May 2005. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04).

Table 3: Peak levels achieved after multiple dosing

Compound measured	C_{max} (µg/L) Mean (95% CI)	
	Rup 10 mg	**Rup 100 mg**
Rupatadine	4.49 (3.84, 5.15)	81.08 (67.86, 94.30)
BCP	2.46 (2.15, 2.76)	35.52 (31.27, 39.77)
BCP-OH	1.58 (1.45, 1.70)	12.27 (10.99, 13.54)

No cardiac concern was raised by this study.

Study DM02RUP/IV/04

This was a single dose, double-blind, randomised, placebo and active controlled, 3-period crossover study of the effect of rupatadine on driving. It was conducted with 22 normal subjects in The Netherlands in 2005. The sponsor explained that the study was conducted along lines suggested in an EU guideline relating to hypnotic drugs (EU, 1998). The Standard Driving Test, used in measuring the first of the primary outcomes, has been well validated in for use in the present context (O'Hanlon et al., 1995).[10] It involves driving over a 100 km circuit, in the company of a safety supervisor, while aiming to maintain a constant speed and steady lateral position. Performance is recorded electronically. The second standard test used, the Car Following Test (Ramaekers et al., 1992), has also been used in testing antihistamines.[11]

Evaluator comment

> The outcomes show that hydroxyzine 50 mg has a greater effect than rupatadine 10 mg in impairing driving performance, but cannot be regarded as providing strong evidence that rupatadine does not impair driving performance. The study was not structured as a non-inferiority safety trial of rupatadine against placebo, and besides, no evidence was offered that the dosage of hydroxyzine was chosen for any reason other than to be sure of a positive control, as recommended by the guideline.

The sponsor noted however that the study was not designed to be a non-inferiority study but rather as a study demonstrating statistical superiority as per the standard international guidelines on evaluation of SNC effects. The study was designed with reference to historical and previous experimental studies, which show the treatment with recommended therapeutic doses of second generation antihistamines (such as desloratadine, ebastine, fexofenadine) results in primary outcome (SDLP) values comparable with placebo. The studies were not designed to be different to international standards but to show primary outcome SDLP values comparable with placebo. The sponsor considered this to have been an incorrect assumption by the evaluator of this evidence as the study did follow precedent and the guidelines as identified clearly by the evaluator.

[10] O'Hanlon JF et al. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. Allergy 1995; 50: 234-242.

[11] Ramaekers JG et al. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. Eur J Clin Pharmacol 1992; 42: 363-369.

Study IC014RUP/1/05

This was a multiple dose, randomised, double-blind, placebo-controlled, two-period crossover study of the pharmacodynamic interaction between rupatadine and lorazepam. In the sponsor's *Clinical Study Report*, the primary objective was stated as: "to assess if the treatment with rupatadine potentiates the CNS depressant effects of benzodiazepines". The analyses were by analysis of variance (ANOVA), seeking to discover statistically significant differences between treatment groups. In most of the assessments

- a marked effect of lorazepam was observed compared with either placebo or rupatadine alone;
- there was no statistically significant difference between rupatadine and placebo; and
- there was no significant difference between lorazepam and lorazepam + rupatadine.

Thus, the question of whether rupatadine potentiates the CNS effects of lorazepam (let alone those of benzodiazepines in general) was not answered.

Evaluator's overall conclusions on pharmacodynamics

Efficacy-oriented studies

The studies of flare induction show a dose-response relationship in the dose range 10-80 mg, for both histamine induced flare and PAF-induced flare.

Safety-oriented studies

The results of the study of effect on the QTc interval were reassuring. Regarding the other studies, in the opinion of the evaluator, UR/FC96/I-01 was not evaluable and UR/FC97/I-01, DM02RUP/IV/04 and IC014RUP/1/05 did not properly address their objective.

Efficacy

Introduction

One major Phase III study was submitted in support of each of the 3 proposed indications: SAR (Study IC05RUP/4/03), RAP (IC06RUP/3/04) and CIU (IC010RUP/3/04). Supporting these were a large number of other studies, involving comparisons between various dosages of rupatadine, or between rupatadine and other antihistamines. For some of the studies, the dosage used was not clear.

Dose-response studies

Seasonal allergic rhinitis (SAR)

Study RD 477/21212 was a Phase II, double-blind, parallel group, randomised study conducted in 12 centres in England and Wales in 1996. There were 57 patients in the placebo arm, 60 patients taking rupatadine 10 mg and 57 patients taking rupatadine 20 mg. The outcome in the per protocol population is shown in Table 4.

Table 4: Outcome in *per protocol* population (Study RD 477/21212)

Mean (sd)	Pbo (n=50)	10 mg rupatadine (n=54)	20 mg rupatadine (n=45)
$DTSS_{mean}$	1.06 (0.61)	0.84 (0.65)	0.66 (0.44)
$DTSS_{max}$	1.71 (0.68)	1.41 (0.81)	1.22 (0.61)

DTSS: Daily total symptom score

Both active treatments were statistically superior to placebo ($p < 0.05$), but the difference between active treatments was not statistically significant. The individual symptom which showed the greatest difference between active and placebo treatments was sneezing.

Study RD 477/22115 was a Phase II, double-blind, parallel group, randomised study conducted in 45 centres in the UK in 1999. There were 76 patients in the placebo arm, 77 taking 2.5 mg rupatadine, 80 taking 5 mg rupatadine, 74 taking 10 mg rupatadine and 85 taking 20 mg rupatadine. The outcome in ITT population is shown in Table 5.

Table 5: Outcome in the ITT population (Study RD 477/22115)

Mean (sd)	Pbo (n=74)	2.5mg (n=76)	5mg (n=79)	10 mg (n=72)	20 mg (n=81)
$DTSS_{mean}$	1.07 (0.57)	0.79 (0.52)	0.77 (0.45)	0.80 (0.50)	0.71 (0.49)

All active treatments were statistically superior to placebo ($p < 0.05$), but the differences between active treatments were not statistically significant.

Study UR/FC97/III-03 was a Phase III, double-blind, parallel group, randomised study conducted in 20 centres in Spain from March 1998 to July 1999. There were 124 patients taking 10 mg rupatadine, 121 taking 20 mg rupatadine and 117 taking ceterizine 10 mg. The outcome in ITT population is shown in Table 6.

Table 6: Outcome in the ITT population (Study UR/FC97/III-03)

Mean (sd)	Rup 10 mg (n=124)	Rup 20 mg (n=121)	Cetirizine 10 mg (n=117)
$DTSS_{mean}$	0.7 (0.4)	0.8 (0.5)	0.7 (0.4)

There were no statistically significant differences between groups.

Study UR/FC97/III-04 was a Phase III, double-blind, parallel group, randomised study conducted in 44 centres in France from April 1998 to July 1999. There were 112 patients taking 10 mg rupatadine, 111 taking 20 mg rupatadine and 116 taking loratadine 10 mg. The outcome in ITT population is shown in Table 7.

Table 7: Outcome in the ITT population (Study UR/FC97/III-04)

Mean (sd)	Rup 10 mg (n=112)	Rup 20 mg (n=111)	Loratadine 10 mg (n=116)
$DTSS_{mean}$	0.92 (0.57)	0.85 (0.51)	0.93 (0.50)

There were no statistically significant differences between groups.

Study UR/FC98/III-04 was a Phase III, double-blind, parallel group, randomised study conducted in 25 centres in South Africa from November 1998 to April 1999. There were 107 patients taking 10 mg rupatadine, 112 taking 20 mg rupatadine and 112 taking loratadine 10 mg. The outcome in ITT population is shown in Table 8.

Table 8: Outcome in the ITT population (Study UR/FC98/III-04)

Mean (sd)	Rup 10 mg (n=107)	Rup 20 mg (n=112)	Loratadine 10 mg (n=112)
$DTSS_{mean}$	0.6 (0.5)	0.5 (0.4)	0.6 (0.4)

There were no statistically significant differences between groups.

Perennial allergic rhinitis (PAR)

Study RD 477/21416 was a Phase II, double-blind, parallel group, randomised study conducted in 17 centres in the UK and 8 centres in Spain from January 1997 to May 1998. There were 83 patients in the placebo arm, 82 taking 10 mg rupatadine and 80 taking 20 mg rupatadine.

The study synopsis states that the "primary efficacy variable for this study was the percentage of days during the study period when the Daily Severest Symptom Score (DSSS) was no worse than mild symptoms" but this appears to be a *post hoc* selection. Anyway, the difference between baseline and study end values did not reach statistical significance for any between-group comparison.

Study UR/FC98/III-03 was a Phase III, double-blind, parallel group, randomised study conducted in 35 centres in France from December 1998 to November 1999. The outcome in ITT population is shown in Table 9.

Table 9: Outcome in the ITT population (Study UR/FC98/III-03)

Mean	Pbo (n=70)	Rup 10 mg (n=65)	Rup 20 mg (n=68)	Cetirizine 10 mg (n=66)
PD_{max} 1†	24.38	40.01	49.56	43.03

† PD_{max} 1 = percentage of days when the score for the most severe symptom is ≤ 1.

Pairwise comparisons (using the Mann-Wittney test) showed a statistically significant difference between each active treatment and placebo, but failed to show such a difference between members of any pair of actives.

Study UR/FC98/III-01 was a Phase III, double-blind, parallel group, randomised study conducted in 12 centres in Poland and 10 centres in the Czech Republic from November 1998 to May 1999. There were 69 patients in the placebo arm, 73 taking 10 mg rupatadine, 71 taking 20 mg rupatadine and 70 taking 10 mg loratadine. The outcome in ITT population is shown in Table 10.

Table 10: Outcome in the ITT population (Study UR/FC98/III-01)

Mean (sd)	Pbo (n=69)	Rup 10 mg (n=73)	Rup 20 mg (n=71)	Lorat 10 mg (n=70)
PD_{max} 1	34.1 (33)	48.7 (35)	50.4 (31)	48.6 (36)

Pairwise comparisons (using an ANCOVA analysis) showed a statistically significant difference between rupatadine 20 mg and placebo (p=0.025), but not between members of any other pairs.

Chronic idiopathic urticaria (CIU)

Study IC02RUP/II/02 was a Phase II, double-blind, parallel group, randomised study conducted in approximately 100 centres in France, Argentina, Hungary and Romania from October 2002 to November 2003. There were 69 patients in the placebo arm, 70 taking 5 mg rupatadine, 74 taking 10 mg rupatadine and 70 taking 20 mg rupatadine. The outcome in ITT population was not presented. The outcome in PP population is shown in Table 11.

Table 11: Outcome in the PP population (Study IC02RUP/II/02)

	LS Mean			
	Pbo (n=64)	**5mg (n=64)**	**10 mg (n=66)**	**20 mg (n=64)**
MPS, baseline	2.48	2.56	2.44	2.53
MPS change, 4 weeks	-1.15	-1.31	-1.52	-1.82

Using a pairwise comparison, the results for placebo vs 20 mg, placebo vs 10 mg and 5 mg vs 20 mg were statistically significant ($p < 0.05$).

Pivotal studies

SAR

Study IC05RUP/4/03

Study IC05RUP/4/03 was a Phase III, double-blind, parallel group, randomised, active and placebo controlled study conducted in 5 centres in France, 4 centres in Germany, 6 centres in Poland, 7 centres in Romania and 4 centres in Spain from April 2004 to September 2004. It was designed to evaluate the efficacy and safety of rupatadine for the treatment of SAR symptoms over 4 week treatment period. Study participants were:

- Patients "older than 12" with documented history of SAR ≥ 2 years and a positive prick test to a relevant seasonal allergen for the geographic area.
- Clinically symptomatic at a Screening visit and with a nasal symptom score of at least 6 points and total non-nasal symptom score of at least 3 and rhinorrhoea score ≥ 2 according to the Table 12.

Table 12: Scoring table for SAR symptoms

Nasal symptoms	Non-nasal symptoms
Rhinorrhoea	Ocular pruritus
Nasal obstruction	Redness
Sneezing	Tearing
Nasal pruritus	
Symptom severity to be scored as follows: 0 = No symptoms. 1 = Mild symptoms (occasionally present, but not troublesome). 2 = Moderate symptoms (frequently present and annoying). 3 = Severe symptoms (continuously present and interfering with work or sleep).	

- Self assessments on a screening diary card made twice daily over 3 consecutive days showing total rhinorrhoea score ≥ 12 and total nasal symptom score of ≥ 36 and total non-nasal score ≥ 18.
- Results of standard laboratory tests within acceptable limits. ECG within acceptable limits, and with QTc interval values (after Bazett's correction) < 430 msec for males and < 450 msec for females.

- Patients using systemic or topical medication for SAR were subjected to various washout periods.

Patients were treated daily for 28 days with rupatadine tablet 10 mg, desloratadine tablet 5 mg, or placebo, administered "preferably in a fasting state, with a glass of water". The following topical or systemic medication was not permitted during the study period: drugs known to interact with CYP3A4 isoenzyme, grapefruit juice, H1-antihistamines, corticosteroids, leukotriene antagonists, decongestants or cromoglycate.

