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Cetirizine

A Review of its Use in Allergic Disorders

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Data Selection

Sources: Medical literature published in any language since 1980 on cetirizine, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'cetirizine'. EMBASE search terms were 'cetirizine'. AdisBase search terms were 'cetirizine'. Searches were last updated 1 February 2003.

Selection: Studies in patients with allergic disorders who received cetirizine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: cetirizine, allergic disorders, allergic rhinitis, asthma, atopic dermatitis, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, urticaria.

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Summary

Abstract

Cetirizine is a selective, second-generation histamine H_1 receptor antagonist, with a rapid onset, a long duration of activity and low potential for interaction with drugs metabolised by the hepatic cytochrome P450 system. Cetirizine was generally more effective than other H_1 receptor antagonists at inhibiting histamine-induced wheal and flare responses.

Cetirizine is an effective and well tolerated agent for the treatment of symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in adult, adolescent and paediatric patients. In adults with these allergic disorders, cetirizine was as effective as conventional dosages of ebastine (SAR, PAR, CIU), fexofenadine (SAR), loratadine (SAR, CIU) or mizolastine (SAR). This agent was significantly more effective, and with a more rapid onset of action, than loratadine in 2-day studies in environmental exposure units (SAR). In paediatric patients, cetirizine was as at least as effective as chlorphenamine (chlorpheniramine) [SAR], loratadine (SAR, PAR) and oxatomide (CIU) in the short term, and more effective than oxatomide and ketotifen (PAR) in the long term.

Cetirizine was effective in reducing symptoms of allergic asthma in adults and reduced the relative risk of developing asthma in infants with atopic dermatitis sensitised to grass pollen or house dust mite allergens. It had a corticosteroid-sparing effect in infants with severe atopic dermatitis and was effective in ameliorating reactions to mosquito bites in adults.

Cetirizine was well tolerated in adults, adolescents and paediatric patients with allergic disorders. In adult, adolescent and paediatric patients aged 2–11 years, the incidence of somnolence with cetirizine was dose related and was generally similar to that with other second-generation H_1 receptor antagonists. Although, its sedative effect was greater than that of fexofenadine in some clinical trials and that of loratadine or fexofenadine in a postmarketing surveillance study. In infants aged 6–24 months, the tolerability profile of cetirizine was similar to that of placebo. Cetirizine did not have any adverse effects on cognitive function in adults, or cognitive function, behaviour or achievement of psychomotor milestones in paediatric patients. Cetirizine was not associated with cardiotoxicity.

Conclusion: Cetirizine is well established in the treatment of symptoms of SAR, PAR or CIU. It demonstrated a corticosteroid-sparing effect and reduced the

relative risk of developing asthma in sensitised infants with atopic dermatitis. Cetirizine was effective in the treatment of allergic cough and mosquito bites; however, its precise role in these indications has yet to be clearly established. On the basis of its favourable efficacy and tolerability profile and rapid onset of action, cetirizine provides an important option for the treatment of a wide range of allergic disorders.

Pharmacodynamic Profile

Cetirizine, the carboxylated metabolite of hydroxyzine, exists as a zwitterion, which may partly account for its high hydrogen-binding capacity, limited biotransformation, low-to-moderate lipophilicity and limited ability to cross the blood-brain barrier. It is a highly selective histamine H_1 receptor antagonist, with very low affinity for several other types of receptors, including adrenergic and serotoninergic receptors. Single or multiple doses of oral cetirizine 10mg inhibited histamine-induced wheal and flare responses in nonatopic and atopic adults and paediatric patients, and was generally more effective than therapeutic doses of several other antihistamine agents, including ebastine or loratadine. The effect of cetirizine peaked at 4–8 hours and was sustained for at least 24 hours. Cetirizine 5–20mg provided dose-dependent protection against inhaled histamine-induced bronchospasm in patients with asthma. Relative to placebo, nasal airway resistance was reduced in patients with allergic rhinitis and forced expiratory volume in 1 second was increased in patients with asthma.

Cetirizine effectively inhibited allergen-induced wheal and flare responses in atopic and nonatopic volunteers, and at therapeutic doses was at least as effective as standard doses of acrivastine, astemizole, fexofenadine or loratadine. Cetirizine has shown several modulatory effects on the inflammatory response.

Cetirizine 10mg once daily generally did not impair CNS function, although somnolence has been reported in clinical trials. At therapeutic dosages, cetirizine was associated with no or mild impairment of driving and psychometric test performance. Cetirizine did not effect cognitive function in adults, or cognitive function, behaviour or psychomotor milestones in paediatric patients.

Unlike terfenadine or astemizole, cetirizine has not been associated with adverse cardiac effects, either as monotherapy, or when administered in combination with agents that are metabolised by the cytochrome P450 system (e.g. macrolides). In healthy adult volunteers and in paediatric patients, cetirizine had no clinically relevant effect on the QT_c interval or ECG parameters. In *in vitro* studies, cetirizine had no significant effect on cardiac potassium channels.

Pharmacokinetic Profile

Oral cetirizine undergoes rapid, dose-dependent absorption in the gut, with maximum plasma concentrations achieved in approximately 1–2 hours. There was no difference in the bioavailability of the drug with tablet and syrup formulations. Steady-state plasma concentrations are achieved within 2 days and remain stable thereafter, with no clinically relevant accumulation of the drug after 2 weeks' treatment with oral cetirizine 10mg once daily. Although the presence of food may have some effect on the rate of absorption, there is no difference in the extent of absorption in the fasted and fed states. Approximately 90% of the drug is bound to plasma proteins, mainly albumin.

Cetirizine is extensively distributed throughout the body. Oral cetirizine was rapidly distributed into tear fluid in patients with allergic conjunctivitis and was

distributed into breast milk; however, the drug does not readily penetrate the blood-brain barrier.

Cetirizine undergoes minimal metabolism and is predominantly excreted via the urine (70% of the administered dose), with a further 10% of the dose eliminated in the faeces. Small quantities of an *O*-dealkylation metabolite were excreted in plasma and faeces and two unidentified metabolites have been recovered in the urine. The mean terminal elimination half-life ($t_{1/2}\beta$) of cetirizine after a single oral 10mg dose was 6.7–8.6 hours in healthy adult volunteers and the apparent total body clearance (CL) at this dosage was 2.76–5.22 L/h.

The $t_{1/2}\beta$ in paediatric patients was generally shorter than that in adults; CL values were higher. Although there were significant differences in absorption and elimination values in elderly volunteers relative to younger volunteers, these differences correlated with creatinine clearance rather than with age *per se*. In patients with mild-to-severe renal impairment, renal clearance and CL are decreased and $t_{1/2}\beta$ is prolonged relative to individuals with normal renal function, with haemodialysis having no clinically relevant effect on pharmacokinetic parameters. There were significant and clinically relevant changes in absorption and elimination parameters in patients with hepatic impairment relative to those with normal hepatic function.

Cetirizine has a low potential for drug interactions, since it is only minimally metabolised by the liver. Concomitant administration of cetirizine with cimetidine, theophylline or a macrolide (erythromycin or azithromycin) had no clinically relevant effect on the pharmacokinetic profiles of cetirizine or the concomitantly administered agent.

Therapeutic Use

In adult, adolescent and paediatric (aged 2–12 years) patients with seasonal allergic rhinitis (SAR), cetirizine 5 or 10mg once daily was significantly more effective than placebo, according to improvements in total symptom severity (TSS) scores and global assessments of efficacy. Cetirizine was effective in improving multiple domains of health-related quality of life (HR-QOL), assessed according to the Rhinoconjunctivitis Quality of Life Questionnaire (paediatric or adult) and the Activity Impairment-Allergy Specific questionnaire.

In adult and adolescent outpatients with SAR, once-daily doses of cetirizine 5 or 10mg were as effective as standard dosages of ebastine, fexofenadine or mizolastine in the treatment of SAR, according to improvements in TSS score and global assessments of efficacy. However, oral cetirizine 10 mg/day was not as effective as treatment with the corticosteroid fluticasone propionate 200 μg/day administered as a nasal spray. In 2-day studies in an environmental exposure unit, cetirizine 10 mg/day was significantly more effective than loratadine 10 mg/day in treating the symptoms of SAR. The onset of action was more rapid with cetirizine than loratadine (2-day study). In paediatric patients with SAR, cetirizine 10 mg/day was as effective as chlorphenamine 2mg administered three times daily; cetirizine 10 mg/day, but not loratadine 10 mg/day, was more effective than placebo.

Cetirizine plus montelukast was as effective as topical corticosteroid (budesonide or mometasone) therapy in improving objective and subjective measures of treatment response in SAR, according to data from two small, single-blind, placebo-controlled, crossover studies.

Cetirizine 5 or 10mg once daily was significantly more effective than placebo in adult, adolescent and paediatric patients with perennial allergic rhinitis (PAR). Cetirizine 10 mg/day was as effective as short-term treatment with standard dosages of ebastine, but not long-term treatment (12 months) with budesonide, in adults and adolescents with PAR. Cetirizine significantly improved HR-QOL in adults with PAR (assessed according to the Short-Form 36 Health Survey). Short-term (1–4 weeks) cetirizine was as effective as oxatomide or loratadine in paediatric patients, but long-term treatment (12 weeks) with cetirizine was significantly more effective than oxatomide or ketotifen.

Cetirizine 10mg once daily was significantly more effective than placebo in reducing the symptoms of chronic idiopathic urticaria (CIU), including the number and size of wheals, the number of urticarial episodes and severity of pruritus. Cetirizine 10 mg/day was as effective as standard dosages of hydroxyzine or loratadine. Cetirizine was less effective than montelukast in adults and adolescents with chronic urticaria due to food additives and/or acetylsalicylic acid. The onset of action of cetirizine was faster than that of hydroxyzine. In paediatric patients (aged 2–6 years), cetirizine 5 mg/day was as effective as oxatomide 25 mg/day in reducing symptoms of CIU. Twice-daily administration of cetirizine 0.25 mg/kg was effective in the prevention of acute urticaria in infants aged 12–24 months with atopic dermatitis.

Cetirizine was associated with a reduction in total symptoms of atopic dermatitis in adult, adolescent and paediatric patients, according to data from a limited number of studies. However, at treatment end, its effect was not significantly different from that with placebo, except in recipients of cetirizine 40 mg/day (higher than the recommended dosage). Nevertheless, in infants with severe atopic dermatitis, twice-daily administration of cetirizine 0.25 mg/kg was associated with a significantly greater corticosteroid-sparing effect than placebo.

The symptoms of asthma were relieved to a significantly greater extent with cetirizine 10mg once daily than with placebo in adults with SAR. Cetirizine 0.25 mg/kg twice daily was effective in preventing the development of asthma in infants (aged 10–28 months) with atopic dermatitis who were sensitised to grass pollen or house dust mite.

Data from a limited number of small studies show that cetirizine attenuated local reactions to mosquito bites (initial wheal response and pruritus) and reduced the intensity and frequency of allergic cough in paediatric patients with allergic rhinitis.

Tolerability

In placebo-controlled studies in adults, the most common adverse experiences associated with cetirizine ≤10 mg/day were somnolence (14%), fatigue (6%), dry mouth (5%), pharyngitis (2%) and dizziness (2%). The incidence of these adverse events in placebo recipients was ≤6%. The incidence of discontinuation due to adverse events was similar in patients treated with cetirizine 5 or 10 mg/day or placebo.