The primary efficacy endpoint was the Change from Baseline in total symptom score (TSS). TSS on any day is the sum of the individual symptom scores recorded by each patient in a diary. (See Table 12: maximum TSS is thus 21).

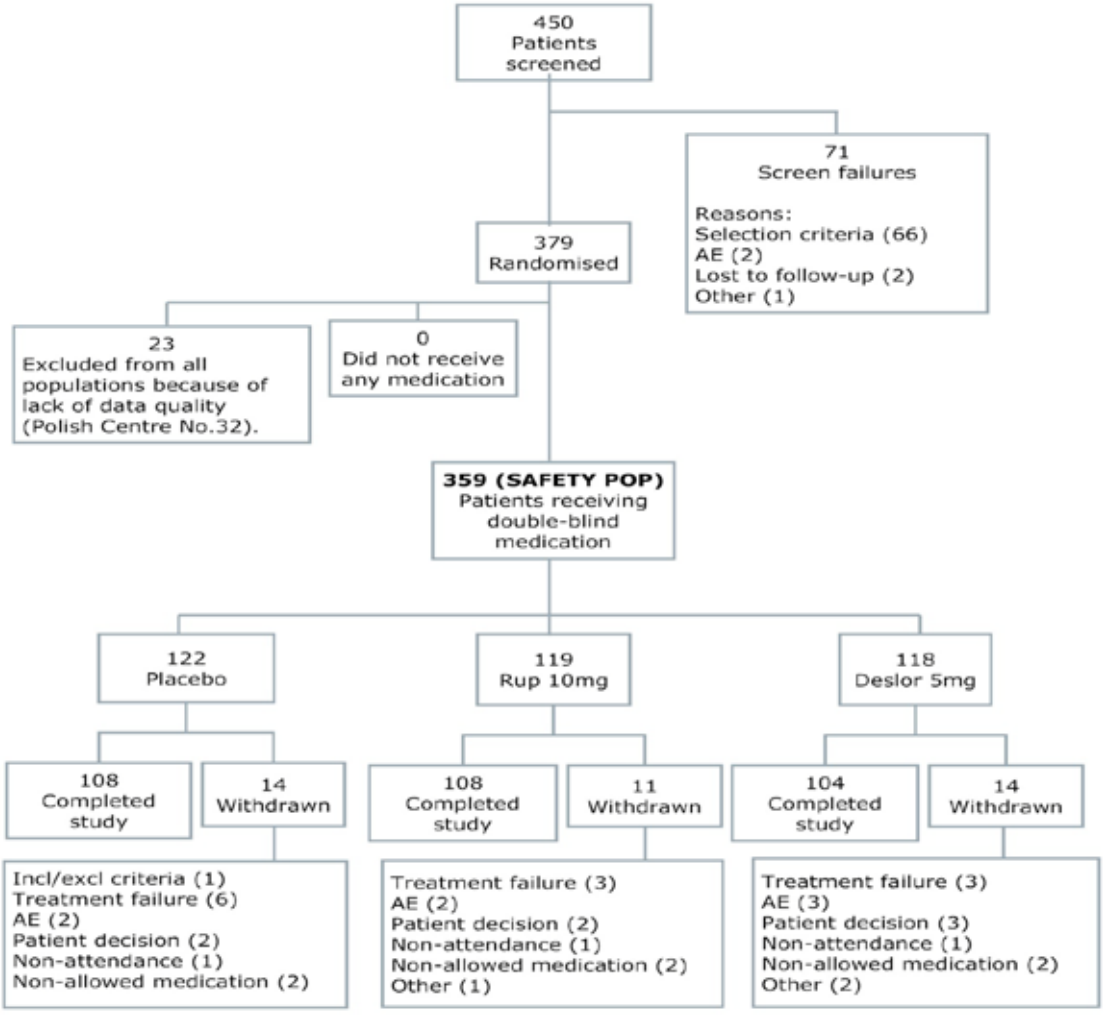
The intended sample size was 122 per group, which was chosen to detect with 80% power and 5% significance level, a difference ≥ 1.8 units in the primary efficacy variable, assuming a standard deviation (SD) of 4.45 and a loss rate of 20%.

The planned analysis was a two-way ANOVA, the main comparison being rupatadine vs placebo.

Results

The participant flow is shown in Figure 1.

Figure 1: Participant flow. Study IC05RUP/4/03



TSS observations at the beginning and end of the study are shown in Table 13 for the ITT population. Using an ANOVA analysis, rupatadine (Rup) was shown to be statistically significantly superior to placebo ($p< 0.05$).

Table 13: TSS change from baseline (Study IC05RUP/4/03)

	TSS change from baseline. Mean (SD)		
	Placebo (n=122)	**Rup 10 mg (n=117)**	**Deslor 5 mg (n=117)**
Baseline	14.01 (2.77)	13.77 (2.68)	13.68 (2.67)
Final	8.79 (4.13)	7.42 (3.70)	6.99 (4.38)
Change	-5.22 (4.21)	-6.35 (3.83)	-6.69 (3.89)

No patients took any rescue medication.

Ancillary analyses included assessments of sleep disturbance and of impairment of daily activities due to allergy symptoms. Presumably the relevant data were collected from the "self-evaluation diary" (see Primary efficacy endpoint, above*).*

Statistically significant differences in sleep disturbance between groups were not demonstrated. Both active treatments showed a statistically significant superiority to placebo in respect of impairment of daily activities.

There was no analysis of responder rate.

PAR

Study IC06RUP/3/04

Study IC06RUP/3/04 was a Phase III, double-blind, parallel group, randomised, active and placebo controlled study conducted in 17 centres in Argentina, 9 centres in Chile and 7 centres in Romania from September 2004 to May 2005.The objective of the study was to evaluate the efficacy and safety of rupatadine for the treatment of PAR symptoms over a 12-week treatment period. Study Participants were:

- Patients "older than 12" with documented history of PAR ≥ 1 year and a positive prick test to an allergen responsible for perennial rhinitis. Patients sensitised to pollen or mould were accepted provided the specific allergen was not in its pollination phase.

Evaluator Comment

Adherence to the second sentence above could not be verified. Besides, patients with a history of SAR, may have been sensitive to multiple seasonal allergens, only some of which were tested for in judging compliance with the criterion.

- In the week before enrolment, a patient had to obtain on 3 days (with 2 assessments per day) a TSS ≥ 45 (of the maximum possible 108). For these 3 days, the total score for nasal obstruction had to be ≤ 12 (of the maximum possible 18). The scale used is shown in Table 14.

Table 14: Scoring scale used in Study IC06RUP/3/04

Nasal symptoms	Non-nasal symptoms
Sneezing	Ocular pruritus
Rhinorrhoea	Ocular redness
Nasal obstruction	
Nasal pruritus	
Symptom severity to be scored as follows: 0 = No symptoms. 1 = Mild symptoms (occasionally present, but not troublesome). 2 = Moderate symptoms (frequently present and annoying). 3 = Severe symptoms (continuously present and interfering with work or sleep).	

- On the enrolment day, the "overall assessment" score for PAR (on a scale of 0-3) had to be ≥ 2. The overall assessment was based on "signs and symptoms in the last 24 hours assessed by the investigator and the patient".
- Results of standard laboratory tests within acceptable limits. ECG within acceptable limits, and with QTc interval values (after Bazett's correction) < 430 msec for males and < 450 msec for females.
- Patients using systemic or topical medication for allergy were subjected to various washout periods.

Treatments were rupatadine tablet 10 mg, cetirizine tablet 10 mg, or placebo, administered daily for 84 days "preferably in a fasting state, with a glass of water". The following topical or systemic medication was not permitted during the study period: drugs known to interact with CYP3A4 isoenzyme, grapefruit juice, non-study antihistamines, corticosteroids, leukotriene antagonists, decongestants, cromoglycate.

The primary efficacy endpoint was the change from baseline in total symptom score (TSS). TSS on any day is the sum of the individual symptom scores recorded by each patient in a diary. (See Table 14 - maximum TSS is 18).

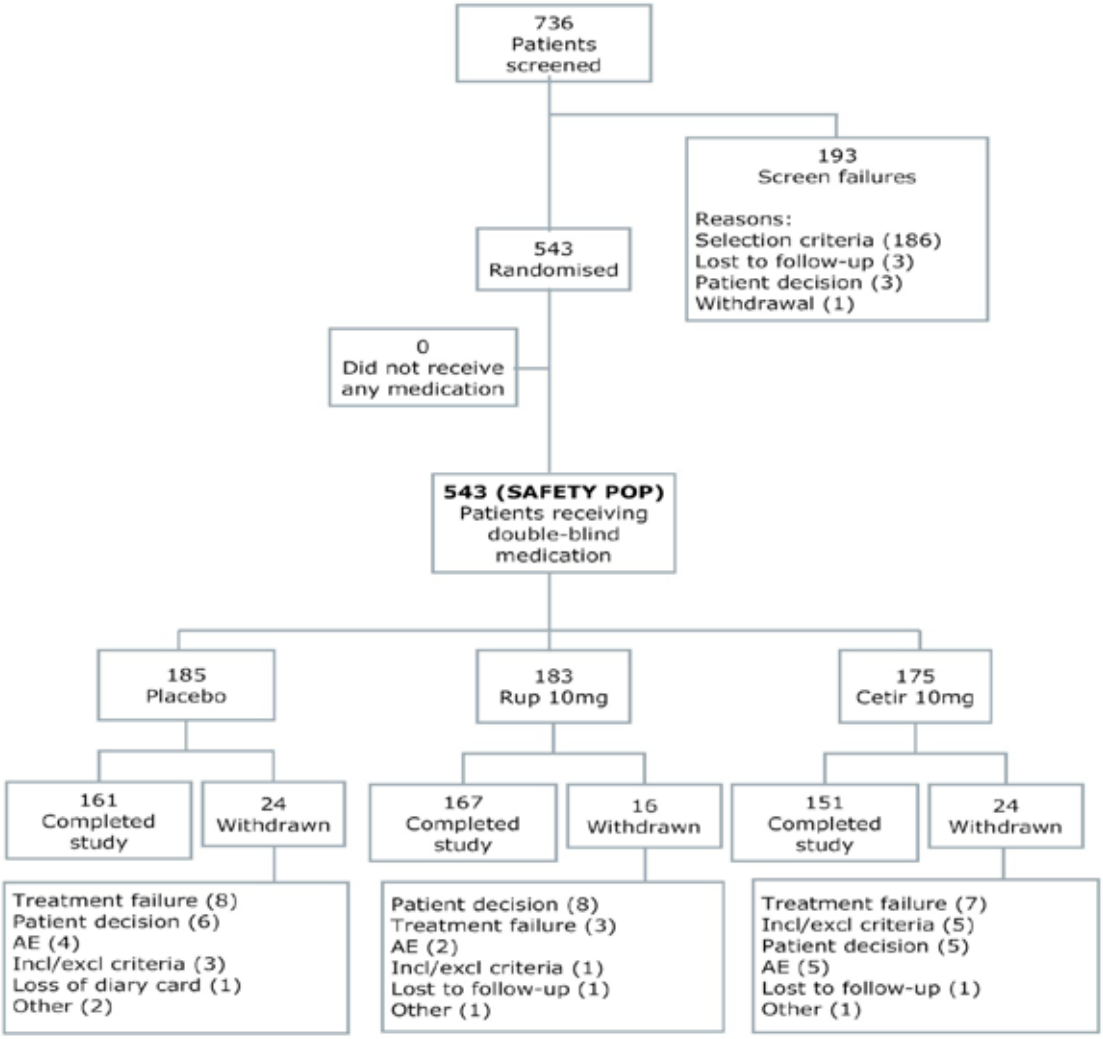
The intended sample size was 170 per group, which was chosen to detect, with 80% power and 5% significance level, a difference of ≥ 0.71 units in the primary efficacy variable, assuming SD 2.18 and a loss rate of 10%.

The planned analysis was a two-way ANCOVA, the main comparison being rupatadine vs placebo.

Results

The participant flow is shown in Figure 2.

Figure 2: Participant flow. Study IC06RUP/3/04



TSS observations at the beginning and end of the study are shown in Table 15, for the ITT population. Using an ANCOVA analysis, rupatadine (Rup) was shown to be statistically significantly superior to placebo (p=0.008).

Table 15: TSS change from baseline (Study IC05RUP/4/03)

	TSS change from baseline. Mean (sd)		
	Placebo (n=185)	**Rup 10 mg (n=183)**	**Cetir 10 mg (n=174)**
Baseline	8.96 (3.25)	8.72 (2.90)	8.21 (3.07)
Final	5.48 (3.65)	4.55 (2.90)	4.53 (3.40)
Change	-3.48 (3.62)	-4.17 (3.23)	-3.67 (3.86)

No patient took rescue medication.

Ancillary analyses included a quality of life assessment, based on completion by the patient of the Rhinoconjunctivitis Quality of Life Questionnaire (Juniper et al., 2000).[12]

[12] Juniper E et al. Development and validation of the Mini Rhinoconjunctivitis Quality of Life Questionnaire. Clin and Experimental Allergy 2000; 30: 132-140.