In placebo-controlled studies in paediatric patients (aged 6 months to 11 years), cetirizine 5 or 10 mg/day was well tolerated. Headache (11–14%), pharyngitis (3–6%), abdominal pain (4–6%), increased coughing (3–4%), somnolence (2–4%) and epistaxis (2–4%) were commonly reported adverse experiences.

In paediatric patients aged 2–11 years, adverse experiences were more common in cetirizine than placebo recipients. In infants aged 6–24 months, the tolerability profile of cetirizine was similar to that of placebo.

The incidence of somnolence in placebo-controlled studies in adults, adolescents and paediatric patients aged 2–11 years was dose dependent. In infants aged 6–24 months, the incidence of somnolence was similar in cetirizine or placebo recipients.

The incidence of somnolence in adults and adolescents treated with cetirizine was significantly less than that in recipients of hydroxyzine, and was generally similar to that of other second-generation H_1 receptor antagonists; although its sedative effect was greater than that of fexofenadine in some clinical studies and that of loratadine or fexofenadine in a postmarketing surveillance study.

Cetirizine administration was not associated with clinically relevant cardiac abnormalities in adults or adolescents (aged ≥12 years) or paediatric patients (aged 6 months to 12 years).

Overdose of cetirizine did not produce clinically significant CNS or cardiovascular toxicity, despite ingestion of a mean dose >4 times the maximum recommended daily dose.

Dosage and Administration

Oral cetirizine, available in a syrup or tablet formulation, is indicated for the relief of symptoms of SAR, PAR and CIU. In the US, cetirizine is approved for use in patients with PAR or CIU (aged ≥6 months) or SAR (aged ≥2 years), whereas in the UK it is approved for use in patients with PAR or CIU (aged ≥6 years) and with SAR (aged ≥2 years). The drug may be taken without regard to food. The recommended dosage varies from country to country, with the dosage adjustments based on age, and the presence of renal and/or hepatic impairment. Cetirizine should be given to pregnant women only if clearly indicated (pregnancy category B rating in the US).

1. Introduction

Oral cetirizine (Zyrtec®[1], Zirtec®), a second-generation, long-acting, selective peripheral histamine H_1 receptor antagonist, has shown good efficacy in the treatment of several allergic disorders in numerous clinical trials in adult, adolescent and paediatric patients and in widespread clinical use. The pharmacological properties and therapeutic efficacy of cetirizine have been extensively reviewed.[1-3] Although cetirizine is approved for administration with pseudoephedrine,[4] the focus of this review is the clinical efficacy and tolerability of cetirizine when administered as monotherapy.

2. Pharmacodynamic Profile

Cetirizine is the carboxylated metabolite of hydroxyzine and a racemic mixture of two enantiomers, levocetirizine (R enantiomer) and dextrocetirizine (S enantiomer).[5] A summary of the pharmacodynamic properties of cetirizine is presented in table I. Several mechanisms of action potentially play a role in the ability of cetirizine to counteract the allergic response to antigenic stimuli, including antiallergic, antihistaminic and anti-inflammatory effects. Some characteristics of the drug may, in part, be explained by the fact that cetirizine exists as a zwitterion (containing separate positively and negatively charged groups), resulting in a high hydrogen-binding capacity, limited biotransformation and

1 Use of brand name is for identification purposes only and does not imply endorsement.

low-to-moderate lipophilicity.[6-9] This zwitterionic state may also limit the ability of the drug to cross the blood-brain barrier, reducing the uptake of cetirizine into the CNS and limiting potential CNS effects, such as somnolence (section 5).[8] The low CNS uptake may also result from the rapid efflux of cetirizine from the brain to the blood.[8]

2.1 Antihistaminic Effects

Cetirizine is a selective H_1 receptor antagonist, with an IC_{50} (concentration producing 50% inhibition of H_1 receptors) value of 0.65 μmol/L and low affinity for calcium channel, α_1-adrenergic, dopamine D_2, serotonin 5-HT_2 and muscarinic receptors (all IC_{50} >10 μmol/L).[115,116] Oral cetirizine 10mg was more effective than therapeutic doses of other antihistamine agents, including ebastine and loratadine, in reducing histamine-induced wheal and flare responses in nonatopic and atopic adults and paediatric patients in numerous double-blind, crossover, multiple-dose and single-dose studies (table I).[10-29] This response peaked 4–8 hours after administration of cetirizine and was sustained for least 24 hours, with the effect superior to placebo throughout this period (table I).[12,15,26,32] Cetirizine was less effective than epinastine and acrivastine in suppressing early (≤1 hour) wheal and flare response, but it demonstrated a longer duration of action.[27-29]

In patients with asthma, cetirizine 5–20mg provided dose-dependent protection against inhaled histamine-induced bronchospasm (table I).[33] Relative to placebo, oral cetirizine increased forced expiratory volume in 1 second in several studies in patients with asthma (table I).[34-37] Nasal airway resistance was significantly reduced relative to placebo with a single 10mg dose of cetirizine (table I),[38,39] but not after a single 10mg dose of loratadine in patients with allergic rhinitis.[38]

2.2 Antiallergic and Anti-inflammatory Effects

Cetirizine effectively reduced wheal and flare responses to various inflammatory mediators, including platelet activating factor and compound 48/80, in atopic[13,18,22,28,40,41] and nonatopic[40] volunteers; a single oral cetirizine 10mg dose was generally at least as effective as therapeutic doses of acrivastine,[28] fexofenadine[28] or loratadine[13,18,22] (table I). For example, in a randomised, double-blind, crossover study in seven atopic volunteers, a single 10mg dose of cetirizine significantly (all $p < 0.05$) inhibited grass pollen-induced skin reactions relative to placebo, whereas there was no statistical difference in the wheal and flare response after a single 10mg dose of loratadine compared with placebo.[22]

Inflammatory responses are pivotal processes in the development of allergic disorders. These responses are complex, multifactorial processes involving numerous types of inflammatory cells (such as eosinophils, macrophages, neutrophils, epithelial cells, fibroblasts and lymphocytes), cytokines and mediators.[117-119] The accumulation of proinflammatory cells at sites of allergic inflammation involves selective adhesion of cells to postcapillary venular endothelium and the subsequent migration of these cells into tissues under the influence of several chemotactic factors.[117-119] Antihistamine agents such as cetirizine not only act via mediation of H_1 receptors, but may also attenuate various steps in the inflammatory process.

Cetirizine has demonstrated several modulatory effects on inflammatory responses. These effects included reducing eosinophil migration induced by inflammatory mediators in atopic and nonatopic adults,[22,44,50-57] reducing the expression of adhesion molecules associated with eosinophil migration and adhesion of eosinophils to epithelial cells in *in vitro* studies[58-60] and in atopic patients,[48,61-63] and inhibiting the expression of various proinflammatory cytokines and mediators in *in vitro* studies[72-75,80-82] and animal models[79] (table I). For instance, in *in vitro*[66,67] studies and in patients with allergic rhinitis,[68] cetirizine inhibited eosinophil activation and chemotaxis via inhibition of the cytokine eotaxin, a key mediator of eosinophil activity associated with the development of allergic disorders (table I). In cultured human fibroblasts grown in the presence of interleukin-4 (0.5 ng/culture well), histamine-in-

Table I. Overview of the key pharmacodynamic properties of cetirizine (CET)

Antihistaminic effects	↓ Histamine-induced wheal and flare formation in atopic paediatric patients[10] and atopic or nonatopic adults;[11-29] single or multiple CET 10mg doses were more effective than therapeutic doses of acrivastine,[11]a astemizole,[12,13] chlorphenamine (chlorpheniramine),[12] ebastine,[14,15,23,24] epinastine,[27,29]a fexofenadine,[15,28,30] loratadine,[10-13,15-22] mizolastine,[25,31] oxatomide[26] or terfenadine[12,15]
	Wheal and flare suppression maintained for ≥24h relative to placebo in healthy adult volunteers[12,15,26,32]b
	Protection against histamine-induced bronchospasm[33] or bronchoconstriction,[34] with ↑ FEV_1[34-37] in patients with asthma[c]
	↓ Nasal airway resistance in patients with allergic rhinitis[38,39]c
Antiallergic effects	↓ Wheal and flare induced by inflammatory mediators[d] in atopic[13,18,22,28,40,41] and nonatopic[40] volunteers; CET 10mg dose at least as effective as acrivastine,[28] astemizole,[13] fexofenadine[28] or loratadine[13,18,22]
	↑ Conjunctival reaction threshold;[42] may ↓ EPR and/or LPR in patients with rhinoconjunctivitis or rhinitis[43-49]
Anti-inflammatory effects	↓ Inhibition of eosinophil chemotaxis induced by inflammatory mediators[e] in atopic and nonatopic volunteers[22,44,50-57]
	↓ Expression of cell adhesion molecules including ICAM-1 on endothelial or epithelial cells in *in vitro* studies[58-60] and in atopic volunteers[48,61-63]
	↓ PAF-induced hyperadherence of human eosinophils to endothelial cells[64,65]
	↓ Histamine-induced eotaxin production and gene expression *in vitro*[66,67] and in patients with allergic rhinitis[68]
	↓ Serum tryptase release from mast cells derived from atopic patients[69-71]
	↓ Proinflammatory cytokine- or PMA-induced expression of IL-8 from epithelial cells[72]
	↓ Histamine-induced endothelial, epithelial, mast and/or basophil cell expression of P-selectin and/or secretion of IL-6 and IL-8 *in vitro*[73]
	↓ LTB_4 generation by fMLP-, GM-CSF- or NaF-stimulated neutrophils[74,75]
	↓ RANTES and MCP-1 levels in atopic volunteers[76,77]
	↓ Antigen-induced release of histamine, LTD_4, LTE_4 *in vitro*[78]
	↓ IL-4, IL-5 and interferon-γ gene expression in nasal lymphoid tissue of mice[79]
	↓ PGD_2, histamine and LTC_4 production in some tissues[80-82]
	↑ Release of PGE_2 from human monocycles and rat peritoneal macrophages[83]
	↓ Monocyte chemotaxis *in vitro* and in nonatopic and atopic volunteers[84]
CNS effects	PET measurements in volunteers showed that CET binds to approximately 30% of the histamine H_1 receptors in the cerebral cortex[85]
	Few effects on subjective and/or objective assessments of drowsiness or cognitive function in adult volunteers[86-98]f
	No CNS dysfunction in volunteers, unlike hydroxyzine and diphenhydramine, according to P300 event-related potential studies[99-101]b
	No impact on cognitive function, behaviour or learning processes in paediatric patients receiving CET 0.25 mg/kg twice daily for 18mo[91]
	Similar or greater sedative effects (but of a similar nature) relative to terfenadine or loratadine at therapeutic doses[102]
	No effect on EEG in healthy volunteers[103]b
	Does not potentiate CNS depressant effects of ethanol (alcohol) in healthy adult volunteers[90,104]g
Cardiac effects	No ECG abnormalities, with no effect on QT_c interval, in healthy adult volunteers (CET 20[105,106] or 60 mg/day[106])
	No ECG abnormalities or clinically relevant effect on QT_c interval in paediatric patients aged 6–11y (CET 5 or 10 mg/day)[107] or 6–24mo (CET 0.25 mg/kg bid)[108,109]
	Concomitant CET plus macrolide (including azithromycin,[108,110] erythromycin[105,108] or clarithromycin[108]) had no effect on QT_c interval in healthy adults[105,110] or atopic paediatric patients[108]