This questionnaire examines 7 domains (limitations in day-to-day activities, deterioration of sleep, non-nasal and non-ocular symptoms, practical problems, eye symptoms, nasal symptoms, and emotional problems), all in relation to the preceding week. Total changes from baseline are shown in Table 16.

Table 16: Changes from baseline in QOL (Study IC06RUP/3/04)

Visit	Pbo (n=185)	Rup 10 mg (n=183)	Cetir 10 mg (n=174)
4 weeks	-1.37 (1.10)	-1.60 (1.09)	-1.71 (1.21)
8 weeks	-1.88 (1.18)	-1.93 (1.21)	-2.05 (1.22)
Last	-1.76 (1.38)	-2.01 (1.32)	-2.10 (1.35)

The difference between placebo and rupatadine at the last visit was statistically significant, as was the difference between placebo and cetirizine (in favour of the active). There was no analysis of responder rate.

CIU

Study IC010RUP/3/04

Study IC010RUP/3/04 was a Phase III, double-blind, parallel group, randomised, placebo controlled study conducted in 5 centres in Argentina, 4 centres in Germany, 4 centres in Italy, 4 centres in Poland, 6 centres in Romania and 3 centres in Spain from November 2004 to July 2005. The objective of the study was to evaluate the efficacy of rupatadine 10 mg and 20 mg for the treatment of CIU symptoms over a 4-week treatment period, and (as a secondary objective) the safety over 6 weeks.

Study Participants were:

- Patients aged 12-65 years, with history of active CIU (urticaria wheals) with or without associated angioedema for ≥ 3 days/week over the 6 weeks before screening.
- In the week before Visit 1, pruritus score ≥ 2 on ≥ 3 days and total pruritus score ≥ 6 over the 3 worst days. The scale used is shown in Table 17.

Table 17: Scoring scale used in Study IC010RUP/3/04

Pruritus symptom severity to be scored as follows:
0 = No symptoms.
1 = Mild symptoms, not annoying or troublesome.
2 = Moderate symptoms, annoying or troublesome.
3 = Severe symptoms, very annoying, substantially interfering with sleep/ daily activities.
4 = Very severe symptoms, warrant physician visit.

- Results of standard laboratory tests within acceptable limits. ECG within acceptable limits, and with QTc interval values (after Bazett's correction) < 430 msec for males and < 450 msec for females.
- Patients using systemic or topical medication for allergy were subjected to various washout periods.

Treatments were rupatadine tablet 10 mg or 20 mg or placebo, administered daily for 42 days "preferably in a fasting state, with a glass of water, and preferably in the morning". The following topical or systemic medication was not permitted during the study period: drugs known to interact with CYP3A4 isoenzyme, grapefruit juice, non-study antihistamines (H1 or H2), corticosteroids, leukotriene antagonists or antidepressants.

The primary efficacy endpoint was the change from baseline in mean Pruritus Score (MPS) over 4 weeks.

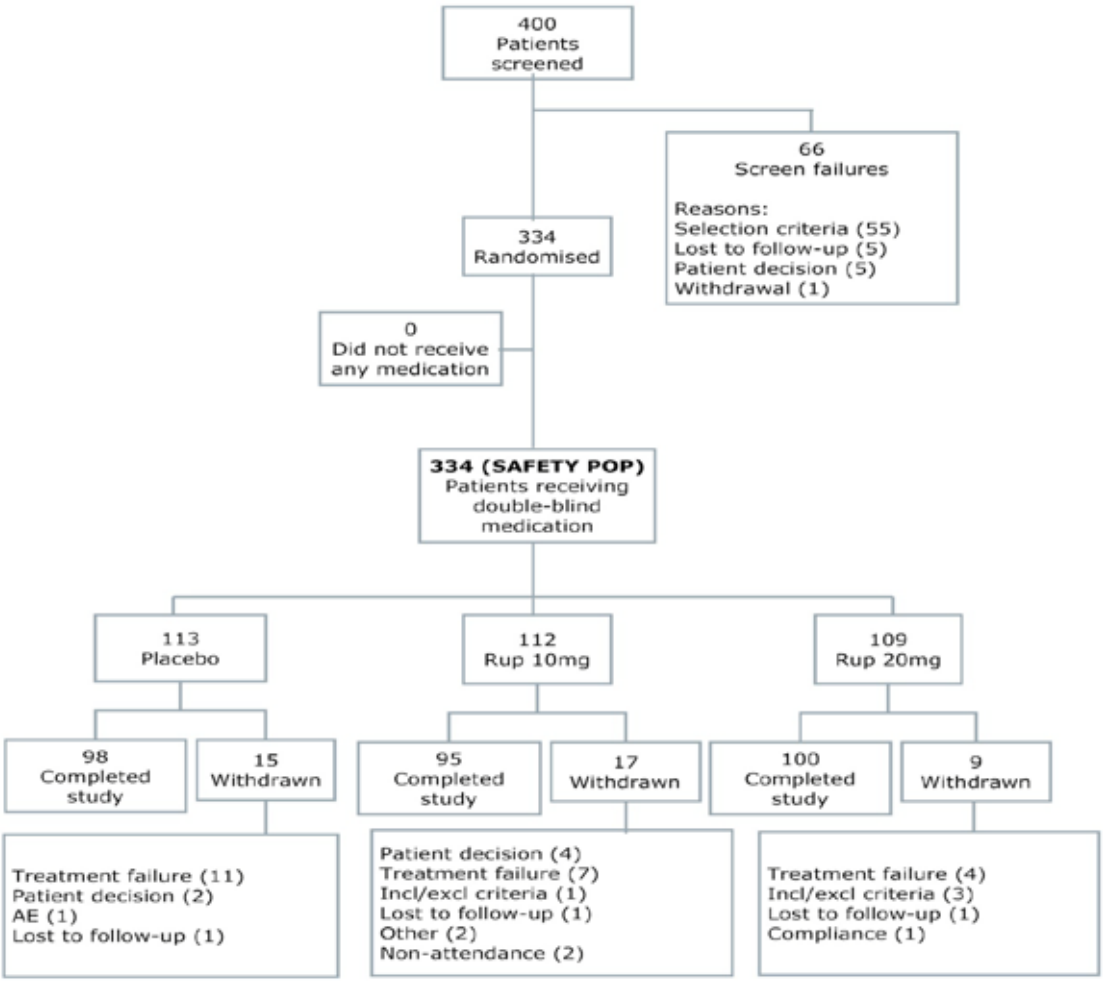
The intended sample size was 100 per group, which was chosen to detect with 80% power and 5% significance level, a difference ≥ 0.5 unit in the primary efficacy variable, assuming an SD of 0.95

The planned analysis was by ANOVA, with terms for investigator, site and treatment.

Results

The participant flow is shown in Figure 3.

Figure 3: Participant flow for Study IC010RUP/3/04



The results for the primary efficacy variable MPS in the ITT population over the first 4 weeks of the study are shown in Table 18.

Table 18: MPS in Study IC010RUP/3/04

	MPS: Mean (sd)		
	Pbo (n=111)	**Rup 10 mg (n=110)**	**Rup 20 mg (n=108)**
Baseline	2.54 (0.46)	2.47 (0.45)	2.51 (0.52)
Final	1.41 (0.82)	1.05 (0.82)	0.92 (0.83)
Change	-1.13 (0.71)	-1.42 (0.73)	-1.59 (0.79)

Using the ANOVA model, statistically significant differences were shown between placebo and each active ($p<0.01$). Also, a statistically significant linear relationship was shown between dose and efficacy variable.

Similar results were obtained for the PP population.

Ancillary analyses included analysis of changes in MPS over the whole study (6 weeks) which showed results similar to those obtained at 4 weeks. A score representing Mean Number of Wheals was analysed over 4 weeks, showing statistically significant superiority of each active over placebo.

Planned secondary analyses also included change from baseline at 4 and 6 weeks in a Dermatology Life Quality Index (Finlay et al., 1994), which had been completed by patients every 2 weeks.[13] The overall score results (covering 6 individual domains) for the ITT population showed statistically significant changes between baseline and 6 weeks for placebo vs rupatadine 20 mg and rupatadine 10 mg vs rupatadine 20 mg.

Evaluator Comment

> The DLQI results should not be accorded much weight, because the cited reference makes clear that the DLQI had undergone only preliminary testing, noting: "It is essential to demonstrate that quality of life assessment methods can detect change in quality of life. Measures of quality of life should not, for example, be used in clinical trials unless responsiveness has been demonstrated in the skin condition being examined. ... External validity testing is also of importance ...".

The sponsor noted however that the use of DLQI is a well established, accepted and internationally valid set of indicators since 1994. There are over 200 published references to the use of and validation of DLQI.

Supportive studies

Studies IC01RUP/IV/02, IC011RUP/4/04 and IC013RUP/1/04 are included in this section for convenience, although their objectives relate to safety rather than efficacy.

Study UR/FC97/III-01

Study UR/FC97/III-01 was a Phase III, double-blind, parallel group, randomised study conducted in 19 centres in Spain from April 1997 to June 1998. It was a comparative study of different agents in SAR involving 81 patients in the placebo arm, 83 taking ebastine 10 mg and 79 taking 10 mg rupatadine.

The outcome in the ITT population is shown in Table 19.

[13] Finlay AY et al. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Experimental Dermatol 1994; 19: 210-216.

Table 19: Outcome in the ITT population (Study UR/FC97/III-01)

Mean (sd)	Placebo (n=81)	Ebastine 10 mg (n=83)	Rupatadine 10 mg (n=79)
$DTSS_{mean}$	0.83 (0.48)	0.72 (0.50)	0.56 (0.38)

Rupatadine was statistically superior to placebo ($p < 0.005$), but the difference between active treatments was not statistically significant.

Study UR/FC98/III-02

Study UR/FC98/III-02 was a Phase III, double-blind, parallel group, randomised study conducted in 24 centres in Spain from January 1999 to January 2000. It was a comparative study of different agents in SAR involving 73 patients in the placebo arm, 77 taking ebastine 10 mg and 69 taking 10 mg rupatadine.

The outcome in the ITT population is shown in Table 20.

Table 20: Outcome in the ITT population (Study UR/FC98/III-02)

Mean (sd)	Placebo (n=72)	Rupatadine 10 mg (n=69)	Ebastine 10 mg (n=77)
PD_{max} 1	41.95 (34)	48.65 (38)	50.85 (36)

Pairwise comparisons (using an ANCOVA analysis) failed to show a statistically significant difference between any of the treatments.

Study IC01RUP/IV/02

Study IC01RUP/IV/02 was a long term open study with initial one month double-blind parallel phase study conducted in multiple centres in Spain from September 2002 to September 2004. It was a long-term safety study of rupatadine in PAR involving 313 treated patients.

In an introductory explanation, the sponsor explains that this study was done in compliance with a guideline specifying that the safety of drugs for chronic or repeated intermittent use for longer than 6 months should be studied in 300-600 patients during 6 months and in 100 patients during a year.[14]

It appears that whereas 294 of the 320 initially randomised patients were reviewable at the end of 6 months' active treatment, the 92 patients followed to 1 year were a self-selected group, comprising those who chose to continue treatment with rupatadine 10 mg tablets on a "prn" (as necessary) basis beyond 6 months, and who chose to attend for review at the end of the year.

Evaluator Comment

> The sponsor's *Clinical Study Report* is difficult to interpret, and the sponsor should be invited to point out whether the above paragraph results from a misunderstanding. If the evaluator's interpretation is correct, then the reported 12-month experience is of little value.

[14] European Union (EU). The extent of population exposure to assess clinical safety for medicines intended for long-term treatment of non-life-threatening conditions. 1998a. *Rules* 3(c) - 3cc5a, pages 121-125.

Study IC011RUP/4/04

Study IC011RUP/4/04 was a one year open study conducted in 3 centres in Spain from July 2004 to November 2005. It was a long-term safety study of rupatadine in PAR involving 85 patients taking 10 mg rupatadine.

Study IC013RUP/1/04

Study IC013RUP/1/04 was a randomised, parallel, placebo-controlled, subject-blind, escalating dose study conducted in one centre in Spain from October 2004 to January 2005. It was a study of the tolerability of escalating dosage, preparatory to the undertaking of Study IC012RUP/1/04 (see above) involving 33 normal subjects.

Evaluator's overall conclusions on clinical efficacy

In the dose finding studies, general experience was that daily dosage of 10 mg or more daily was superior to placebo, but that statistically significant difference between different dosages of rupatadine could not be demonstrated. Thus, it seemed appropriate to choose the 10 mg daily dose for further study.

The pivotal studies confirm the efficacy of rupatadine in the claimed indications.

Safety

Introduction

The safety evidence presented comprises routine safety monitoring from the clinical studies (AEs and clinical laboratory monitoring), special studies relating to aspects of safety and Periodic Safety Update Reports (PSURs).

Patient exposure

The evaluator noted that information on overall exposure was summarised in the submission but a count of the patients exposed in the studies presented, classified by type of study, was also provided. It was noted that some subjects have been counted multiple times - once for each dosage they have received. The comparison between these counts is shown in Table 21.

Table 21: Numbers of patients exposed

Rupatadine Daily or One-time Dosage	Summary	Addition of individual studies
Placebo	1315	1405
2 mg	6	6
2.5 mg	77	77
5 mg	156	156
10 mg	2025	2011
20 mg	1053	1079
40 mg	79	78
60 mg	8	8
80 mg	38	36
100 mg	48	49
Any > 0	Not stated	3332

The sponsor was requested to identify the cause of the column differences for placebo, 10 mg and 20 mg. This was explained in terms of the difference in numbers recruited and randomised versus those who actually received a dose of the test medication.

Adverse events

Pharmacokinetic and pharmacodynamic studies

Safety monitoring observations made in the pharmacokinetic and pharmacodynamic studies were presented in summary tables for each study. In general, the numbers were small and no conclusions can be drawn. The AEs reported, however, were included in an overall pool.

Pivotal efficacy studies and major safety studies

AEs relating to these studies were displayed separately, as follows:

IC05RUP/4/03: AEs are shown in Table 22, classified by System Organ Class (SOC).

Table 22: Patient numbers with AEs (Study IC05RUP/4/03)

SOC Preferred term[1]	Placebo n=122	Rup 10 mg n=119	Deslor 5 mg n=118
Cardiac disorders	4 (3.3%)	1 (0.8%)	3 (2.5%)
Gastrointestinal Disorders	10 (8.2%)	8 (6.7%)	9 (7.6%)
Abdominal pain	3 (2.5%)	1 (0.8%)	1 (0.8%)
Abdominal pain upper	3 (2.5%)	0 (0.0%)	1 (0.8%)
Diarrhoea	3 (2.5%)	1 (0.8%)	3 (2.5%)
Nausea	2 (1.6%)	4 (3.4%)	2 (1.7%)
General Disorders And Administration Site Cond.	9 (7.4%)	8 (6.7%)	4 (3.4%)
Fatigue	5 (4.1%)	5 (4.2%)	1 (0.8%)
Infections And Infestations	8 (6.6%)	7 (5.9%)	6 (5.1%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	3 (2.5%)
Nasopharyngitis	3 (2.5%)	0 (0.0%)	0 (0.0%)
Injury, Poisoning And Procedural Complications	6 (4.9%)	1 (0.8%)	2 (1.7%)
Investigations	3 (2.5%)	5 (4.2%)	4 (3.4%)
Raised CPK	1 (0.8%)	3 (2.5%)	2 (1.7%)
Musculoskeletal and connective tissue disorders	2 (1.6%)	4 (3.4%)	4 (3.4%)
Nervous system disorders	14 (11.5%)	28 (23.5%)	24 (20.3%)
Headache	12 (9.8%)	16 (13.4%)	16 (13.6%)
Somnolence	0 (0.0%)	13 (10.9%)	8 (6.8%)
Respiratory, Thoracic and Mediastinal Disorders	10 (8.2%)	5 (4.2%)	4 (3.4%)
Epistaxis	3 (2.5%)	0 (0.0%)	1 (0.8%)
Pharyngolaryngeal pain	3 (2.5%)	3 (2.5%)	1 (0.8%)
Skin and Subcutaneous Tissue Disorders	3 (2.5%)	4 (3.4%)	1 (0.8%)

[1]The SOC data include all reported AEs, but a preferred term is included only when frequency is ≥ 2% for ≥ 1 group. Rup = rupatadine, Deslor = desloratadine

IC06RUP/3/04: AEs are shown in Table 23, classified by SOC.

Table 23: Patient numbers with AEs (Study IC06RUP/3/04)

SOC Preferred term[1]	Placebo n=185		Rup 10 mg n=183		Cet 10 mg n=175	
Blood and lymphatic system disorders	4	(2.2%)	2	(1.1%)	1	(0.6%)
Cardiac disorders	8	(4.3%)	1	(0.5%)	1	(0.6%)
Eye disorders	4	(2.2%)	2	(1.1%)	2	(1.1%)
Gastrointestinal Disorders	26	(14.1%)	35	(19.1%)	28	(16.0%)
Abdominal pain	5	(2.7%)	8	(4.4%)	4	(2.3%)
Abdominal pain upper	9	(4.9%)	12	(6.6%)	6	(3.4%)
Diarrhoea	1	(0.5%)	4	(2.2%)	4	(2.3%)
Dry mouth	1	(0.5%)	4	(2.2%)	4	(2.3%)
Nausea	4	(2.2%)	2	(1.1%)	4	(2.3%)
Toothache	8	(4.3%)	7	(3.8%)	3	(1.7%)
Vomiting	3	(1.6%)	5	(2.7%)	0	(0.0%)
General Disorders And Administration Site Cond.	15	(8.1%)	11	(6.0%)	9	(5.1%)
Pyrexia	5	(2.7%)	6	(3.3%)	3	(1.7%)
Infections And Infestations	47	(25.4%)	38	(20.8%)	33	(18.9%)
Gastroenteritis	4	(2.2%)	3	(1.6%)	1	(0.6%)
Influenza	6	(3.2%)	2	(1.1%)	3	(1.7%)
Nasopharyngitis	19	(10.3%)	12	(6.6%)	16	(9.1%)
Tonsillitis	0	(0.0%)	5	(2.7%)	0	(0.0%)
URTI	4	(2.2%)	4	(2.2%)	5	(2.9%)
Injury, Poisoning And Procedural Complications	4	(2.2%)	6	(3.3%)	0	(0.0%)
Investigations	9	(4.9%)	12	(6.6%)	9	(5.1%)
Raised CPK	4	(2.2%)	5	(2.7%)	3	(1.7%)
Metabolism and nutrition disorders	2	(1.1%)	4	(2.2%)	6	(3.4%)
Musculoskeletal and connective tissue disorders	16	(8.6%)	16	(8.7%)	10	(5.7%)
Back pain	5	(2.7%)	9	(4.9%)	3	(1.7%)
Myalgia	2	(1.1%)	4	(2.2%)	1	(0.6%)
Pain in extremity	4	(2.2%)	2	(1.1%)	4	(2.3%)
Nervous system disorders	68	(36.8%)	68	(37.2%)	62	(35.4%)
Dizziness	4	(2.2%)	4	(2.2%)	3	(1.7%)
Headache	66	(35.7%)	53	(29.0%)	51	(29.1%)
Somnolence	8	(4.3%)	19	(10.4%)	14	(8.0%)
Psychiatric disorders	3	(1.6%)	4	(2.2%)	3	(1.7%)
Reproductive system and breast disorders	10	(5.4%)	7	(3.8%)	6	(3.4%)
Dysmenorrhoea	9	(4.9%)	7	(3.8%)	4	(2.3%)
Respiratory, Thoracic and Mediastinal Disorders	30	(16.2%)	13	(7.1%)	7	(4.0%)
Asthma	6	(3.2%)	5	(2.7%)	1	(0.6%)
Epistaxis	6	(3.2%)	0	(0.0%)	1	(0.6%)
Pharyngolaryngeal pain	7	(3.8%)	4	(2.2%)	3	(1.7%)
Skin and Subcutaneous Tissue Disorders	14	(7.6%)	3	(1.6%)	3	(1.7%)
Urticaria	4	(2.2%)	1	(0.5%)	1	(0.6%)

[1]The SOC data include all reported AEs, but a preferred term is included only when frequency is ≥ 2% for ≥ 1 group. Rup = rupatadine, Cet = cetirizine

IC010RUP/3/04: A table showing AEs with reported frequency > 2% is shown at Table 24.

Table 24: Patient numbers with AEs (Study IC010RUP/3/04)

SOC Preferred term[1]	Placebo n=113	Rup 10 mg n=112	Rup 20 mg n=109
Gastrointestinal Disorders			
Nausea	3 (2.7%)	2 (1.8%)	
Infections And Infestations			
Influenza	1 (0.9%)	4 (3.6%)	2 (1.8%)
Investigations			
Raised CPK	1 (0.9%)	4 (3.6%)	1 (0.9%)
Nervous system disorders			
Headache	9 (8.0%)	5 (4.5%)	9 (8.3%)
Somnolence	6 (5.3%)	3 (2.7%)	9 (8.3%)

[1]Only AEs with frequency > 2% in any group are included. Rup = rupatadine

IC01RUP/IV/02: AEs reported in the initial 28 day double blind period and classified at least possibly study drug related are shown in Table 25. AEs reported in the initial period of 6 months active treatment (which for those randomised to active includes the 28 day double blind period) and classified at least possibly study drug related are shown in Table 26. AEs reported in the period of 12 months active treatment (which for those randomised to active includes the 28 day double blind period) and classified at least possibly study drug-related are shown in Table 27.

Table 25: Patient numbers with AEs classified as at least possibly study-drug related - double-blind period (Study IC01RUP/IV/02)

SOC Preferred term	Rup 10 mg n=213	Pbo n=107
Eye disorders	1	0
Eye pruritus	1	
Gastrointestinal Disorders	5	1
Diarrhoea	1	1
Constipation	1	
Dry mouth	3	
Nausea	1	
General Disorders And Administration Site Cond.	5	0
Asthenia	2	
Fatigue	3	
Feeling cold	1	
Malaise	1	
Pyrexia	1	
Investigations	2	0
QRS complex prolonged	1	
Weight increased	1	
Metabolism and nutrition disorders	0	1
Appetite increased		1
Nervous system disorders	20	5
Dizziness	2	
Headache	10	2
Somnolence	12	3
Psychiatric disorders	1	0
Disturbance in attention	1	
Respiratory, Thoracic and Mediastinal Disorders	3	0
Cough	1	
Nasal congestion	1	
Pharyngolaryngeal pain	1	
Throat irritation	1	
Skin and Subcutaneous Tissue Disorders	0	2
Pruritus		1
Rash		1

Table 26: Patient numbers with AEs classified as at least possibly study-drug related - first 6 months' open treatment (Study IC01RUP/IV/02)

SOC Preferred term[1]	Rup 10 mg n=294
Eye disorders	1
Gastrointestinal Disorders	6
Dry mouth	4
General Disorders And Administration Site Cond.	10
Asthenia	3
Fatigue	4
Malaise	2
Thirst	2
Investigations	3
QRS complex prolonged	0
Weight increased	2
Liver function test abnormal	1
CPK increased	1
Nervous system disorders	29
Dizziness	2
Headache	16
Somnolence	15
Psychiatric disorders	1
Renal and urinary disorders	1
Reproductive system and breast disorders	1
Respiratory, Thoracic and Mediastinal Disorders	8
Cough	3
Nasal dryness	2
Skin and Subcutaneous Tissue Disorders	1

[1]The SOC data include all reported AEs, but only selected preferred terms are included. Rup = rupatadine

Table 27: Patient numbers with AEs classified as at least possibly study-drug related - 12 months' open treatment (Study IC01RUP/IV/02)

SOC Preferred term	Rup 10 mg 92<n<294
Gastrointestinal Disorders	2
Dry mouth	2
General Disorders And Administration Site Cond.	1
Asthenia	1
Investigations	1
AST increased	1
CPK increased	1
Nervous system disorders	6
Hyposmia	1
Headache	1
Somnolence	5
Respiratory, Thoracic and Mediastinal Disorders	1
Nasal dryness	1

IC011RUP/4/04: AEs reported in the initial period of 6 months are shown in Table 28.

Table 28: Patient numbers with AEs during the first 6 months' treatment (Study IC011RUP/4/04)

SOC Preferred term[1]	Rup 10 mg 50<n<85
Ear and labyrinth disorders	1
Eye disorders	8
Conjunctivitis allergic	8
Gastrointestinal Disorders	13
Vomiting	4
Diarrhoea	2
Dry mouth	3
Dyspepsia	3
Odynophagia	5
General Disorders And Administration Site Cond.	9
Fatigue	4
Malaise	2
Oedema peripheral	2
Infections and infestations	35
Injury, Poisoning And Procedural Complications	2
Metabolism and nutrition disorders	2
Musculoskeletal and connective tissue disorders	8
Back pain	3
Neoplasms	1
Nervous system disorders	23
Dizziness	2
Headache	12
Somnolence	12
Psychiatric disorders	8
Anxiety	3
Reproductive system and breast disorders	7
Respiratory, Thoracic and Mediastinal Disorders	19
Asthma	3
Catarrh	6
Cough	3
Rhinalgia	2
Skin and Subcutaneous Tissue Disorders	9
Surgical and medical procedures	3

[1]The SOC data include all reported AEs, but only selected preferred terms are included.

IC013RUP/1/04: AEs were as follows:

- placebo: somnolence (1 report), headache (2)
- rupatadine 60 mg: somnolence (1), headache (2), raised CPK (1), raised AST (1)
- rupatadine 80 mg: somnolence (6), headache (1)
- rupatadine 100 mg: fatigue (1), somnolence (7)

Other studies

AEs reported in these studies were displayed as pooled data.

Serious adverse events and deaths

No death was reported in any study included in the submission. Serious AEs were reported as follows:

RD 477/22115: 1 serious AE (foreign body in eye) - classified unrelated.

UR/FC97/III-03: 1 serious AE (treated with rupatadine 20 mg; hepatic function abnormal, resolved within 20 days) - considered as drug-induced subclinical acute hepatitis.