Continued next page

Table I. Contd

	No ventricular tachycardia or torsades de pointes with CET, unlike astemizole, in a canine model[111]
	Little or no effect on K^+ channels *in vitro*[112-114]

a Effect significantly greater in cetirizine than comparator from 2h.

b CET 10mg administered as a single dose.

c CET 5–20mg administered as once-daily single or multiple doses.

d Inflammatory mediators included allergen (grass pollen, ragweed), methacholine, PAF and compound 48/80.

e Inflammatory mediators included fMLP, PAF, LTB_4, IL-8, C5a.

f CET 5–20mg administered as a single dose.

g Multiple doses of once-daily CET 10mg.

bid = twice daily; **C5a** = 5th complement component; **EEG** = electroencephalogram; **EPR** = early-phase allergic response; **FEV_1** = forced expiratory volume in 1 second; **fMLP** = f-Met-Leu-Phe; **GM-CSF** = granulocyte macrophage- colony stimulating factor; **ICAM-1** = intercellular adhesion molecule-1; **IL** = interleukin; **LPR** = late-phase allergic response; **LT** = leukotriene; **MCP** = monocyte chemotactic protein; **NaF** = sodium fluoride; **PAF** = platelet activating factor; **PET** = positron emission tomography; **PG** = prostaglandin; **PMA** = phorbol 12-myristate 13-acetate; **RANTES** = Regulated upon Activation Normal T-cell Expressed and Secreted cytokine; ↑ indicates a increase/stimulation; ↓ indicates a decrease/inhibition.

duced upregulation of eotaxin mRNA expression and synthesis of eotaxin was inhibited by cetirizine at concentrations of 0.5–500 ng/culture well.[67] Moreover, in 13 patients with allergic rhinitis, mean serum eotaxin levels were reduced by approximately 30% from basal levels after 15 days of cetirizine 10 mg/day (mean serum eotaxin levels 133.5 vs 196.7 pg/mL; $p < 0.03$).[68]

2.3 CNS Effects

Current clinical evidence suggests that at recommended therapeutic dosages, cetirizine is without significant CNS activity (table I).[86-104] Although cetirizine can cross the brain barrier and bind to approximately 30% of the H_1 receptors in the cerebral cortex (table I), numerous studies using objective assessments of the CNS effects of cetirizine have demonstrated that the drug, at the standard 10 mg/day dosage, generally did not impair CNS function.[86-97,99-101] In the elderly, cetirizine caused fewer adverse CNS effects than chlorphenamine (chlorpheniramine) or diphenhydramine according to the latency of the P300 event-related potential in which increased latency reflects a decreased level of cognitive functioning.[101] At therapeutic dosages, cetirizine was associated with no or mild impairment of driving and psychometric test performance; these effects were not generally considered to have a significant impact on driver's ability.[87,89,90,97,104] Cetirizine did not potentiate the impairment of skilled performance and driving caused by ethanol (alcohol).[90,104]

According to data from a recent pooled analysis of 76 randomised, double-blind, placebo- or active comparator-controlled, cross-over studies of numerous antihistamine agents, cetirizine is not associated with significant sedative effects,[120] although somnolence has been reported in some clinical trials (see section 5). Interestingly, recent evidence suggests that sedation may in fact be a reflection of the disease rather than be caused by the drug *per se*.[102] In the pooled analysis, the sedative properties of various antihistamines were determined using the proportional impairment ratio (PIR; 0 = no sedation), which takes into account both positive and negative data and ranks each antihistamine agent in relation to the others.[120] The overall PIR (included both subjective and objective measures of sedation and both first- and second-generation antihistamine agents) for cetirizine was low at 0.25, indicating the drug was unlikely to be associated with significant sedative effects. Furthermore, the PIR as determined using only data from studies of second-generation antihistamine agents showed that cetirizine (PIR 0.92) was no more likely to cause sedation than loratadine (1.94) or other agents in this group, whereas mizolastine (3.29) was associated with greater sedation than other second-generation antihistamine agents. Fexofenadine (PIR 0) and

terfenadine (0.48) caused no sedation with respect to other second-generation antihistamine agents.[120]

Notably, in a randomised, double-blind, placebo-controlled trial in approximately 600 paediatric patients with atopic dermatitis aged 12–24 months at study entry, long-term treatment (18 months) with cetirizine 0.25 mg/kg twice daily had no effect on behaviour or cognitive function both during the study and during follow up (table I).[91] There were also no effects on achievement of psychomotor milestones, including gross (sit, crawl, walk, stand, climb stairs, run) and fine motor development (pincer grip, pencil grip, match cubes, hand preference) and speech and language development (use first five words, name many objects, use short sentences). Behaviour was assessed using the Behaviour Screening Questionnaire (≈200 paediatric patients in each group assessed on five occasions) and cognition was assessed using the McCarthy Scales of Children's Abilities (≈100 paediatric patients per group assessed on three occasions) using validated, standard scales.[91]

2.4 Cardiac Effects

Unlike terfenadine and astemizole (which have been withdrawn from the US and other markets), cetirizine has not been associated with adverse cardiac effects when administered either as monotherapy or in combination with agents that are metabolised by the cytochrome P450 (CYP) system.[2,3,105-114] In healthy adult volunteers[105,106] and in paediatric patients,[107-109] cetirizine had no clinically relevant effect on the QT or QT_c interval, even at dosages up to 6-fold higher than those recommended (e.g. 60 mg/day for 7 days in adults;[106] table I). Furthermore, concomitant administration with macrolide antibacterial agents (including azithromycin,[108,110] erythromycin[105,108] or clarithromycin[108]) had no effect on the QT_c interval in healthy adult volunteers[105,110] or infants with atopic dermatitis aged 12 months to 24 months[108] (table I). Cetirizine shows no significant or clinically relevant inhibition of cardiac potassium channels that regulate the duration of the action potential and as a consequence the duration of the QT interval (table I).[112-114]

3. Pharmacokinetic Profile

The pharmacokinetic properties of cetirizine have been investigated in adult[121-126] and elderly[122] healthy volunteers, in paediatric patients,[126-129] and in adults with renal[122,130] or hepatic impairment[131] (table II). Plasma and urine concentrations were assessed using gas chromatography and high-performance liquid chromatography (HPLC), whereas dialysate concentrations in those with end-stage renal failure (ESRF) undergoing haemodialysis were measured using HPLC.

3.1 Absorption and Distribution

Oral cetirizine (tablets or solution/syrup formulations) is rapidly absorbed from the gut in a dose-dependent manner, with mean maximum concentrations (C_{max}) in plasma achieved in approximately 0.5–2 hours in healthy adult volunteers (table II).[121-126] There was also no difference in the bioavailability of cetirizine between the tablet and syrup formulations.[132]

Steady-state plasma concentrations are achieved within 2 days.[124] In 22 healthy adult volunteers receiving cetirizine 10mg twice daily, 20mg once daily or 30mg once daily, mean C_{max} values on day 1 were 272.7, 547.8 and 852.7 ng/mL, respectively, with corresponding values on day 7 of 424.2, 624.5 and 832.7 ng/mL. Mean t_{max} values at days 1 and 7 were 1.6–1.8 hours at these dosages.[124]

At steady state, there was no clinically relevant accumulation of cetirizine in serum after administration of oral cetirizine 10mg once-daily for 2 weeks in 20 healthy adult volunteers.[133] In this randomised, double-blind, two-way crossover trial, the mean rate of accumulation was 1.15, as determined by the ratio of the mean maximum serum concentration at day 1 versus that at steady state.

Although the presence of food may have some limited effects on the rate of absorption, there is no effect on the extent of absorption.[2,3] In the presence of food, C_{max} was reduced by 23% and t_{max} was prolonged by 1.7 hours, but the area under the

Table II. Summary of mean pharmacokinetic parameters of oral cetirizine (CET) in different populations after a single dose

Reference and study design (mean age; y) [n]	Dose (mg) [formulation]	C_{max} (μg/L)	t_{max} (h)	AUC (μg • h/L)	Vd (L/kg)	$t_{½β}$ (h)	CL (L/h)	CL_R (L/h)
Healthy adult volunteers								
Baltes et al.,[121] r, nb, co (35) [24]	10 [sol][a]	499	1[b]	4044	0.60[c]			
(24.6) [16]	20 [sol]							
Desager et al.[126] (24.6) [16]	20 [sol]	2729[g]	0.62	21 575[bg]	0.58	8.60	0.8[g]	
Muscara and de Nucci,[123] r, nb, co (30) [14]	10 [tab][d]	302–307	0.5[e]	2776–2784[f]		8.3–8.4		
Sasa et al.[124] (≥18) [15]	10 [NR]	215	1.44	1979	50.73[g]	6.73	5.22	
	20 [NR]	438	1.5	3859	51.11[g]	6.79	5.49	
	30 [NR]	679	2.2	8664	42.81[g]	8.13	3.55	
Wood et al.[125] (range 27–36) [6]	10 [sol]	359[h]	0.5–1			7.4		
Healthy elderly volunteers								
Matzke et al.[122] (77) [16]	10 [cap]	460*[i]	0.9	5600	0.38	11.8*	1.68	0.78
Control group (53) [14]	10 [cap]	384[i]	1	3300	0.39	7.4	2.76	1.44
Pts with renal impairment								
Awini et al.[130] ESRF/HD (50.2) [5]	10 [NR]	285[i]	2			19.3		0.84[j]
Matzke et al.[122] Control group[k] (47) [5]	10 [cap]	313[i]	0.9	2700	0.50	7.4†	47†[g]	40.5†
Mild[k] (56) [5]	10 [cap]	356[i]	1.1	6900	0.46	19.2	17[g]	7.1
Moderate[k] (40) [5]	10 [cap]	357[i]	2.2†	10 700	0.54	20.9	15[g]	2.8
Pts with moderate hepatic impairment								
Simons et al.[131] (64) [6]	10 [tab]	498[i]	1.1	6438	0.44	13.8	0.44[g]	0.15[g]
Paediatric pts								
Desager et al.[126] (2–4) [8]	5 [sol]	1974‡[g]	1.44‡‡	12 034‡‡‡[b,g]	0.63	4.91‡‡‡	1.48‡‡‡[g]	
Pariente-Khayat et al.[128] (3.84) [8]	5 [sol]	607	1.93	4772[b]	0.60	5.55	1.27[g]	0.42[g,l]
Špičák et al.[127] (1.25) [15]	0.25 mg/kg [sol]	390	2.0	2704	0.44	3.1	2.13[g]	
Watson et al.,[129] r, db (8) [10]	5 [NR]	428	1.4	2872	0.7	7.1	1.04[g]	0.49[g]
(8) [9]	10 [NR]	978	0.8	6376	0.7	6.9	1.10[g]	0.38[g]

a Volunteers received a sol of CET or levocetirizine, with a 7d washout period between each. Data are for CET.

b Median value.

c Significantly higher than levocetirizine (0.41 L/kg), although no p-value reported.

d Volunteers received two different tab formulations of CET, with a 7d washout period between each. Data are for both formulations.

e Median value. Same for both formulations.

f AUC_{∞}.

g Vd units L;[124] C_{max} units ng/mL per mg/kg and AUC units ng • h/mL per mg/kg;[126] CL and CL_R units mL/min/kg[126-129,131] or mL/h/kg.[122]

h Mean C_{max} of radioactivity after oral ^{14}C-cetirizine. Units are μg equivalents/L.

i Serum cetirizine concentration.

j Haemodialysis clearance.

k CL_{CR} in pts with normal renal function (control group), or mild or moderate renal impairment were 122 mL/min (7.32 L/h), 44 mL/min (2.64 L/h) or 19 mL/min (1.14 L/h), respectively.

l Six pts evaluated.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **cap** = capsule; **CL** = apparent total body clearance; **CL_{CR}** = creatinine clearance; **CL_R** = renal clearance; **co** = cross-over; **db** = double-blind; **ESRF/HD** = end-stage renal failure undergoing haemodialysis; **n** = number of participants; **nb** = nonblind; **NR** = not reported; **pts** = patients; **r** = randomised; **sol** = solution/syrup; **$t_{½β}$** = elimination half-life; **tab** = tablet; **t_{max}** = time taken to reach C_{max}; **Vd** = volume of distribution; * $p < 0.05$ vs younger adult volunteers; † $p < 0.05$ vs other groups; ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ vs adults.

plasma-concentration time curve (AUC) value was similar in the fasted and fed state (no data reported).[132]

Cetirizine is highly protein bound (≈90%; predominantly to albumin) in a concentration-independent manner over a range of 25–1000 ng/mL (includes therapeutic plasma concentrations).[8,132,134] In healthy adult volunteers (mean age <65 years), the volume of distribution (Vd) after a single oral 10mg dose was low (0.39–0.6 L/kg[121,122] or 50.73L;[124] table II).