RD 477/21416: 1 serious AE (atrial fibrillation in a patient taking placebo).

UR/FC98/III-03: Serious AEs: The ethics committee concerned had requested that abnormal hepatic enzyme increases after treatment withdrawal should be reported as serious AEs. A total of 15 cases were reported as serious AEs for this reason alone. AEs which were reported as serious under the usual definition were reported in 3 patients as follows:

- Placebo: 1 elective plastic surgery; 1 appendectomy
- Rupatadine 20 mg: 1 pregnancy, abdominal pain, metrorrhagia, abortion

UR/FC98/III-01: 1 serious AE was reported (raised hepatic enzymes in a patient on placebo, first noted during treatment, and improving after cessation of treatment).

IC06RUP/3/04: Serious AEs were reported in 2 patients:

- Placebo: dead retained zygote
- Cetirizine 10 mg: metrorrhagia

IC02RUP/II/02: Serious AEs were reported in 2 patients:

- Placebo: pregnancy
- Rupatadine 5 mg: raised CPK, normalised after completing treatment.

IC010RUP/3/04: Serious AEs were reported in 2 patients on rupatadine 20 mg (1 deterioration of arterial hypertension; 1 metrorrhagia)

IC01RUP/IV/02: Serious AEs were reported in 6 patients:

- Double-blind period, rupatadine group: 1 (ligament sprain)
- Open period to 6 months' active: 4 (1 breast neoplasm; 1 bone injury; 1 bone cyst; 1 bronchitis)
- Open period, remainder: 1 (raised AST, ALT and CPK)

IC013RUP/1/04: Serious AE reported in 1 subject on rupatadine 60 mg (raised CPK)

Adverse events leading to discontinuation

Reasons for discontinuation were incompletely recorded but fatigue, somnolence and asthenia were mentioned.

Laboratory findings in clinical efficacy and safety studies

Patients were generally excluded from the studies unless QTc < 430 msec (men) and < 450 msec (women). Many of the studies included baseline and end of study ECGs but in general, although these studies did not demonstrate clinically significant change, nor were they structured to provide reassurance. A special study (IC012RUP/1/04) was done, focusing on QTc.

Individual abnormal values

In general, the abnormal values presented in the sponsor's *Clinical Study Reports* are those observed at the final visit. Usually, only abnormalities considered "clinically significant" were presented. Where a broader category was used, this was preferred, and the study footnoted. The time course of the abnormality was generally not available from the submission.

Laboratory values: trend over time

Cases where the changes in laboratory mean values between baseline and study end were significantly different (at 0.05 level) between rupatadine dosage groups or between rupatadine and another drug group, or where (for example) an ANOVA test showed significant differences among groups, possibly implicating a rupatadine group, are listed below. Statistical analysis varied and details were generally omitted. Note that the populations from which baseline, final, and change are calculated are not identical, so when "Change" is estimated, it is not necessarily equal to "Final" minus "Baseline".

Evaluator Comment

None of the data produced in this way raise any cause for concern (Table 29). The evaluator noted however that the remark "no significant clinical trends" seems inappropriate in a situation where the analysis is directed at searching the data for clues to an as yet unrecognised hazard, or for signs of the beginning of a trend which may continue. A finding of "no significant trends", on the other hand (presumably meaning "no statistically significant trends") is in order.

Table 29: Laboratory values: trend over time

Study Comparison	Measurement	Baseline mean (sd)	Final mean (sd)	Change mean (sd)
RD 477/21212	"No significant trends"			
RD 477/22115	"No significant trends"			
UR/FC97/III-01				
rupatadine 10 mg	bilirubin	11.3	12.6	
vs placebo		10.4	11.4	
UR/FC97/III-03	"No significant clinical trends"			
UR/FC97/III-04	No analysis presented			
UR/FC98/III-04	No analysis presented			
IC05RUP/4/03				
rupatadine 10 mg	glucose	5.1	5.1	0.2
vs placebo		5.4	5.1	-0.3
RD 477/21416	"No significant trends"			
UR/FC98/III-03				
rupatadine 20 mg	bilirubin	9.6 (5.3)	8.8 (3.8)	
vs placebo		10.4 (7.1)	10.1 (5.4)	
UR/FC98/III-02	"No significant trends"			
UR/FC98/III-01	"No significant trends"			
IC06RUP/3/04				
rupatadine 10 mg	haemoglobin			-0.22 (0.64)
vs placebo				-0.03 (0.68)
rupatadine 10 mg	AST			0.85 (6.9)
vs placebo				-0.50 (5.6)
IC02RUP/II/02	No analysis presented			
IC010RUP/3/04				
rupatadine 20 mg	neutrophils	4.01 (1.44)	3.59 (1.13)	-0.44 (1.51)
vs placebo		4.15 (1.59)	4.15 (1.49)	0.09 (1.45)
rupatadine 20 mg	basophils	0.02 (0.03)	0.01 (0.02)	-0.01 (0.03)
vs placebo		0.02 (0.03)	0.02 (0.02)	0.00 (0.04)
IC01RUP/IV/02	No analysis presented			

Post-marketing experience

The sponsor submitted PSURs numbers one to seven. AEs reported in PSURs 5-7 (other than AEs occurring in clinical trials included in the present submission) were pooled. No signal emerges from these reports, which are remarkably few in the context of the amount of product distributed.

Evaluator's overall conclusions on clinical safety

Somnolence is an AE which has been observed more frequently with rupatadine 10 mg daily than with placebo and which tends to be more frequent with higher dosage. This is shown in the pooled results and also in individual tables of AEs for most of the major controlled studies. Reports of AEs leading to discontinuations are consistent.

From the reports of serious AEs, and from the clinical laboratory monitoring, raised hepatic enzymes and CPK emerge as possibly requiring future vigilance.

The overall number of patients studied is compliant with the relevant guideline but the evaluator had some concern about the adequacy of the length of exposure in trials.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

Efficacy

The sponsor should be asked for evidence that Study RD 477/21416 was in fact done outside the hay fever season in both UK and Spain.

The sponsor should be asked about the extent to which Studies UR/FC98/III-03, UR/FC98/III-02 and UR/FC98/III-01 were done outside the hay fever season.

The sponsor should be asked for further details of how double-blinding was achieved in Study IC010RUP/3/04.

Safety

The sponsor should be asked whether it can identify the cause of discrepancies in the tabulations of exposure to rupatadine.

Regarding Study IC01RUP/IV/02, the sponsor should be asked about the dosage in the final 6-month period of the study.

The responses to these questions are described by the Delegate under *Overall Conclusion and Risk/Benefit Assessment*.

Clinical Summary and Conclusions

The evaluator summarised the submission as follows:

SAR

The primary endpoint in the studies was appropriate and efficacy was established. There were no studies specifically designed as superiority studies, although some of the studies included an active comparator, presumably to assist in selecting dosage.

Quality of life (QoL) measures were included as an ancillary assessment but added little to the primary efficacy measure, which was based on patient assessment.

Duration of the efficacy studies was adequate but the 12-month safety study appeared to be flawed.

Studies were done in a variety of environments and the evaluator believed they were relevant to Australian conditions.

PAR

The primary endpoint in the studies was appropriate and efficacy was established. There were no studies specifically designed as superiority studies, although some of the studies included an active comparator, presumably to assist in selecting dosage.

QoL measures were included as an ancillary assessment and were supportive.

Duration of the efficacy studies was adequate but the 12 month safety study appeared to be flawed.

Studies were done in a variety of environments and the evaluator believed they were relevant to Australian conditions.

Allergen testing of patients proposed for admission to trials appeared adequate. However, there is a question of whether studies were always conducted in such a way as to exclude possible SAR effects.

CIU

The primary endpoint in the studies was appropriate. There were no studies specifically designed as superiority studies.

QoL measures were included as an ancillary assessment but the instrument used was not of proven validity.

The duration of the pivotal study (6 weeks) was in the opinion of the evaluator only marginally adequate. The evaluator considered a 3 or 6 month efficacy study should be conducted in a condition like this, which is chronic and whose aetiology is not well understood.

Benefit-risk assessment and conclusion

The benefits are efficacy in the claimed indications for SAR and PAR. Evidence for efficacy in CIU has not been demonstrated beyond 6 weeks. No evidence has been presented to show that rupatadine is more effective than some other antihistamines.

The known specific risk relates to CNS effects. Rupatadine appears to have sedating properties at 10 mg, with a dose-response relationship at higher doses and no adequate evidence has been submitted of non-inferiority (in sedation) to drugs which are currently classified as non-sedating. Possible risks relating to hepatic enzyme and CPK elevation remain to be clarified.

There is also risk relating to the apparent inadequacy of the long-term safety study IC01RUP/IV/02.

The overall benefit-risk balance is negative.

- for SAR and PAR, at least until the sponsor can provide reassurance regarding Study IC01RUP/IV/02; and
- for CIU, at least until the sponsor can provide (in addition to this safety reassurance), evidence of efficacy in the longer term.

The evaluator recommended refusal of registration.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The OPR evaluator noted that the RMP is dated June 2006. The RMP was incomplete in that it lacked updated information regarding adverse events occurring in the post-marketing period, does not report on the outcome status of clinical trials commenced in 2006 and lacks an adequate evaluation on the need for risk minimisation activities. The document referred to the Summary of Product Characteristics rather than the Australian Product Information. The non-clinical safety specifications were brief and did not adequately convey some important safety related outcomes such as those from animal studies on pregnancy, lactation and fertility. The pharmacological class effects section did not include analysis of central nervous system, cardiovascular and drug interaction class effects. Insufficient evaluation was made of the potential for off-label and paediatric off-

label use and there was no assessment on the potential for medication errors. The safety concerns identified by the sponsor are shown in Table 30.

Table 30: Safety concerns for rupatadine

Important identified risk	Headache
Important potential risks	Muscle damage Hepatic damage
Important missing information	Studies in children Studies in pregnant or lactating women Studies in patients with hepatic or renal disorders

In terms of the safety concerns, the sponsor did not identify interactions with concomitant CNS medications and alcohol, use in patients with cardiovascular disease, CNS adverse events, off-label use including paediatric off-label use and the effects on fertility as additional areas of important missing information in the pharmacovigilance (PhV) plan and risk minimisation assessments for Rupafin.

Routine PhV was planned for the identified risk of headache and the two potential risks of muscle damage and hepatic damage.[15] For the potential risks, the sponsor indicated that CPK and LFT determinations will be included in all clinical trials and that "these studies will start in 2006". Important missing information detailed in the RMP consists of studies in children, pregnant or lactating women, and patients with hepatic and renal disorders. No PhV plan was outlined for the missing information items.

The OPR evaluator commented that it was not considered necessary to include headache as an important identified risk or in the PhV plan as it is a well known non-serious adverse reaction common to the antihistamine class.

With regard to the clinical trials referred to, the sponsor should be required to provide a synopsis of these studies including the study design, objectives, sample size, and whether these are specific pharmacoepidemiological safety studies. It was stated that these studies were commenced in 2006 and so a summary of the study results or interim data should be provided and milestones for reporting identified.

No planned PhV actions have been outlined in the RMP for the important missing information. The sponsor should be required to include these.

Due to their potential seriousness, the following were considered important areas of missing information and it was the evaluator's opinion that they should be included in the RMP along with planned PhV actions or the sponsor should justify their exclusion:

[15] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- Interactions (pharmacokinetic and pharmacodynamic) with concomitant CNS medications.
- Cardiac adverse events and use in patients with known cardiovascular disease.
- CNS adverse events.
- Off label use, including paediatric off-label use.
- Effect on fertility.

Missing information items should be reported on separately in the PSUR and the sponsor should make reasonable attempts to follow-up with the reporter all notifications of exposure during pregnancy or through lactation to determine any abnormal outcomes.

The sponsor stated that "according to the safety specification and pharmacovigilance plan, risk minimization activities are not considered necessary."[16]

The OPR evaluator commented that an assessment of the need for risk minimisation activities was not done. For each safety concern the sponsor should be requested to assess whether any risk minimisation activities are needed

In addition, the sponsor did not provide an assessment on the potential for medication errors and should be required to do so.

A revised RMP was submitted by the sponsor that addressed the deficiencies in the initial document. A list of all suspected ADRs spontaneously reported to the company was included in this version and reference was made to the proposed Australian PI. A listing of the cases where off label use was identified was included in RMP V2.0. Furthermore, a Drug Utilisation Study that will be performed in the GPRD database in the UK was proposed. There was a reference to a published study that provided evidence that rupatadine 10 mg in combination with alcohol did not produce more cognitive and psychomotor impairment than alcohol alone.

Use in patients with cardiovascular disease and cardiac damage were added as potential risks. Moreover, electrocardiograms will be performed in patients enrolled in future clinical trials with rupatadine. Sales representatives will ask clinicians for information about possible heart rhythm disorders in patients treated with rupatadine.

Regarding missing information, the sponsor indicated that two clinical trials in children with allergic rhinitis aged 6-11 years have been performed with rupatadine oral solution. No safety concerns have been identified in these studies. Two more studies in children aged 2-5 years, with allergic rhinitis and urticaria, respectively, will be performed in the future. This can be considered a PV action.

Risk minimisation activities for off-label use are considered necessary and will consist in the education of the commercial representatives of the sponsor that they must remind clinicians that rupatadine must be used only in the approved indications. Also, they must ask clinicians periodically about off-label use of rupatadine in their clinical practice and remind to them that this use is not authorized. This education will be done in periodical meetings with them.

[16] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator noted that loratadine has structural similarities to azatadine, loratadine and desloratadine. It is achiral and the pharmaceutical form contains a single polymorph. Impurities above 0.15% have been toxicologically qualified. The proposed tablet is an immediate release tablet. A shelf life of three years below 25°C has been supported. The formulation that was used in the Phase III efficacy studies is the same as is proposed for marketing.

Bioavailability

Two bioavailability studies were submitted both of which were evaluated. The analytical methods were acceptable and the serum levels of one of the metabolites, desloratadine, was also measured.

Study UR/FC99/I-02 determined the bioavailability of the proposed 10 mg tablet relative to a 1 mg/mL compounded oral solution [with excipients] and a 1 mg/mL simple (extemporaneous) oral solution all at a dose of 10 mg. This study was intended to test whether the tablet is well-formulated or not. The rate and extent of absorption of an immediate release tablet should not be much dissimilar from a solution or a micronised suspension. The results were not suggestive that this goal was reached.

The relative AUC of rupatadine 10 mg tablet to on oral solution was about 45% but the median T_{max} was not delayed relative to the oral solution. The evaluator also noted a large coefficient of variation (47%) in regard to the extent of absorption from the tablet.

Study UR/FC98/I-02 was a food study, using fasted vs fed (high fat breakfast) conditions and a dose of 2 x 10 mg tablets. Food did not have a significant effect on the bioavailability (AUC) of rupatadine, but the 90% confidence intervals were broad and bioequivalence of the two treatments has not been proven. The AUC results after tablet administration were highly variable (CV = 64%).

It was noted that food delayed absorption. The clinical evaluator of this study found that the protocol "was inconsistent and vague".

The evaluator raised the issue of not conducting an absolute bioavailability study. This is necessary for new chemical entities not just for pharmaceutical assessment but to interpret toxicokinetic data. The applicant contended that a safe IV solution could not be prepared [for which no specific evidence was produced and it is quite obvious that it was feasible to make a simple oral solution]; a study performed against an oral solution is sufficient; and no adverse events have been observed since overseas launch in 2003.

In regard to the evaluator's concerns about erratic absorption, the obvious suggestion that the tablet is sub-optimally formulated (with potential inter-tablet variability) has been countered by the sponsor with the assertions that this variability is pharmacokinetic in nature due to a transitory saturation effect of the first pass metabolism, which does not affect the tablet formulation due to a non-immediate release of the active substance from tablets and to other factors such as gastrointestinal transit time.

The application was considered by the Pharmaceutical Subcommittee. Numerous issues required resolution.

The evaluator recommended registration on quality grounds but left the bioavailability issues as clinical ones.

The Delegate noted that the extent of absorption of unchanged rupatadine from the tablet is rather low and is highly variable. The variability is similar from an oral solution but the difference in the extent of absorption is striking. The "pharmacokinetic" justifications for the variability seen would need to shown to be specifically applicable to the tablet presentation. Hypothetically, an escalating dose pharmacokinetic study using an oral solution and arms that included interventions such as agents that increase and decrease gastric emptying and an intravenous administration would usefully address this.

T_{max} was almost formulation independent but AUC was definitely not. Moreover, a large difference in T_{max} was not attended by a similarly large difference in the extent of absorption. Taken together, these may be used to dismiss the "gastrointestinal transit time" hypothesis. In regard to the "transitory saturation effect of the first pass metabolism", it is noted that the study derived data were based on a dose that is 20 mg, twice that in the first table. A cross-study comparison may point to some nonlinearity of absorption but the very large coefficient of variation is more striking. It is therefore not possible to dismiss the most obvious explanation – that the tablets are sub-optimally formulated. The advice of the PSC was sought about this. The sponsor was invited to point to the specific data that support "a transitory saturation effect of the first pass metabolism".

Nonclinical

Studies conducted *in vitro* and *in vivo* support antihistamine (H1) and platelet-activating factor (PAF) receptor antagonism. Desloratadine is an active metabolite. Safety pharmacology studies did not suggest other actions and cardiac conduction abnormalities were not seen in dogs at high doses.

Metabolism of rupatadine was primarily catalysed by CYP3A4, with some involvement of CYP2C19 and CYP2D6. Rupafin did not inhibit these systems at clinically relevant doses.

Mutagenicity and carcinogenicity studies imply no positive findings at clinical doses.

Repeat dose toxicity studies of up to 26 weeks duration by the oral route were conducted in rats and dogs. Exposures were adequate but the duration was suboptimal. Toxic effects manifested in:

- the livers of rats and mice; the kidneys of rats, mice and dogs;
- inflammatory cell infiltrates in the lungs of rodents, including eosinophilic alveolar material and foamy alveolar macrophages in rats, were seen – a class effect, perhaps;
- thymic atrophy and thyroid follicular cell adenoma was increased in male rats at 40 mg/kg/day.

Reproductive toxicity occurred at relatively high exposures but the relevance of these findings to humans has not been excluded.

The evaluator concluded that there were no nonclinical objections to the registration of Rupafin for the proposed indications.

The Delegate noted that animals survived the intravenous and intraperitoneal administration of rupatadine.

Clinical

Pharmacokinetic/bioavailability data

The evaluator commented that "in general, it was not clear which of the studies used a rupatadine product identical to that now proposed for registration."

There was a radiolabel study (URC 023/993407) that suggested that absorption of the label was essentially complete in six healthy men of median age 65.5 years. Around 96% of the 40 mg dose, dissolved in 50 mL of distilled water, was excreted within 168 hours (35% in urine and 61% in faeces), mostly as inactive metabolites (UR-12335, O-glucuronide conjugate of desloratadine-OH, in urine).

Dose proportionality is relevant to the application. The clinical evaluator remarked that "this is not easy to assess from the information available. In Study RD 477/20996, approximate dose proportionality was observed between 10 mg and 20 mg single doses, but the product used may not have been that for which registration is sought." This study was a single dose pharmacokinetic study of rupatadine in eight healthy male volunteers.

There was notable inter-subject variability in the measured pharmacokinetic parameters. However, age (younger vs older adults) was not significant in this (Study UR/FC99/I-01). Elimination half-life following multiple daily rupatadine dosage at 10 mg/day (Study UR/FC99/I-01) was approximately 6-8 hours for rupatadine; and 27-33 hours and 35-41 hours, respectively, for the active metabolites desloratadine and desloratadine-OH. Inter-subject variability was high.

In vitro studies had shown the major role of CYP3A4 in rupatadine metabolism and the results of studies IC03RUP/I/02 (effect of grapefruit juice), UR/FC98/I-04 (effect of erythromycin), and UR/FC98/I-03 (effect of ketoconazole) were consistent with this, showing increased levels of unchanged rupatadine.

Studies in patients with renal or hepatic impairment are lacking. The Delegate noted that this is usual for a drug that is extensively metabolised by the liver and that has active metabolites. It would have been desirable to assess the changes to the ratio "therapeutic moiety" (unchanged drug + active metabolites): inactive metabolites in various degrees of hepatic impairment.

The evaluator commented in regard to pharmacokinetics that "the main gap in data results from absence of an intravenous preparation and the result of this is absence of values for absolute bioavailability and volume of distribution".

Pharmacodynamics

These studies were divided into studies that explore dose response with respect to efficacy and safety pharmacology studies. The evaluator was generally dissatisfied with the safety studies excepting IC012RUP/1/04. Of note were the following:

Dose Finding/Efficacy

Study IC04RUP/II/02 was a multidose placebo controlled study in 45 patients with proven sensitivity to grass pollen. Rupatadine 10 mg/day was superior to placebo on a multipoint symptom score.

Study RD 477/21289 used higher doses but suggested a treatment effect on platelet aggregation.

Safety Pharmacology

Study IC012RUP/1/04 was an assessment of the effect of rupatadine on the QTc interval of the standard ECG (Table 3). The trial was adequate in terms of the relevant guideline. No

safety concerns arose. It is pertinent to add that C_{max} does reflect some non-linearity of pharmacokinetics but not to a remarkable degree:

Study DM02RUP/IV/04 involved a standard driving test, in a single dose, three-period, double-blind design. Placebo, rupatadine 10 mg and hydroxyzine 50 mg were used with the last as a positive control. The evaluator commented that "the outcomes show that hydroxyzine 50 mg has a greater effect than rupatadine 10 mg in impairing driving performance but cannot be regarded as providing strong evidence that rupatadine does not impair driving performance. The study was not structured as a non-inferiority safety trial of rupatadine against placebo…"

The sponsor noted however that the study was not designed to be a non-inferiority study but rather as a study demonstrating statistical superiority as per the standard international guidelines on evaluation of SNC effects. The study was designed with reference to historical and previous experimental studies, which show the treatment with recommended therapeutic doses of second generation antihistamines (such as desloratadine, ebastine, fexofenadine) results in primary outcome (SDLP) values comparable with placebo. The studies were not designed to be different to international standards but to show primary outcome SDLP values comparable with placebo. The sponsor considered this to have been an incorrect assumption by the evaluator of this evidence as the study did follow precedent and the guidelines as identified clearly by the evaluator.

Efficacy

One pivotal Phase III study was submitted for each indication. They were of randomised, double-blind, parallel group design.

Compared with the pivotal studies, supportive studies were of shorter duration; six were in seasonal allergic rhinitis (14 days), four in perennial allergic rhinitis (28 days) and one in chronic idiopathic urticaria (28 days) and were all somewhat smaller in terms of patient numbers per study. These studies contributed to dose ranging information. The seasonal allergic rhinitis studies did not show a strong dose response. The perennial allergic rhinitis dose finding studies suggested some advantage of rupatadine 20 mg over rupatadine 10 mg daily in one of three studies but a dose below 10 mg daily was not tested. Inspection of the data from the chronic idiopathic urticaria study IC02RUP/II/02 suggests a dose dependent response but this was not statistically analysed.

The evaluator concluded that "in the dose-finding studies, general experience was that daily dosage of 10 mg or more daily was superior to placebo, but that statistically significant difference between different dosages of rupatadine could not be demonstrated. Thus, it seemed appropriate to choose the 10 mg daily dose for further study."

Seasonal allergic rhinitis (SAR)

Study IC05RUP/4/03 used a placebo and an active comparator (desloratadine 5 mg daily) against rupatadine 10 mg per day. It was of 28 days' duration. The primary efficacy endpoint was the change from baseline in total symptom score (TSS). The evaluator commented that "using an ANOVA analysis, rupatadine was shown to be statistically significantly superior to placebo ($p< 0.05$), but not to desloratadine" (Table 13)

The Delegate noted that desloratadine is a major metabolite of rupatadine. The "active moiety" of unchanged rupatadine and its active metabolites imply a higher dose than desloratadine 5 mg/day. Also, placebo was an effective drug in this study. Rescue medication was not required. The quantum of benefit vs placebo was <1.8 points.

Perennial allergic rhinitis (PAR)

Study IC06RUP/3/04 used a placebo and an active comparator (cetirizine 10 mg daily) against rupatadine 10 mg per day. It was of 12 weeks' duration. Patients were enrolled on the basis of a documented history of PAR ≥ 1 year and a positive prick test to an allergen responsible for perennial rhinitis. The evaluator concluded that "using an ANCOVA analysis, rupatadine was shown to be statistically significantly superior to placebo (p=0.008), but not to cetirizine" (Table 15).

The Delegate noted that cetirizine was used at a typical dose. Placebo was an effective drug in this study. Recue medication was not required. The quantum of benefit vs placebo was <0.71 points.

Chronic idiopathic urticaria (CIU)

Study IC010RUP/3/04 used a placebo and no active comparator but two doses of rupatadine 10 mg or 20 mg per day. It was of 6 weeks' duration. Efficacy was assessed over a four week period.

Patients enrolled had a history of active CIU (urticaria wheals) with or without associated angioedema for ≥ 3 days/week over the 6 weeks before screening. The outcome variable was itch, "Change from Baseline in mean Pruritus Score (MPS) [a five point scale] over 4 weeks". The evaluator concluded that "the difference against placebo is statistically significant and so is the dose response" (Table 18).

The Delegate noted that there was no active comparator. Placebo was an effective drug in this study. Rescue medication was not reported. The quantum of benefit vs placebo was <0.5 points on a five point scale.

In regard to efficacy, the evaluator concluded that "the pivotal studies confirm the efficacy of rupatadine in the claimed indications." However, regarding chronic idiopathic urticaria, "the duration of the pivotal study (6 weeks) was only marginally adequate". The evaluator considered "a 3 or 6 month efficacy study should be conducted in a condition like this, which is chronic and whose aetiology is not well understood." As a matter of fact, efficacy relative to other antihistamines has not been shown.

Safety

The safety data were not reported to the evaluator's satisfaction.