Animal studies indicate that cetirizine is extensively distributed throughout the body, although data in humans are limited.[132] Oral cetirizine was rapidly distributed into tear fluid in 40 patients with allergic conjunctivitis, with mean concentrations after a single oral 10mg dose similar to those achieved in serum (mean C_{max} range 70–96 vs 79–105 μg/L).[135] Corresponding t_{max} values were 90 and 30 minutes. However, although C_{max} in tear fluid appeared to be attained slightly later than in serum, values at 60 and 120 minutes were 98% and 92% of the 90 minute value and, thus, the between-site difference in t_{max} was not considered clinically relevant.[135] Cetirizine is distributed into the milk of humans and animals, with levels in the milk of dogs being approximately 3% of the administered dose.[132,136] The drug does not readily penetrate the blood-brain barrier, a reflection of the polarity of cetirizine (section 2.3); animal studies indicated that concentrations in the brain were 10% of those in the plasma.[132]

3.2 Metabolism and Elimination

As with other H_1 receptor antagonists that exist in zwitterionic form (e.g. levocabastine and fexofenadine), cetirizine undergoes minimal metabolism.[8,125] Cetirizine is predominately excreted in the urine as unchanged drug, with 60% (≈50% as unchanged drug[132]) of the drug excreted during the first 24 hours postdose in six healthy adult volunteers administered a single radiolabelled 10mg dose.[125] During the subsequent 4 days, a further 10% of the drug was recovered in the urine. Faecal recovery accounted for 10% of the dose, mainly as unchanged cetirizine. In addition, small quantities of the drug were excreted in plasma and faeces as a metabolite derived from *O*-dealkylation and two unidentified metabolites were recovered in the urine.[125]

The mean terminal elimination half-life ($t_{1/2}\beta$) of cetirizine after a single oral 10mg dose was 6.7–8.6 hours in healthy adult volunteers (mean age <65 years) [table II].[122-126] Apparent total body clearance (CL) values at this dose were 2.76[122] and 5.22[124] L/h (table II). According to the manufacturer's prescribing information,[132] $t_{1/2}\beta$ and CL values for cetirizine were 8.3 hours and 53 mL/min in 146 healthy volunteers involved in several pharmacokinetic studies.

3.3 Special Patient Populations

Pharmacokinetic properties of oral cetirizine in paediatric patients, healthy elderly volunteers, and patients with renal or hepatic impairment are summarised in table II. According to the manufacturer's prescribing information,[132] race has no effect on the pharmacokinetic parameters of cetirizine, although the effects of gender remain to be adequately studied.

In older children aged 5–12 years (mean age 8 years) administered a single dose of cetirizine 5 or 10mg, $t_{1/2}\beta$ was similar to, but CL values were higher than, those in studies in healthy adults table II).[129] Compared with adults administered a single 20mg dose, the CL of cetirizine was also higher in younger paediatric patients aged 2–4 years administered a single 5mg dose, but $t_{1/2}\beta$ was shorter (table II).[126] The rate and extent of absorption was lower in paediatric patients of this age than in adults (table II), as was the cumulative urinary excretion of a dose over 24 hours (37.8% vs 57.7%; $p < 0.001$). Similarly, in another studies in paediatric patients aged 6 months to 6 years, there was a reduction in $t_{1/2}\beta$ and an increase in the CL in cetirizine recipients (table II),[127,128] with less recovery of the dose in the urine (38.4% in children vs 51–66% in adults), relative to historical data from adults.[128]

In elderly volunteers (mean age 77 years) there were significant (all $p < 0.05$) differences in the

mean serum C_{max}, $t_{1/2}\beta$, renal clearance (CL_R) and the CL values relative to younger volunteers (mean age 53 years) [table II].[122] Linear regression analyses indicated that these differences were significantly ($p < 0.001$) correlated with creatinine clearance rather than with age *per se* ($p = 0.08$ for correlation with age).[122]

The predominantly renal excretion of cetirizine underlies the need to study the pharmacokinetics of this agent in individuals with renal impairment (section 3.2). As might be expected, CL_R and CL are decreased and $t_{1/2}\beta$ prolonged in patients with mild-to-severe renal impairment relative to individuals with normal renal function, although there were no clinically relevant effects on the V_D (table II).[122,130] C_{max} values are also increased in those with renal impairment (table II).[122] Hence patients with moderate-to-severe renal impairment require lower dosages of cetirizine than those with normal renal function (section 6).

Less than 10% of a 10mg dose (administered 3 hours prior to dialysis) was removed during haemodialysis in five patients with ESRF.[130] Furthermore, there were no clinically relevant changes in the elimination of cetirizine during dialysis, suggesting that supplemental administration of the drug after dialysis is not required.[130] Mean serum cetirizine concentrations remained within the effective therapeutic range (14 ng/mL) in eight patients with ESRF undergoing chronic dialysis who received cetirizine 5mg three times weekly.[137] These patients did not require supplemental doses of cetirizine.

Although only a minimal amount of cetirizine is eliminated via the liver (section 3.2), clinically relevant alterations in pharmacokinetic parameters have been reported in patients with hepatic impairment.[131,132] In six patients with moderate hepatic impairment (primary biliary cirrhosis),[131] there were significant (all $p < 0.05$) changes in mean C_{max} (498 vs 384 ng/mL), AUC (6438 vs 3300 ng • h/mL), CL (0.44 vs 0.6 mL/min/kg) and $t_{1/2}\beta$ (13.8 vs 7.4) values, and in the fraction of the single 10mg dose excreted as unchanged drug in the urine (32% vs 65%) compared with an historical group of healthy adult volunteers.[131] In 16 patients with chronic liver disease, after a single 20mg dose $t_{1/2}\beta$ increased by 50% relative to that of 16 healthy volunteers with normal liver function, with a corresponding 40% decrease in CL.[132] Thus, dosage adjustments are recommended in patients with hepatic impairment (section 6).

3.4 Drug Interactions

Cetirizine has a low potential for drug interactions, since it is only minimally metabolised by the liver. In particular, the drug is unlikely to interact with agents that are metabolised by the CYP isoenzyme system, with cetirizine 100 μmol/L showing no inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 isoenzymes in human liver microsomes in an *in vitro* study.[138] Administration of cimetidine 600mg twice daily for 10 days did not effect the pharmacokinetics or wheal and flare suppression produced by a single dose of cetirizine in 16 patients with chronic urticaria.[139] There were also no clinically relevant changes in the pharmacokinetic profiles of cetirizine (10mg orally) or theophylline (1-hour intravenous infusion of theophylline 240mg or placebo) when these agents were coadministered to six healthy volunteers in a placebo-controlled, 3-way crossover study.[140] There was no significant pharmacokinetic interaction between cetirizine 20 mg/day and azithromycin 250 mg/day[110] or erythromycin 1500 mg/day[105] when these agents were coadministered in healthy volunteers.

4. Therapeutic Efficacy

The therapeutic efficacy of oral cetirizine has been evaluated in well designed clinical trials in patients with seasonal allergic rhinitis (SAR; section 4.1.1), perennial allergic rhinitis (PAR; section 4.1.2), urticaria (especially chronic idiopathic urticaria [CIU]; section 4.2), atopic dermatitis (section 4.3), allergic asthma (section 4.4), allergic cough (section 4.5) and local reactions to mosquito bites (section 4.6). The efficacy of cetirizine has been compared with first- and second-generation H_1 receptor antagonists. Although astemizole and

terfenadine have been withdrawn from the US and other markets (associated with isolated instances of QTc interval prolongation and torsades de pointes;[141,142] section 2.4), studies involving these agents represent a substantial proportion of the available comparative clinical data for cetirizine and are therefore included in this review.

4.1 Allergic Rhinitis

Allergic rhinitis results from early- and late-phase immunoglobulin (Ig)E-modulated responses to allergens.[141] SAR is commonly the result of exposure to airborne pollens and mould spores, and persists as long as the specific seasonal allergen is present. Typically PAR arises because of sensitivity to, and contact with, allergens present in the environment throughout the year. Allergens such as housedust mites, cockroach, danders of animals or mould may be involved.[141]

The efficacy of cetirizine has been evaluated in large, randomised, double-blind, parallel-group comparative trials in adults, adolescents and paediatric patients with SAR[143-163] (section 4.1.1) or PAR[164-174] (section 4.1.2).

Inclusion criteria to the trials were generally diagnosis and a history of moderate-to-severe SAR or PAR symptoms and a positive skin test (prick, intradermal or radioallergosorbent) response to seasonal (SAR) or nonseasonal (PAR) allergens.[143-174]

Symptoms of allergic rhinitis evaluated in the trials were nasal (rhinorrhoea, sneezing, nasal obstruction, nasal itch), ocular (itch, discharge, conjunctivitis) and/or pharyngeal (itch and cough). Symptoms of acute rhinoconjunctivitis predominate in SAR, while nasal inflammation and obstruction are more prominent in PAR.[143-174]

In most outpatient studies, both patients and/or investigators subjectively rated individual symptom severities using a 4-, 5- or 10-point point scale (0 = absent to 3/4/9 = severe or very severe). In 2-day studies in more controlled environments (the field[158] or an environmental exposure unit[156,157]), individual symptom severities were rated on 5-, 6- or 8-point scales.

The primary efficacy measure was generally the overall reduction from baseline (denoting an improvement) in the total symptom severity (TSS) score. The TSS score was a composite of up to ten (commonly 4–7) individual symptom severity scores; nasal congestion was commonly excluded from the TSS score.[144,145,147,148,151,156-158,163,166] The 2-day studies in controlled environments also assessed major symptom complex (MSC) scores (a composite of up to six individual severity symptom scores of major symptoms) as a primary end point.[156-158] A global assessment of efficacy (using a 4- or 5-point scale or a visual analogue scale [VAS]) was also reported in most studies. The percentage of days with no or only mild symptoms,[171,172] and changes in disease severity scores (changes in the most troublesome symptom)[159,160] were also used as measures of efficacy.

Studies generally excluded patients who had used medications to treat allergies during the immediate period (24 hours to 3 months depending on the medication used) prior to study entry, although some asthma medications were permitted in some studies.[159,160,163]

Where stated, statistical analysis of primary endpoints in the trials was generally conducted on an intention-to-treat basis.[146-148,150-152,155-159,164,167]

4.1.1 Seasonal Allergic Rhinitis

In Adults and Adolescents

The efficacy of cetirizine as treatment for SAR has been investigated in adults and adolescents (aged ≥12 years) in randomised, double-blind, parallel-group, multicentre trials in outpatients[143-155,175-180] and patients exposed to allergens in environmental exposure units[156,157,181] or in the field.[158] This review focuses on larger trials with greater than 150 patients (tables III and IV). Cetirizine 5 or 10mg was administered as a once-daily dose for 1–4 weeks.

In large comparative trials (table III and IV), cetirizine 5 or 10 mg/day was significantly more effective than placebo in relieving the symptoms of SAR.[145,148-152,156-158] In placebo-controlled studies in outpatients,[145,148-152] significantly greater reductions in TSS scores from baseline occurred with

Table III. Comparative efficacy of cetirizine (CET) in adult and adolescent patients (pts) with seasonal allergic rhinitis. Studies are randomised, double-blind, parallel-group studies in >150 evaluable pts. Pts underwent an appropriate washout period for previous medications prior to study entry. Studies were multicentre, unless otherwise stated

References	Treatment	Duration (wk)	No. of evaluable pts	Overall reduction from baseline in TSS[a] score (%)	Global efficacy assessment[b] (% pts)
Backhouse et al.[143]	CET 10mg od	1	141	55[c]	59
	TER 120mg od		144	55[c]	59
Berkowitz et al.[144]	CET 5mg od[d]	2	87	36†[c,e,f]	65[g]
	CET 10mg od[d]		89	38†[c,e,f]	
	AST 10mg od[d]		87	29†[c,e,f]	59
Falliers et al.[145]	CET 5mg od	1	102	39*[c]	73*
	CET 10mg od		106	52*[c]	79*
	CET 20mg od		104	62*[c]	77*
	PL		103	26[c]	53
Gehanno et al.[146]	CET 10mg od	2	116	51[e]	73
	EBA 10mg od		116	52[e]	78
	EBA 20mg od		111	56[e]	85‡
Hampel et al.[147]	CET 10mg od	2	238	22[h]	
	FEX 180mg od		241	19[h]	
Howarth et al.[148]	CET 10mg od	2	207	45**[e,h]	
	FEX 120mg od		211	42**[e,h]	
	FEX 180mg od		202	45**[e,h]	
	PL		201	27[e,h]	
Lockey et al.[149]	CET 10mg od	2	103	43[e] (37**[i])	
	TER 60mg bid		103	38[e] (29[i])	
	PL		105	38[e] (23[i])	
Murray et al.[150]	CET 10mg od	2	431	29**	
	PL		431	13	
Noonan et al.[151]	CET 10mg od	2	202	34**[c]	43**
	PL		198	18[c]	23
Sabbah et al.[152]	CET 10mg od	4	125	49 (46**)[i]	
	MIZ 10mg od		122	52 (46**)[i]	
	PL		128	40 (28)[i]	
Vervloet et al.[153]	CET 10mg od	3	118	53	63
	FLU 200μg od[j]		119	77‡	88 ‡

a Composite of individual symptom severity scores (generally excluding nasal congestion); rated by investigators on a 4-, 5- or 10-point scale.

b Responses considered by investigator to be good or excellent.

c Estimated from a graph.

d Pseudoephedrine 30mg was taken as rescue medication if nasal congestion was too severe.

e Primary endpoint.

f Patient assessment.

g Cetirizine 5 and 10mg od combined.

h Reflective 24h assessment.

i Assessment after 1 week.

j Intranasal administration.

AST = astemizole; **bid** = twice daily; **EBA** = ebastine; **FEX** = fexofenadine; **FLU** = fluticasone propionate; **MIZ** = mizolastine; **od** = once daily; **PL** = placebo; **TER** = terfenadine; **TSS** = Total Symptom Severity; * $p < 0.05$, ** $p < 0.001$ vs PL; † $p < 0.05$ vs baseline; ‡ $p < 0.001$ vs CET.

cetirizine (29–52%) than placebo (13–40%; table III). Moreover, changes in individual symptom scores were generally reduced to a significantly greater extent with cetirizine than placebo ($p < 0.05$).[145,148,149,152,156-158] For example, in one large comparative trial, symptoms of sneezing, rhinorrhoea, itchy nose palate or throat, itchy, watery or red eyes were reduced by 42–44% in cetirizine recipients compared with 24–27% in placebo recipients ($p < 0.001$).[148] Nasal congestion was also reduced to a significantly greater extent in cetirizine (22%) than placebo recipients (16%; $p < 0.05$).[148] The efficacy of cetirizine was rapid, with the reduction in TSS score being significantly different from that of placebo after one day;[149,152] in one study the difference versus placebo was apparent within 2 hours.[152] Similarly, cetirizine reduced overall TSS to a significantly greater extent than placebo in 2-day studies in a rigorously controlled environmental exposure unit[156,157] and in a 2-day field study in a park[158] (table IV), with the cetirizine being more effective than placebo in reducing TSS and MSC 1 hour after administration ($p \leq 0.01$) in the environmental exposure unit studies.[156,157] Changes in MSC score were consistent with the changes in TSS score in the environmental exposure unit studies (table IV).[156,157]

Cetirizine 5 or 10 mg/day was as effective as astemizole 10 mg/day,[144] ebastine 10 mg/day,[146] fexofenadine 120[148] or 180 mg/day,[147,148] mizolastine 10 mg/day[152] and terfenadine 120 mg/day[143,149] in the treatment of outpatients with SAR, according to improvements in TSS score and global assessments of efficacy (table III). However, cetirizine was significantly less effective than ebastine 20 mg/day (global assessment of efficacy only[146]) and the corticosteroid fluticasone propionate 200 µg/day administered in a nasal spray (TSS scores and global assessment of efficacy;[153] table III).

After 1 week of treatment, the reduction in TSS from baseline in recipients of cetirizine 10 mg/day was significantly greater than that in recipients of terfenadine 10 mg/day (reduction in TSS −11.5 vs −9.1; $p = 0.046$),[149] but was significantly less than that in recipients of ebastine 20 mg/day (reduction in TSS −9.9 vs −11.9; $p = 0.027$).[146] In both studies, the improvement in TSS scores in cetirizine recipients was maintained at 2 weeks; however, the between-group difference was no longer significant.

Cetirizine reduced overall TSS and MSC scores from baseline to a significantly greater extent than loratadine in 2-day studies in an environmental exposure unit[156,157] and in a field study in a park[158] (table IV).[156] Global assessments of efficacy also favoured cetirizine over loratadine in the field study (table IV).[158] Moreover, the onset of action was earlier with cetirizine (1 hour) than loratadine (3 hours).[156,157]

Combined inflammatory mediator blockade with both an H_1 receptor antagonist (cetirizine) and a leukotriene-receptor antagonist (montelukast) was as effective as low-dose topical corticosteroid therapy in improving objective and subjective measures of treatment response in SAR, according to data from two small ($n = 22$[182] or 21[183]), 2-week, single-blind, placebo-controlled, crossover studies conducted during the pollen season.[182,183]

The efficacy of combined prophylactic therapy for 8 weeks with oral cetirizine 10 mg/day and fluticasone propionate 200µg administered once daily as a nasal spray was not significantly different from that of monotherapy with nasal fluticasone propionate 200µg administered once daily to 454 patients with a history of SAR.[184] In this double-blind, parallel group, multicentre trial, there was no between-group difference in the nasal or ocular symptom severity scores scores or the number of days that patients were symptom free (45% vs 46% of days). Investigators considered treatment to be successful in 86% of cetirizine plus fluticasone propionate recipients and 83% of fluticasone propionate recipients.

Cetirizine was effective in improving health-related quality of life (HR-QOL; assessed according to the Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ] or the Work Productivity and Activity Impairment-Allergy Specific [WPAI-AS] questionnaire) in adults with SAR.[150,151] In two large trials (table III),[150,151] the improvement in overall RQLQ was significantly greater with cetirizine than place-

bo (36% vs 22%[150] and 39% vs 21% [estimated from a graph];[151] $p < 0.001$ for both studies). Improvements in individual domain scores (activities, sleep, non-nasal/ocular symptoms, practical problems, nasal symptoms, ocular symptoms, emotional) were also significantly greater with cetirizine (all $p < 0.01$ vs placebo).[150,151] In one of the studies,[150] cetirizine was associated with significantly greater improvements than placebo in several domains (impairment at work, overall work and classroom impairment, activity impairment) of the WPAI-AS questionnaire ($p < 0.001$). Improvements in overall RQLQ were correlated with the improvements in TSS score (0.73[150] and 0.68;[151] $p < 0.001$).

In Paediatric Patients

The efficacy of oral cetirizine 5 or 10 mg/day has been investigated in several randomised, double-blind, parallel-group, multicentre studies of 2–4 weeks' duration in paediatric patients (aged 2–6,[159] 6–11[161,162] or 6–12[160] years) and in a 2-week, randomised, nonblind, parallel-group, multicentre study in paediatric patients aged 6–11 years.[163] Cetirizine was administered once or twice daily as a syrup/solution or tablet (table V). Data from one study were presented as an abstract.[162]

In some studies,[159,160,163] children with asthma were permitted to continue stable treatment with theophylline, β-adrenoceptor agonists, inhaled sodium cromoglycate, nedocromil, and in some instances,[159,160] inhaled corticosteroids.

In paediatric patients, cetirizine 5 or 10 mg/day was significantly more effective than placebo in relieving symptoms of SAR (table V).[159-162] Recipients of cetirizine 5 or 10 mg/day experienced significantly more days in which symptoms were mild or absent (assessed from DSS) than placebo recipients (table V).[160] Cetirizine 10 mg/day,[161,162] but not loratadine 10 mg/day,[162] was associated with greater improvements from baseline in patient- and/or investigator-assessed overall TSS scores than placebo in paediatric patients aged 6–11 years (table V). Moreover, according to the global evaluation of SAR at the end of treatment by investigators, responses were good or excellent in significantly more cetirizine than placebo recipients (table V).[159,160]

Cetirizine 10 mg/day had similar efficacy to that of chlorphenamine 2mg administered three times daily,[163] with no significant between-group difference in the reduction in TSS score (table V). Reduction in TSS score occurred rapidly (within one day)

Table IV. Comparative efficacy of cetirizine (CET) in adult or adolescent patients (pts) with seasonal allergic rhinitis conducted in controlled environments (environmental exposure units[156,157] or in an outdoor park[158]). Studies are randomised, double-blind and parallel group in design

References	Treatment	Duration (days)	No. of evaluable pts	Mean change from baseline in TSS[a] score (%)[b]	Mean reduction from baseline in MSC[c] score (%)[b]	Global efficacy assessment[d] (% pts)
Day et al.[156]e	CET 10mg od	2	120	−25**††	−23**††	55**
	LOR 10mg od		116	−11*	−8**	54**
	PL		119	+5	+12	30
Day et al.[157]e	CET 10mg od	2	67	−37*††	−37*††	61
	LOR 10mg od		67	−15	−15	50
	PL		68	−12	−7	43
Meltzer et al.[158]	CET 10mg od	2	93	−45*††	−46*††	74†
	LOR 10mg od		93	−36	−36	57
	PL		92	−40	38	59

a Composite of individual symptom severity scores; rated by investigators.

b Primary endpoint.

c A composite of individual severity symptom scores of major symptoms; rated by investigators.

d Pts considered to be improved (major or moderate).

e Pts were exposed to ragweed pollen 3500 grains/L (5–7 hours daily).