Of common adverse events, somnolence is an AE which has been observed more frequently and dose-dependently with rupatadine 10 mg and 20 mg daily than with placebo. Reasons for discontinuation were incompletely recorded but fatigue, somnolence and asthenia were mentioned.

From the reports of serious AEs, and from the clinical laboratory monitoring, raised hepatic enzymes and CPK emerge as possibly requiring future vigilance.

In regard to safety, the evaluator remarked that Study IC01RUP/IV/02 is of importance because it provides necessary long term open data on safety. It was noted that 313 patients were treated for PAR; of these 294 continued to 6 months on active; and 92 continued to 1 year on treatment. The dosing schedule was unclear and the evaluator was unsure about exposure to the drug.

Study IC011RUP/4/04, also provided open data on safety in PAR to 12 months. It was noted that 85 patients were treated; of these 50 continued > 180 days on treatment.

The Delegate commented that these numbers are small if the medication were intended to be taken long term and more or less continually

Overall, the safety data led to concerns about use in individuals with cardiac conduction abnormalities and in anyone who might require a "non-sedating" antihistamine.

Recommendations of Clinical Evaluator

Overall, the evaluator concluded:

"The overall benefit-risk balance is negative

- for SAR and PAR, at least until the sponsor can provide reassurance regarding Study IC01RUP/IV/02 ["..the 92 patients followed to 1 year were a self-selected group, comprising those who chose to continue treatment with rupatadine 10 mg tablets on a "prn" basis beyond 6 months, and who chose to attend for review at the end of the year"; It is not clear what was the dosage used prn in the final 6-month period of the study; "If my interpretation is correct, then I believe the reported 12-month experience is of little value."]; and
- for CIU, at least until the sponsor can provide (in addition to this safety reassurance), evidence of efficacy in the longer term."

The evaluator asked numerous questions of the sponsor.

Response to Clinical Evaluation Report

The response answered the clinical evaluator's questions. The Delegate summarised the response as follows.

The formulations used in the studies were mostly as proposed for registration.

The supportive study in PAR (RD 477/21416) was conducted outside the hay fever season; the supportive studies (UR/FC98/III-03, UR/FC98/III-02 and UR/FC98/III-01) recruited mostly (80%) outside the hay fever season;

In the pivotal study in CIU (IC010RUP/3/04), double blinding was achieved by use of identical containers and by encapsulating the test medications in red opaque capsules;

The sponsor was asked about the dosage in the final 6-month period of the study but it is evident that this has not been correctly answered with the response "iNova can confirm that all subjects were informed to take rupatadine 10 mg every day during the first 6 months".

The studies presented in the submission were chosen from the sponsor's larger collection of studies of rupatadine in allergic rhinitis and "a pooled analysis was performed with all Phase II and Phase III studies, according to the recommendations of the TGA-adopted EU guideline.[17] The existing 12 studies, under the classification of seasonal or perennial rhinitis, were evaluated using a placebo-controlled design as a principal criterion. Nine studies met this predetermined criteria for inclusion in this pooled analysis." This was used by the sponsor to define the supportive studies as "pivotal".

The evaluator did not accept the claim that rupatadine is non-sedating. The sponsor provided the following tabulation with the statement that Table 31 "shows the incidence of somnolence, disturbance in attention, sedation and fatigue of rupatadine compared to placebo and other anti-H1 compounds. This table demonstrates that there are no differences between rupatadine 10 mg and the other second-generation antihistamines. The percentages cannot be added because one patient can report more than one adverse event."

[17] EMEA. Committee for Medicinal Products for Human Use (CHMP), 27 October 2004. Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Allergic Rhino-conjunctivitis CPMP/EWP/2455/02.

Table 31: Incidences of somnolence, disturbance in attention, sedation and fatigue

		Daily doses											
SOC MedDRA[18]	PT MedDRA	Rupatadine 10 mg		Placebo		Cetirizine 10 mg		Ebastine 10 mg		Loratadine 10 mg		Desloratadine 5 mg	
		n	%	n	%	n	%	n	%	n	%	n	%
Nervous system disorders	Somnolence	192	9.48	45	3.42	42	11.08	13	8.13	17	5.70	8	6.78
	Disturbance in attention	4	0.19	1	0.08	.	.	.	.	.	.	.	.
	Sedation	2	0.10	1	0.08	.	.	.	.	.	.	.	.
General disorders and administration site conditions	Fatigue	64	3.16	26	1.98	3	0.79	2	1.25	6	2.01	.	.

The sponsor stated that, despite appearances, the pharmacokinetics can be modelled as linear between 10 and 40 mg doses.

The Delegate noted that these answers were somewhat helpful but do not materially affect the overall findings of fact. The incorrectly answered question will have to be answered again in the pre-ACPM Response.

Risk Management Plan

The Risk Management Plan (RMP) was dated June 2006. The sponsor commented that the available data does not raise any major safety concern for Rupafin. Headache is an identified risk. Potential risks that require further evaluation are muscular damage and hepatic damage. Routine pharmacovigilance (PhV) is proposed.

The evaluator concluded that "the RMP has not been updated with relevant post-marketing information and this has made interpretation of the RMP difficult. It is the view of the evaluator that the RMP in its current form is not acceptable."

In brief, the RMP, as originally provided, was unacceptable but several maters in the PI and CMI require attention (updates to the PI, protocols for some proposed studies, further information on use in paediatric and pregnant/lactating women).

A response was received from the sponsor. The revised RMP included additional potential risks, information on off label use, PV activities to identify important missing information (for example, a GPRD study for off label use,) together with risk minimisation activities for off-label use. There were also action plans described for the safety issues of muscular damage, hepatic damage and cardiovascular damage. The pregnancy categorisation is still not agreed and the timelines for new studies have been provided. The OPR considered

[18] MedDRA = Medical Dictionary for Regulatory Activities.

that the changes that have been made to the RMP are satisfactory but the pregnancy categorisation has not been agreed.

Risk-Benefit Analysis

Delegate Considerations

The clinical evaluator's conclusions on dose finding are somewhat flawed. The minimal effective dose has not been found and it seems probable that rupatadine 5 mg could be as effective in PAR or SAR as rupatadine 10 mg or 20 mg per day, particularly in view of the fact that desloratadine is a major metabolite that is given at a daily dose of 5 mg.

One pivotal study was submitted for each indication. In general, studies should be replicated unless very convincing both statistically and clinically. However, it could be argued that these studies are somewhat mutually supportive owing to the common therapeutic action of rupatadine. The pivotal studies excluded patients with cardiac conduction abnormalities and agents that would cause metabolic interactions due to CYP3A4 inhibition.

In the TGA-adopted EU guideline on allergic rhino-conjunctivitis it is remarked that:[17]

"The developmental programme for drugs for the treatment of allergic rhino-conjunctivitis may frequently fail to show effectiveness, due in part to the subjective nature of the assessments, variability in allergen exposure and spontaneous variability of the disease. This makes the use of randomisation, placebo control and blinding of crucial importance."

"Although SAR/PAR can alter school performance and work productivity it is not a serious life-threatening disease. It is imperative therefore that the agents used in this condition are safe, given their repeated and often long-term use."

In regard to efficacy, the guideline states:

"An appropriate primary efficacy endpoint is the change from baseline in the relevant patient symptom sumscore during the entire double-blind period. The applicant should provide a value for a clinically meaningful change in the primary efficacy endpoint and the basis for choosing this value. A merely statistical significant difference of xx points on a scale might not be sufficient. An analysis in terms of responder (e.g. patients with a 50% reduction in symptom score) might be helpful.

For an efficacy claim in allergic rhino-conjunctivitis, efficacy for the nasal and eye symptom score should be proven separately e.g. as the symptom-score is a composite scale, the overall effect should be balanced so that e.g. i.e. the overall outcome is not driven by a large effect on a limited number of items and no effect or even worsening in the other items of the scale. The lack of effect in any symptom(s) should be discussed."

The comparatively small experience of efficacy in the pivotal studies is partly excused by the guideline:

"Pharmacodynamically SAR and PAR are considered comparable. For approval of the SAR/PAR indication for a new product at least two adequate and well controlled Phase III clinical trials preferably one each in SAR and PAR, are recommended. For drugs of established classes (i.e. where mode of action is known) this might be two SAR or two PAR studies or one study in each condition"

However, the limited dose ranging and lack of evidence of efficacy from Phase II studies is not excused.

The Delegate indicated that the data deficiencies were significant. Even if registration occurs, Rupafin is not suitable for S2 or S3 listing in terms of the Poisons Standard entry. It

is not known to be safe in individuals with cardiac conduction abnormalities or hepatic disease. It cannot be said to be non-sedating and, if registered, such claims should be prohibited. The daily dose is probably too high and this may be mitigated by the suboptimal formulation but not on all occasions. A better formulated 5 mg tablet might well be more consistently absorbed and as effective.

The nonclinical data are satisfactory. The clinical data are probably inadequate to support CIU. Another dose-finding study with an active control is warranted. The extent of long term data is scant and may be very poor after 6 months. The Committee's advice on this and all other matters raised was sought. The Delegate did not accept the sponsor's contention that, "in terms of evaluation of CIU beyond 6 weeks, no clinical studies with antihistamines of the second generation have been published in the recent years. The criteria we have used to assess the efficacy in the CIU studies, in agreement with the previous evidence with other antihistamines, were to evaluate the change from baseline in mean pruritus severity over the 4 or 6-week treatment period." This application is about rupatadine, not others.

The Delegate proposed to approve the application for the indication:

Symptomatic treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents (over 12 years of age).

The part of the indication, *and chronic idiopathic urticaria (CIU),* should be rejected to insufficient data on efficacy and safety.

Response from Sponsor

CIU Indication

Regarding chronic idiopathic urticaria (CIU) the sponsor believed that the CIU indication is supported by adequate clinical efficacy and safety data and those data are from the same clinical studies accepted by all 41 countries where rupatadine is registered for the 3 indications.

The 6 week pivotal study for CIU is of adequate duration to support a positive benefit:risk balance for the CIU indication.

Efficacy and Study Duration

The 6 week pivotal study for CIU is of adequate duration due to a) the episodic nature of CIU and the fact that pharmacological therapy aims to relieve active symptom flares during an episode and b) consistency with internationally accepted standards and guidelines for conducting efficacy studies in CIU. This is founded upon the following rationale:

CIU Disease Pattern

Chronic idiopathic urticaria, also known as chronic spontaneous urticaria (CSU), often has a variable course with spontaneous remissions and relapses over periods of several years.[19,20] Characterised by the spontaneous occurrence of symptoms such as wheals, erythemas, pruritus with or without angioedema, CIU persists as episodes of 6 or more weeks and the course of symptoms is unpredictable.[19,20] Episodes typically occur daily or for most days of the week and in clinical practice, pharmacotherapy is often taken on-demand to relieve symptom flare rather than on a regular basis.[19] Given this disease pattern, the spontaneous nature of symptoms and the need to control symptom flares,

[19] Maurer M, Weller K, Bindslev-Jensen C et al. Unmet needs in spontaneous urticaria. A GA²LEN task force report. Allergy 2010; DOI: 10/1111j. 1398-9995.2010.02496.x.
[20] Mullol J et al. Rupatadine in allergic rhinitis and chronic urticaria. Allergy 2008; 3 (Suppl 87): 28.

Phase III study IC010RUP/3/04, which included patients with an active episode of CIU for a mean of 5 days per week, is appropriate.

Importantly, since CIU persists for 6 weeks, or for more in duration, the length of treatment in the study for an active episode meets the minimum criterion characterising the disease.[19] In keeping with the pattern of disease, the study recruited patients with both a minimum 6 week history of CIU and an active flare for at least 3 days per week. The focus was to relieve active symptoms.

Also relevant is that 50% of patients with chronic urticaria are symptom free after a period of 3 months.[19] This suggests that patients in a 3 or 6 month efficacy study would not be representative of real world sufferers.

CIU Efficacy Study Standards and Guidelines

Clinical studies have generally been of 4 to 6 weeks duration and no 6 month studies are identified. Treatment duration in the rupatadine pivotal Study IC010RUP/3/04 and in the Phase II study is entirely consistent with other second generation anti-histamine CIU/urticaria studies, for which the accepted global benchmark appears to be efficacy studies of 4 to 6 weeks duration. This is reflected in published clinical studies of second generation anti-histamine drugs in patients with CIU, including those approved in Australia and in approved PIs for second generation antihistamines registered in Australia (Table 32).

Table 32: Studies of second generation antihistamines registered in Australia

Product name	Active ingredient	Study	Dosage	Source
Telfast	Fexofenadine hydrochloride	- one 6 week CIU study - one 28 day dosing study only for "skin weal and flare inhibition"	180 mg Once daily "when required"	[21]
Aerius	desloratadine	two CIU clinical efficacy studies of 6 weeks duration.	5 mg Once daily	[22]

Further evidence for the efficacy of rupatadine in the CIU indication comes from a published responder analysis which pooled data from the 4 and 6 week rupatadine studies contained in the current registration dossier to analyse a total intention-to-treat population of 538 patients.[23]

Efficacy outcomes were "responder rates", that is the percentage of patients after 4 weeks of treatment achieving a reduction of symptoms by at least 50% and 75% compared with baseline, each for mean pruritus score, mean number of wheals and mean urticaria activity score (pruritis score plus number of wheals). For all six efficacy outcomes, the analysis found statistically significantly higher responder rates for rupatadine 10 mg (n=183) and 20 mg (n=175) compared with placebo (n=180).[23] The authors strongly

[21] Telfast and Tefodine Product Information, MIMs December 2010.
[22] Aerius Product Information, MIMs December 2010.
[23] Giménez-Arnau A et al. The use of responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. JEADV 2009; 23: 1088-1091.

recommend performing and reporting responder analyses for established and new drugs in chronic urticaria, which the Delegate pointed out, was recommended in the adopted Guideline as "helpful".