LOR = loratadine; **MSC** = major symptom complex; **od** = once daily; **PL** = placebo; **TSS** = Total Symptom Severity; * $p < 0.01$, ** $p < 0.001$ vs PL; † $p < 0.05$, †† $p \leq 0.01$ vs LOR.

Table V. Comparative efficacy of cetirizine (CET) in paediatric patients (pts) with seasonal allergic rhinitis. Studies were randomised, double-blind, parallel-group, multicentre studies with >100 evaluable pts, unless otherwise indicated. Pts underwent an appropriate washout period for previous medications prior to study entry. Concomitant medication for asthma was permitted in some studies[159,160,163]

References	Age range (y)	Treatment	Duration (wk)	No. of evaluable pts	Change from baseline in mean TSS score (%)[a]	Global efficacy assessment[b] (% pts)	Days when DSS was ≤1 (%)[c]
Comparisons with placebo (PL)							
Allegra et al.[159]	2–6	CET 5mg od[d]	2	54		63*	57**[e]
		PL[d]		53		45	36[e]
Masi et al.[160]	6–12	CET 5mg bid[f]	2	63		79***	56***[e]
		PL[f]		61		50	30[e]
Pearlman et al.[161]	6–11	CET 5mg od[d]	4	69	−2.4[e,g,h]		
		CET 10mg od[d]		70	−3.2*[e,g,h]		
		PL		66	−2.1[e,g,h]		
Comparisons with active comparator or PL							
Ratner et al.[162i]	6–11	CET 10mg od[d]	2	228	− 2.1 (28)**[e,h]		
		LOR 10mg od[d]		220	−1.8 (24)[e,h]		
		PL[d]		229	−1.6 (21)[e,h]		
Tinkelman et al.[163j]	6–11	CET 5 or 10mg od[k,d]	2	62	−2.6 (43)[g,e]		
		CET 2.5 or 5mg bid[k,d]		61	−2.6 (45)[e,g]		
		CHL 2mg tid[d]		63	−2.6 (45)[e,g]		

a TSS is a composite of individual symptom severity scores (excluding nasal congestion) assessed on a 4-point scale, that ranges from 0 = none to 3 = severe.

b Responses considered to be 'good' or ' excellent' by investigator.

c The maximum score of the most severe symptom assessed from the parent's daily record card; 0 = no symptoms, ≤1 = symptoms absent or mild; ≤2 = symptoms absent to moderate.

d Administered as a syrup/solution.

e Primary endpoint.

f Administered as a tablet.

g Pt assessed.

h 24-hour reflective scores.

i Data presented in an abstract.

j Nonblind study.

k CET was administered at a dosage of 5 mg/day in pts weighing <25kg and at a dosage of 10 mg/day in pts weighing ≥25kg.

bid = twice daily; **CHL** = chlorphenamine; **DSS** = Disease Severity Score; **LOR** = loratadine; **od** = once daily; **tid** = three times daily; **TSS** = Total Symptom Severity; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL.

in both treatment groups.[163] Similarly, there was no between-group difference in the investigator's global evaluation of efficacy, with treatment being rated as effective in 97% of cetirizine and 90% of chlorphenamine recipients.

Cetirizine was effective in improving HR-QOL assessed according to Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) in children (aged 6–11 years) with SAR.[185] In a large (n = 544), 4-week, noncomparative trial,[185] the PRQLQ score was reduced by 43% from baseline at week 4 ($p < 0.001$) in recipients of cetirizine 10mg syrup administered once daily in the evening. Moreover at week 4, overall PRQLQ scores were significantly reduced (−38% to −50%) from baseline ($p < 0.001$) for each of the five individual domains (nasal symptoms, eye symptoms, practical problems, other symptoms, activity). TSS scores (exclusive of nasal congestion) were reduced by 53% from baseline at week 4 ($p < 0.001$). The improvement from baseline to week 4 in overall PRQLQ was correlated with improvements in overall TSS score (0.48; $p < 0.001$).[185]

4.1.2 Perennial Allergic Rhinitis

The efficacy of oral cetirizine has been investigated in randomised, double-blind, multicentre studies (n >50 evaluable patients) in adults[165-169] and paediatric patients (aged 2–14 years)[170-174] with PAR (table VI).

In Adults and Adolescents

Cetirizine 10 or 20mg once daily was significantly more effective than placebo in relieving symptoms of PAR in adults (see table VI for reduction in TSS score[166] or number of days with no or mild symptoms[186]). The improvement in TSS score was similar with cetirizine 10 or 20 mg/day,[166] ebastine 10 mg/day,[167] astemizole 10 mg/day[165] or terfenadine 120 mg/day[168] (table VI). The improvement in TSS was greater with cetirizine than with ebastine during the first week of treatment (46% vs 33%; $p < 0.05$)[167] and greater than with astemizole during the first 2 weeks of treatment ($p < 0.05$).[165] Moreover, the onset of action was more rapid with cetirizine than with astemizole (0.58 vs 13.6 hours; $p < 0.01$).[165] However, in a long-term study (12 months) in 143 adults with PAR, cetirizine 10 mg/day was significantly less effective than budesonide (nasally delivered dosage 280μg once daily) in improving TSS (table VI).[169] After discontinuation of treatment, 38% of budesonide and 56% of cetirizine recipients had a relapse within the first month ($p = 0.04$). The median time to relapse was 62 and 20 days, respectively, although the between-group difference was not significant.[169]

After 6 weeks' treatment, all HR-QOL dimensions (physical and social functioning, role limitations in physical and emotional problems, mental health, vitality, bodily pain, general perception of health, change in health) improved to a significantly greater extent with cetirizine 10 mg/day than placebo ($p < 0.001$) in 274 adults with PAR.[186] HR-QOL was assessed by the Short-Form Health Survey (SF-36B). Moreover, this advantage was maintained after a further 5 weeks of therapy for all HR-QOL dimensions ($p < 0.05$), except bodily pain.[187]

Table VI. Comparative efficacy of cetirizine (CET) in adult and adolescent patients (pts) with perennial allergic rhinitis. Studies are randomised, double-blind, parallel-group, multicentre studies in >50 evaluable pts, unless otherwise stated

References	Treatment	Duration (wk)	No. of evaluable pts	Reduction from baseline in TSS[a] score at treatment end (%)	Global evaluation of efficacy (% pts)[b]	Days with no or mild symptoms (%)
Bousquet et al.[186]	CET 10mg od	6	136			43***
	PL		138			3
Chaweewan et al.[165]	CET 10mg od	4	30	CET ≡ AST		
	AST 10mg od		29			
Mansmann et al.[166]	CET 10mg od	8	72	43***	48*[c]	
	CET 20mg od		71	42***	55**[c]	
	PL		73	23	25[c]	
Murris-Espin et al.[167]	CET 10mg od	4	106	54		
	EBA 10mg od		108	45		
Renton et al.[168][d]	CET 10mg od	3	57	49‡		
	TER 120mg od		57	46‡		
Rinne et al.[169]	CET 10mg od	52	72	27	50	26[e]
	BUD 280μg od[f]		71	44†	74†	45†[e]

a Composite of individual symptom severity scores; rated on a 4- or 5-point scale; 0 = none to 3/4 = severe.

b Investigator assessment of 'good' or 'excellent' improvement.

c Estimated from a graph.

d Crossover study.

e Assessed at 6mo.

f Intranasal delivered dose.

AST = astemizole; **BUD** = budesonide; **EBA** = ebastine; **od** = once daily; **PL** = placebo; **TER** = terfenadine; **TSS** = total symptom severity; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL; † $p < 0.01$ vs CET; ‡ $p < 0.001$ vs baseline.

Table VII. Comparative efficacy of cetirizine (CET) in paediatric pts (pts) with perennial allergic rhinitis. Studies are randomised, double-blind, parallel-group, multicentre studies in >50 evaluable pts, unless otherwise stated

References	Age range (y)	Treatment	Duration (wk)	No. of pts	Reduction from baseline in TSS[a] score at treatment end (%)	Global evaluation of efficacy (% pts)[b]	Days with no or mild symptoms (%)
Baelde & Dupont[170]	2–14	CET 2.5mg bid	2	43	53[c,d]		
		CET 5mg bid		42	64[c,d]		
		PL		40	41[c,d]		
De Benedictis et al.[171]	2–6	CET 5mg od	1.4	50	74	74	49
		OXA 12.5mg bid		52	72	69	49
Jobst et al.[172]	6–12	CET 2.5mg od	2	84		52***	46[e]
		CET 5mg od		85		66***	47[e]
		CET 10mg od		76		66***	50*[e]
		PL		83		38	37[e]
Lai et al.[173]	6–12	CET 10mg od	12	19	63**†‡[c]		
		OXA 1 mg/kg bid		18	49**[c]		
		KET 1mg bid		16	44**[c]		
		PL		16	5[c]		
Sienra-Monge et al.[174]	2–6	CET 0.2 mg/kg od	4	38		63	
		LOR 0.2 mg/kg od		40		65	

a Composite of individual symptom severity scores; rated on a 4- or 5-point scale.

b Investigator assessment of 'good' or 'excellent' improvement.

c Estimated from a graph.

d Parent assessment.

e Primary endpoint.

bid = twice daily; **KET** = ketotifen; **LOR** = loratadine; **od** = once daily; **OXA** = oxatomide; **PL** = placebo; **TSS** = total symptom severity; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL; † $p < 0.05$ vs KET; ‡ $p < 0.05$ vs OXA.

In Paediatric Patients

In large randomised studies, cetirizine 2.5–10 mg/day demonstrated significantly greater efficacy than placebo in relieving symptoms of PAR in paediatric patients (table VII).[170,172,173] Patients treated with cetirizine 10 mg/day had significantly greater improvements in symptoms of PAR, when assessed by average symptom score,[170] investigators' global evaluation of efficacy[170,172] or reduction in TSS from baseline.[173]

Cetirizine 5mg once daily was similar in efficacy to oxatomide 12.5mg twice daily for 10 days[171] and investigator global evaluation of efficacy was similar for cetirizine and loratadine both administered at 0.2 mg/kg/day for 4 weeks (table VII).[174] However, according to daily patient assessments, rhinorrhoea, sneezing, nasal obstruction and nasal pruritus improved to a greater extent with cetirizine than loratadine (all $p < 0.001$).[174] Long-term treatment (12 weeks) with cetirizine 10 mg/day was significantly more effective than oxatomide 1 mg/kg twice daily or ketotifen 1mg twice daily (table VII).[173] Cetirizine and oxatomide, but not ketotifen, improved HR-QOL (assessed according to the mean PRQLQ) to a significantly greater extent than placebo (both $p < 0.01$).[173]

4.2 Urticaria

Urticaria is a cutaneous syndrome characterised by dermal oedema (wheal) and erythema (flare).[188-191] The lesions typically last less than 24 hours and are usually pruritic. Episodes of urticaria persisting for more than 6 weeks are considered to be chronic.[192] The disease is termed 'idiopathic', when the causative features provoking the disease are not identified. However, in 30–50% of patients with chronic idiopathic urticaria,[192] the condition has an autoimmune basis. Circulating IgG autoantibodies react specifically with the a-chain of the

high-affinity IgE receptor on dermal mast cells and basophils, evoking release of histamine and other mediators, which cause urticaria and angio-oedema.[188,192]

4.2.1 Chronic Idiopathic Urticaria

Randomised, double-blind, parallel-group trials have investigated the efficacy of cetirizine in the relief of symptoms of chronic idiopathic urticaria (CIU) in adults or adolescents (aged >12 years)[193-201] or paediatric patients (aged 2–6 years)[202]; studies in >50 evaluable patients are the focus of this review (table VIII). Cetirizine was administered once daily for 2–12 weeks.

Patients had symptoms of urticaria (wheals, erythema, pruritus, oedema) that occurred episodically for at least 6 weeks.

In Adults and Adolescents

Efficacy was determined according to the improvement in the severity of total or individual urticaria symptoms (assessed using investigator- and/or patient-rated scales (4- or 5-point),[194-202] global evaluations of efficacy (rated by investigators or patients on a 4- or 5-point scale or

Table VIII. Comparative efficacy of cetirizine (CET) in patients (pts) with chronic idiopathic urticaria. Studies are randomised, double-blind, parallel-group studies (n > 50 evaluable) in adult or adolescent[196-201] and paediatric[202] patients

References	Treatment	Duration (wk)	No. of evaluable pts	Reduction from baseline in symptom scores (%)[a]					Global evaluation of efficacy (% pts)[b]
				total	pruritus	no. of wheals	erythema	oedema	
Adults and adolescents									
Breneman et al.[196]	CET 10mg od	4	60						75*
	AST 10mg od		57						61*
	PL		57						47
Breneman[197]	CET 10mg od	4	60		[0.83**[c]]	[0.98**[c]]			NR**
	HYD 25mg tid		63		[0.68**[c]]	[0.94**[c]]			NR**
	PL		65		[1.49[c]]	[1.63[c]]			NR
Kalivas et al.[198]	CET 5–20mg od	4	60		[0.8*[c,d]]	[1.0*[c,d]]			
	HYD 25–75 mg/day		60		[0.8*[c,d]]	[1.0*[c,d]]			
	PL		68		[1.4[c,d]]	[1.5[c,d]]			
Kietzmann et al.[199]	CET 10mg od	6	43						77†
	TER 60mg bid		41						51
Parsad et al.[200][e]	CET 10mg od	12	24	37[d]					29
	CET 10mg od + STA 2mg bid		26	67††[d]					65††
Patel and Danzig[201]	CET 10mg od	2	22	74	63	95	98		79
	LOR 10mg od		24	76	73	70	62		76
Paediatric pts[f]									
La Rosa et al.[202]	CET 5mg od	4	28		88	85	81	100	87
	OXA 25mg od		29		87	79	70	94	90

a Scores rated on a 4- or 5-point scale; 0 = none and 3/4 = severe.

b Investigator assessment of 'good' or 'excellent' improvement.

c Investigator-rated scores at endpoint.

d Estimated from a graph.

e In pts refractory to conventional treatment (details of medication not stated).

f Pts aged 2–6y.

AST = astemizole; **bid** = twice daily; **HYD** = hydroxyzine; **LOR** = loratadine; **NR** = values not reported; **od** = once daily; **OXA** = oxatomide; **PL** = placebo; **STA** = stanozolol; **TER** = terfenadine; **tid** = three times daily; * $p < 0.05$, ** $p < 0.001$ vs PL; † $p < 0.05$, †† $p < 0.01$ vs comparator.

VAS),[193,195-199,202] or the percentage of symptom-free days during treatment.[203] Individual symptoms that were assessed included the number and size of wheals, pruritus, oedema and erythema.

In patients with CIU, cetirizine 10mg once daily was significantly more effective than placebo.[196-198] At the end of a 4-week treatment period, cetirizine was significantly ($p < 0.05$) more effective than placebo in reducing the number and size of the wheals, the number of urticarial episodes and severity of pruritus (table VIII).[196-198] Global assessment of efficacy confirmed these results (table VIII).[196-198]

The efficacy of cetirizine 10mg once daily in the treatment of symptoms of CIU was similar to that of astemizole 10mg once daily,[196] hydroxyzine 25mg three times daily[197,198] and loratadine 10mg once daily[201] (table VIII). According to global evaluations by investigators, cetirizine was significantly more effective than terfenadine 60mg twice daily[199] (table VIII).

Cetirizine was as effective as astemizole,[196] hydroxyzine,[197,198] terfenadine[199] and loratadine[201] in reducing the number and size of wheals and the symptoms of pruritus. Cetirizine was similar to astemizole[196] and hydroxyzine[197,198] in the reducing the number of urticarial episodes and similar to loratadine[201] in reducing erythema.[196-198,201] Cetirizine was more effective than terfenadine in controlling the symptoms of erythema ($p = 0.02$).[199]

The response to treatment was more rapid with cetirizine (on day 1) than astemizole (days 2–3)[196] and hydroxyzine (day 2),[197] according to patient and investigator ratings of urticaria symptom severity in large comparative studies. Analysis of patient diaries indicated that cetirizine was more effective than hydroxyzine in controlling the number of episodes of urticaria and the severity of pruritus during the first week of therapy ($p < 0.05$).[197] Likewise, analysis of patient diaries showed that cetirizine was significantly more effective than astemizole in controlling the number of wheals and pruritus (days 1–5), number of episodes (days 1–6), size of the wheals (days 1 and 2) and duration of wheals (days 1–5).[196]

Combination therapy with cetirizine 10mg once daily and stanozolol 2mg twice daily was significantly more effective than monotherapy with cetirizine 10mg once daily, with increases in the total mean score of urticaria symptoms being significantly greater with combination therapy (table VIII).[200] The patients in this study were refractory to conventional therapy for CIU.

In Paediatric Patients

In paediatric patients (aged 2–6 years), cetirizine 5mg once daily was as effective as oxatomide 25mg once daily in reducing erythema, wheals, oedema and pruritus (table VIII).[202] Global evaluations of efficacy supported these results.

Cetirizine was also effective in the prevention of acute urticaria in infants aged 12–24 months.[204] Although the prevention of acute urticaria was not the primary endpoint in the large (n = 817) Early Treatment of the Atopic Child (ETAC) [see section 4.4.2 for details of study design], the study showed that acute urticaria occurred in significantly fewer paediatric patients treated with cetirizine 0.25 mg/kg twice daily than in those who received placebo during the 18-month treatment period (6% vs 16%; $p < 0.001$).[204] During the 6-month, treatment-free, follow-up period, there was no between-group difference in the incidence of acute urticaria.

4.2.2 Chronic Urticaria in Patients with Food Additive and/or Acetylsalicylic Acid Sensitivity

Cetirizine was not as effective as the leukotriene receptor antagonist montelukast in patients with chronic urticaria due to food additives and/or acetylsalicylic acid. In a 4-week randomised, double-blind parallel study in 51 patients, montelukast 10mg once daily was associated with a significantly higher percentage of days without pruritus, wheals or angioedema than cetirizine 10mg once daily (45% vs 17%; $p < 0.05$, data estimated from a graph).[203] Moreover, more nights were free from interference from urticaria after treatment with montelukast than cetirizine (58% vs 22%; $p < 0.001$, data estimated from a graph).

Table IX. The efficacy of cetirizine (CET) in adults or adolescents with atopic dermatitis. Studies were randomised, double-blind, parallel group and multicentre in design

References	Treatment	Duration (wk)	No. of evaluable patients	Mean reduction in symptom severity from baseline at endpoint (%)[a]			
				pruritus	erythema	excoriation	lichenification
Hannuksela et al.[207]	CET 10mg od[b]	2	127[c]	46**	36**	39**	33**
	CET 10mg bid[b]			41**	42**	54**	44**
	CET 20mg bid[b]			39**†	49**†	55**	58**††
	PL[b]			36**	30**	30**	26**
Patel et al.[208]	CET 10mg od	4	56	38	15	29‡	27
	LOR 10mg od		60	40	14	10	16

a Assessed by investigators on a 4-point or visual analogue scale.

b Patients were also treated with emollients and hydrocortisone 1%.

c Total number assessed for efficacy.

bid = twice daily; **LOR** = loratadine; **od** = once daily; **PL** = placebo; * $p < 0.01$, ** $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.001$ vs PL; ‡ $p < 0.01$ vs LOR.

4.3 Atopic Dermatitis

Atopic dermatitis is a chronic, inflammatory, eczematous skin disease and is often present in paediatric patients or young adults with a personal or family history of atopy.[205,206] The pathogenesis of atopic dermatitis is unclear; however, an interaction between the immune system and the skin involving multiple mediators is thought to play a role. Although histamine is not thought to have a central role in this disease, its level in the skin and plasma are elevated in affected patients; hence antihistamines have been used in the treatment of the symptoms of disease (in particular pruritus).[205]

A limited number of randomised, double-blind studies have investigated the efficacy of cetirizine in adults or adolescents (aged ≥12 years)[207,208] (table IX) or paediatric patients (aged 1–12 years)[209,210] with atopic dermatitis.

In three of the studies,[207-209] the primary endpoint was the reduction in severity of atopic dermatitis-associated symptoms. However in the ETAC study (section 4.4.2 for details of study design),[210] this was a secondary endpoint.

The severity of the symptoms of atopic dermatitis were evaluated on 4-point scales or VAS in three of the studies,[207-209] while the ETAC study[210] used the severity scoring or atopic dermatitis (SCORAD) system.[211] Symptoms assessed included erythema, vesiculation, papules, excoriation, scaly crusts and lichenification. Concomitant medications (corticosteroids, sodium cromoglycate, procaterol, emollients) were permitted in three of the studies.[207,209,210]

4.3.1 In Adults and Adolescents

Cetirizine was effective in improving symptoms of atopic dermatitis in adults and adolescents (table IX).[207,208] In patients also treated with emollients and 1% hydrocortisone, improvements in the symptoms of atopic dermatitis (pruritus, erythema, vesicles, excoriation, lichenification) occurred with both cetirizine and placebo.[207] Cetirizine 40 mg/day (higher than the maximum recommended dosage; section 6) was significantly more effective than placebo in improving the TSS and some individual symptoms scores (erythema, pruritus and lichenification; table IX).[207] The improvement in pruritus, but not skin lesions, was correlated with the degree of sedation in patients treated with cetirizine 20 or 40 mg/day.[207] However, in the other randomised study (details of concomitant medications not stated),[208] the improvements in symptoms of atopic dermatitis in patients treated with the lower dosage of cetirizine (10 mg/day) or with loratadine (table IX) were not considered by the researchers to depend on the sedative effects of the drugs. There was no between-group difference in the improvement in symptoms (table IX).

4.3.2 In Paediatric Patients

Studies in paediatric patients involved the large 18-month ETAC study[210] in which 817 infants (aged 12–24 months) were treated with cetirizine 0.25 mg/kg twice daily and a smaller 8-week placebo-controlled study in which 22 evaluable patients (aged 6–12 years) were treated with cetirizine 5 or 10mg once daily.[209]

In the large ETAC study in infants,[210] the severity of atopic dermatitis symptoms at 18 months decreased from baseline with both cetirizine (SCORAD 24.9 to 15.2; $p < 0.001$) and placebo (SCORAD 25.1 to 15.7; $p < 0.001$), without any significant between-group difference. Other oral antihistamines were used to a significantly greater extent in placebo than cetirizine recipients (25% vs 19% of patients; $p < 0.05$). Mild topical corticosteroids (class I) were used for a similar percentage of days in the placebo and cetirizine groups (21% and 25%). However, there was a trend for moderate-to-strong corticosteroids to be used less frequently in cetirizine than placebo recipients (19% vs 25% of days; $p = 0.067$).[210] In the sub-group of infants with more severe atopic dermatitis at baseline (SCORAD score ≥25), the corticosteroid-sparing effect was significantly greater in cetirizine than placebo recipients (26% vs 35% of days; $p = 0.014$).[210]

Similar results occurred in the small study ($n = 22$),[209] with symptoms of atopic dermatitis improving over the 8-week treatment period in both placebo and cetirizine recipients. Concomitant medications (e.g. sodium cromoglycate and topical corticosteroids) were required by significantly fewer cetirizine recipients (18%) than placebo recipients (82%; $p < 0.01$).