Relevant to this evaluation are current European Guidelines recommendations for the use of second generation antihistamines as first line therapy in CIU/urticaria, which are based on clinical studies with durations of 4 to 6 weeks and included those with rupatadine.[24]

Somnolence

The sponsor noted the evaluator's comment that rupatadine "…cannot be said to be non-sedating" and will update the PI accordingly.

The 2011 ICD-9-CM (International Classification of Diseases) Diagnosis code (780.09) for somnolence includes: a dulled or reduced level of alertness or consciousness; loss of ability to perceive and respond; or loss of ability to maintain awareness of self and environment combined with markedly reduced responsiveness to environmental stimuli. It is well recognised that second generation antihistamines are generally non-sedating therapies, which avoid the somnolence and impaired psychomotor activity predominant with first generation anti-histamines.[20] Consistent with its selectivity for peripheral rather than CNS histamine H1 receptors, rupatadine behaves similarly to second generation antihistamines and so is widely described in the published literature as "non-sedating".[25,26,27] This does not mean that somnolence never occurs with these therapies. The sponsor suggested that a non-sedating second generation antihistamine with zero somnolence does not currently exist and, as somnolence is reported in a small minority of patients, it should be concluded that second generation antihistamines are relatively non-sedating compared with first generation antihistamines.

Similar to other non-sedating second generation antihistamines available in Australia for which somnolence is reported in < 10% of patients (excluding cetirizine) somnolence occurred in 9.5% of rupatadine recipients from pooled clinical study data on 2025 patients as submitted in the submission.[21,22] Moreover, somnolence appears to decrease with time since it was reported in < 6% of rupatadine patients during the entire 12 month treatment period of pooled safety studies (IC01RUP/IV/02 and IC011RUP/4/04).

Of further relevance is the lack of CNS effects such as cognitive and psychomotor impairment in both clinical and preclinical studies and widely reported in the literature for the recommended therapeutic dose of rupatadine (10 mg). [20,25,26,27,28] A tabulation of human studies which provide consistent evidence of absence of rupatadine-induced cognitive and psychomotor impairment was provided. Additional to this, the non-significant effects of rupatadine on driving performance are also highlighted in a comprehensive report by Jáuregui et al.[29]

[24] Zuberbier et al. EAACI/GA2LEN/EDF/WAO guideline: management of urticaria. Allergy 2009; 64: 1427-1443.
[25] Metz M et al. Rupatadine for the treatment of allergic rhinitis and urticaria. Expert Rev Clin Immunol 2011; 7: 15-20.
[26] Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. Expert Opin Pharmacother 2006; 7: 1989-2001.
[27] Katiyar S et al. Pharmacological profile, efficacy and safety of rupatadine in allergic rhinitis. Prim Care Resp J 2009; 18: 57-68.
[28] Keam SJ et al. Rupatadine. A review of its use in the management of allergic disorders. Drugs 2007; 67: 457-474.
[29] Jáuregui I et al. H1 antihistamines: psychomotor performance and driving. J Investig Allergol Clin Immunol 2006; 16 (Suppl 1): 37-44.

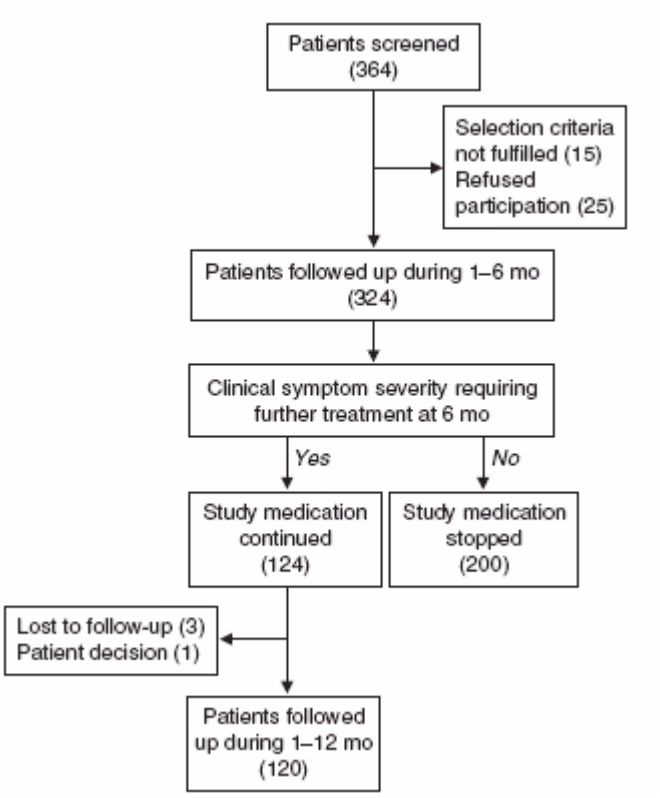
Safety Matters Raised

Drug exposure and dosage in long term safety studies IC01RUP/IV/02 and IC011RUP/4/04

The rupatadine studies (IC01RUP/IV/02 and IC011RUP/4/04) which assessed the safety and tolerability of rupatadine 10 mg once daily over a 12 month period for persistent allergic rhinitis (PAR) are identical studies to those recently published, as a pooled study, by the peer reviewed journal Drug Safety.[30] Pooling the two identical studies meets both the EMEA Guideline for assessing the clinical safety of drugs for allergic rhinoconjunctivitis and the ICH Guideline criteria for assessing long term safety of drugs for non-life threatening conditions.[Error! Bookmark not defined.], [31] These studies require > 300 patients treated during 6 months and > 100 patients treated during 1 year.

Figure 4 presents a pictorial summary of the pooled studies. All patients enrolled in these studies received rupatadine 10 mg once daily for 6 or 12 months. At end of study, 120 patients had completed 12 months rupatadine treatment 10 mg once daily. The 324 (post screening of 364) and 120 patients receiving rupatadine 10 mg once daily for 6 and 12 months, respectively, exceed EMEA and ICH guidelines recommending a minimum 300 and 100 patients for these treatment periods in assessing safety.

Figure 4: Patient disposition and drug exposure



Reproduced from Valero et al, Drug Safety 2009[30]

Reviews published as recently as January 2011 conclude the above study confirms the "excellent tolerability" of rupatadine observed in short term studies, while Mullol et al also states: "of the recently introduced antihistamines, rupatadine is one of the first to have

[30] Valero A et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis. Drug Safety 2009; 32: 33-42.

[31] International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Topic E1A note for guidance: Population exposure: the extent of population exposure to assess clinical safety, 1995.

such extended long-term safety data. There was clear evidence that with time the incidence of adverse effects decreased with rupatadine 10 mg once daily. Furthermore, no clinically relevant ECG or laboratory changes were reported during this clinical trial."[20,25]

During the open label phase of the studies all patients were treated with the active compound rupatadine 10 mg (orally, daily) during the first 6 months of the study. After this period, only patients with evidence of clinical symptoms that would require continuing with the same dose for more than six months were followed up until the end of the study. The sponsor confirmed that the dosage in the final six months period was the same dose, 10 mg (orally, daily) as was administered during the first six months.

In addition to well documented clinical studies demonstrating the safety and tolerability of rupatadine, the benefit:risk balance of rupatadine is well established from almost 10 years of postmarketing data captured in 11 successive Periodic Safety Update Reports (PSURs). These reports collectively show a cumulative patient exposure of 787,666 patient years to 30 June 2010 (921,111 patient years expected to 31 December 2010) and conclude the risk:benefit balance remains unchanged. This concurs with the Delegates view that the PSURs "were not remarkable."

Regarding safety in CIU, and considering the pattern of disease for which relief of symptom flare is paramount, the findings from all rupatadine clinical studies, irrespective of indication, are applicable to CIU.

This is reasonable given the similar age demographics of the study populations for the three indications and, importantly, that the same dosage and administration of one tablet taken once daily applies to CIU, SAR and PAR. The sponsor believed there is no biologically plausible explanation as to why the safety profile of rupatadine would vary among patients because patients are taking this therapy for different on-label indications.

Additionally, the sponsor proposed there is no basis for assuming rupatadine has differing pharmacokinetic or pharmacodynamic actions according to whether it is used for CIU, SAR or PAR. In considering efficacy and safety, the underlying mechanisms for allergic rhinitis (SAR/PAR) and urticaria symptoms are similar, whereby histamine release from activated mast cells, for example, is one of the main factors producing symptoms in these conditions.[32]

Therefore, the study results in allergic rhinitis and CIU studies support rupatadine efficacy and safety at the same dose of 10 mg in all three conditions and reinforce one another.

The sponsor asserted that for these reasons, the 12 month safety results from rupatadine PAR studies can be extrapolated to CIU and therefore are consistent with the Delegate's comment regarding applicability of a study from one indication to another whereby "…it could be argued that these studies [across indications] are somewhat mutually supportive owing to the common therapeutic action of rupatadine."

Cardiac Conduction Abnormalities

The sponsor expressed the opinion that there is strong consensus in the published literature on the cardiac safety of rupatadine based on both extensive preclinical and clinical assessment.[20,26,27,28,33] Clinical evaluation of rupatadine has shown a lack of cardiotoxic or proarrhythmic potential and rupatadine produced no clinically relevant changes in QT/QTc intervals, although drugs that increase systemic exposure of the

[32] Leung DY et al, Allergic and immunologic skin disorders. JAMA 1997; 278: 1914-23.

[33] Donado E, et al. No cardiac effects of therapeutic and supratherapeutic doses of rupatadine: results from a 'thorough QT/QTc study' performed according to ICH guidelines. Br J Clin Pharmacol 2010; 69: 401-410.

antihistamine (erythromycin and ketoconazole are potent cytochrome P450 3A4 isoenzyme inhibitors) were administered during these studies.[20,28] ECG evaluation in the 12 month safety study showed no evidence of arrhythmias, while QTcB results suggested a lack of cardiotoxicity at the 10 mg therapeutic dose.[30] The cardiac safety of rupatadine is further reinforced by the published study IC012RUP/1/04, which was a "thorough QT/QTc study" of rupatadine 10 mg and 100 mg in 160 healthy volunteers and which confirmed no proarrhythmic potential and was conducted in accord with published guidelines.

The Delegate noted that "No safety concerns arose" from study IC012RUP/1/04, yet also states rupatadine "…is not known to be safe in individuals with cardiac conduction abnormalities…" because they were excluded from the pivotal studies. The sponsor responded that these individuals represent a high risk patient group who would normally be excluded from drug studies. Individuals with cardiac conduction abnormalities are not representative of the on-label population for whom rupatadine is intended and, in keeping with other second generation antihistamine studies, they have appropriately been excluded from the rupatadine studies.

The sponsor was prepared to add a suitable Precaution to the proposed Rupafin PI if required.

Hepatic Disease and Renal Impairment

The evaluator commented that the safety of rupatadine in hepatic disease is unknown, while studies in patients with hepatic or renal impairment are lacking, yet also notes "this is usual for a drug that is extensively metabolised by the liver and that has active metabolites".

Relevant are findings from use of rupatadine in the elderly since ageing can diminish hepatic capacity and renal function, which may contribute to the reduced clearance of drugs with first pass pharmacokinetic profiles. Evidence shows age does not have a significant clinical influence on rupatadine pharmacokinetics.[28] Importantly, rupatadine 10 mg once daily was well tolerated in healthy elderly patients, and so adjustments to this therapeutic dose are not required in the elderly.[26,28] Given this data and an absence of evidence of increased risk, the sponsor considered it is appropriate that patients with hepatic disease, renal impairment and the elderly are classified as special populations under Precautions in the Rupafin PI.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission.

In making this recommendation, the ACPM considered that there was insufficient nonclinical data submitted and inadequate pharmacokinetic and bioavailability data, including data to confirm the adequacy of the proposed formulation. There was a lack of studies in renally or hepatically impaired patients, a lack of data in the aged and no exploration of a minimal effective dose, all of which are considered essential for a submission as a new chemical entity.

The sponsor noted however that this statement by the ACPM was not consistent with the statements by the nonclinical evaluator that "the general quality of the submitted studies was high "(page 8) and that "There were no nonclinical objections to the registration of Rupafin for the proposed indications" (page 21).

The ACPM advised that a 6 week study in chronic urticaria was of insufficient duration to

provide clear evidence of either efficacy or safety. The committee also had a concern over a lack of data on the non-sedating effect of the product and was concerned about its effect on cardiac conduction.

Outcome

The sponsor withdrew the submission before a decision was made.

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Reference/Publication #