4.4 Allergic Asthma

There is a strong association between the presence of allergic diseases (such as SAR, PAR or atopic dermatitis) and the development of asthma.[212-214] Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements (in particular mast cells, eosinophils, T lymphocytes, neutrophils and epithelial cells) are involved.[214,215] Moreover, elevated plasma histamine levels occur with both early and late phase asthmatic responses to antigen challenge.[216-218] The disease represents a considerable economic/public health burden.[214]

In addition to its antihistaminic effects, cetirizine inhibits eosinophil recruitment in the skin, nose, eyes and lungs, and inhibits *in vivo* ICAM-1 expression in nasal and conjunctiva epithelium during allergic inflammation (table I and section 2). Consequently, several randomised, double-blind studies have investigated the efficacy of cetirizine in the treatment and prevention of allergic asthma. Cetirizine was administered as once- or twice-daily doses.

4.4.1 In Adults and Adolescents with Concomitant Seasonal Allergic Rhinitis

Cetirizine 10–30 mg/day was effective in controlling the symptoms of asthma in a number of randomised, double-blind studies in patients with mild-to-moderate asthma concomitant with seasonal allergic rhinitis.[154,219-223] Most studies were small (<50 evaluable patients), although two multicentre studies included 93[221] and 186[154] evaluable patients (table X). Several of the studies used terfenadine 60mg twice daily as control medication for concomitant symptoms of allergic rhinitis;[221,222] at this dosage terfenadine is ineffective in controlling asthma.

In the largest of the multicentre studies,[154] mean total asthma symptom scores were improved to a significantly greater extent in cetirizine 10 mg/day than placebo recipients for 5 of the 6 weeks of treatment (table X). In particular, chest tightness, shortness of breath, wheezing and cough were reduced to a significantly greater extent with cetirizine than placebo (p values not stated). However, there were no between-group differences in the pulmonary function tests (determined by spirometry). These results are in agreement with those from the other multicentre study,[221] although the dosage of cetirizine (30 mg/day) that provided significantly greater relief of asthma symptoms than the comparator (table X) is higher than that recommended (section 6). In cetirizine recipients, there were no changes in lung function tests (daily peak expiratory

flow rates [PEFRs] or weekly pulmonary function parameters) in one of the studies,[154] although morning and evening PEFRs improved versus baseline in the other study (significance not stated).[221]

4.4.2 In Paediatric Patients with Concomitant Atopic Dermatitis

The large (n = 817), randomised, double-blind, multicentre ETAC study investigated the efficacy of cetirizine for preventing the onset of asthma in infants (aged 10–28 months) with atopic dermatitis.[224,225] The primary endpoint was the time to the onset of asthma. The infants received twice-daily doses of cetirizine 0.25 mg/kg or placebo for 18 months, and were then followed up for another 18 months. Secondary endpoints in this study included the severity of atopic dermatitis (section 4.3) and the prevalence of acute urticaria (section 4.2).

After 18 months of treatment, the relative risk (RR) of developing asthma was increased in infants with a raised level of total IgE (≥30 kU/L) or specific IgE (≥35 kUA/L) for grass pollen, house dust mite, or cat dander (RR 1.4–1.7).[224] Cetirizine, compared with placebo, significantly reduced the incidence of asthma in patients sensitised to grass pollen (RR = 0.5; p = 0.002) or to house dust mite (RR = 0.6; p = 0.005). This effect was sustained in the grass pollen-sensitised infants for a further 18 months after treatment had stopped (36-month follow-up) [p = 0.008],[225] suggesting that the early use of cetirizine was preventing rather than suppressing symptoms of asthma. Even in house dust mite-sensitised infants, there was no evidence of rebound asthma immediately after stopping the treatment (p = 0.04); at the 36-month follow-up there was a small, but no longer significant, difference between active and placebo treatments.[225] In the intention-to-treat population (all infants with normal or elevated total or specific IgE), there was no significant difference in the number of cetirizine or placebo recipients who developed asthma (both 38%).[224]

4.5 Allergic Cough

Cetirizine 0.15 mg/kg once daily was effective in patients with cough associated with allergic rhinitis, according to a 4-week, randomised, double-blind, placebo-controlled, parallel-group study in 20 paediatric patients (age 6–15 years).[226] The frequency of cough (from week 2–4) and the intensity of cough (from week 1–4) was reduced to a significantly greater extent with cetirizine 10 mg/day than placebo ($p < 0.05$). No change occurred in PEFR or FEV_1.

4.6 Mosquito Bites

Mosquito bites can cause cutaneous reactions, including immediate wheals and delayed papules, which are associated with intense pruritus.[227] Mosquito-bite whealing is mediated by antisaliva IgE antibodies and histamine.[227]

Placebo-controlled, double-blind, crossover studies (n = 18–29) conducted in the field[228,229] or laboratory[230] showed that cetirizine 10mg once-daily given prophylactically was effective in preventing the development of symptoms of mosquito bites.[228-230] Cetirizine, compared with placebo, significantly decreased initial (at 15 minutes) wheal response and pruritus.[228-230] For example, in the study conducted in the laboratory,[230] the wheal size was 25 versus 28mm ($p < 0.01$) and pruritus (assessed by 100mm VAS) was 0 versus 50 ($p < 0.001$) in cetirizine and placebo recipients. In this study, cetirizine was more effective than ebastine or loratadine in reducing pruritus at 15 minutes (VAS; 0, 10 and 30, respectively; $p < 0.001$ vs comparator antihistamines). In one of the studies,[229] cetirizine, compared with placebo, also decreased the wheal size at 12 hours (8.5 vs 13.7mm; $p < 0.01$) and 24 hours (7.4 vs 12.6mm; $p < 0.01$) and total pruritus response (8.4 vs 25.4; $p < 0.001$).

5. Tolerability

5.1 In Adults and Adolescents

Cetirizine 5 or 10 mg/day was generally well tolerated in adults and adolescents with allergic diseases.[132]

Adverse events occurring in adults and adolescents (aged ≥12 years) treated with cetirizine 5 or 10

mg/day in the clinical trials outlined in section 4 were generally mild-to-moderate in intensity.

In placebo-controlled studies conducted in the US, the most common adverse experiences in recipients of cetirizine ≤10 mg/day were somnolence, fatigue, dry mouth, pharyngitis or dizziness (figure 1).[132] The incidence of discontinuation due to adverse events was similar in patients treated with cetirizine (5 or 10 mg/day) or placebo (2.9% vs 2.4%).

In clinical trials reviewed in section 4, the overall adverse event profile of cetirizine was generally similar to that of astemizole,[144,165,179,196] ebastine,[146,167] fexofenadine,[148] loratadine,[156-158,201,208] mizolastine[152] or terfenadine.[143,149,155,168,199]

The incidence of somnolence in cetirizine recipients in placebo-controlled studies was dose dependent.[132] The incidence of somnolence with cetirizine 5 or 10 mg/day was 14% and with placebo was 6% (as reported in the US manufacturer's prescribing information; statistical analysis not provided) [figure 1].[132] Likewise, in several trials outlined in section 4, the incidence of somnolence was greater in recipients of cetirizine 10 mg/day than placebo (9–13% vs 2–4%; $p < 0.05$).[148,149,158] In two comparative trials, the incidence of somnolence was 15–22% in cetirizine recipients and 22–36% in recipients of the first generation H_1 receptor antagonist hydroxyzine.[197,198] The incidence of somnolence associated with cetirizine was similar to that of other second-generation H_1 receptor antagonists in many large (n > 150), randomised, double-blind trials outlined in section 4.[143,144,146,152,155,167,196] However, in several studies, the incidence of somnolence was significantly greater with cetirizine (7–12%) than with terfenadine (1–2%; $p < 0.05$)[143,149] or fexofenadine (4%; $p < 0.05$).[148] In one trial,[147] fexofenadine, but not cetirizine, reduced drowsiness versus baseline (−2.33 vs +0.37; $p = 0.011$). In a postmarketing study (n = 43 363), the incidence of sedation was low in recipients of cetirizine, loratadine, acrivastine or fexofenadine (<8%; estimated from a graph). According to the age- and sex-adjusted odds ratios, cetirizine (3.53; $p < 0.0001$ vs loratadine) and acrivastine (2.79; $p < 0.0001$ vs loratadine) were associated with a higher incidence of drowsiness and sedation than loratadine (1.0) or fexofenadine (0.63).[231]

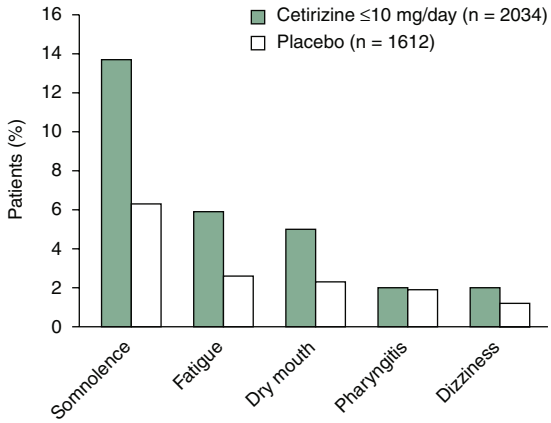

Fig. 1. Adverse experiences reported in ≥2% of patients treated with cetirizine 5 or 10 mg/day.[132] Pooled data from randomised, placebo-controlled studies conducted in the US in adults and adolescents aged ≥12 years. Study duration ranged from 1 week to 6 months (mean 30 days).

There were no reports of cardiac abnormalities in recipients of cetirizine in the clinical trials in section 4 (see also section 2).

In a case-series study of patients who had taken an overdose,[232] cetirizine 80-500mg did not produce clinically significant CNS or cardiovascular toxicity in the adolescent or adult patients (attempted suicide); although mild tachycardia and hypertension were reported, but no specific intervention was necessary (see also section 5.2).

Occasional instances of transient, reversible elevations in hepatic transaminases have occurred during cetirizine treatment.[132] Several cases of hepatitis (including a case of severe liver reaction[233]) have been reported in recipients of cetirizine.[233-237] Other rare adverse events in recipients of cetirizine include urticaria[238-241] and fixed-drug eruptions.[241,242]

In a small, prospective, matched-case control study, no between-group differences in pregnancy outcomes (rate of livebirths, spontaneous or therapeutic abortion or stillbirth) in pregnant women treated with hydroxyzine (n = 81) or cetirizine (n =

39) and the control group.[243] There were no differences between the treatment groups and the control group in the rates of major or minor malformations in live births, mean birth weight, mode of delivery, gestational age or presence of neonatal distress (see also section 6).

5.2 In Paediatric Patients

Cetirizine 2.5–10 mg/day was generally well tolerated in paediatric patients (aged 6 months to 11 years).[132]

In placebo-controlled trials conducted in the US in paediatric patients aged 6–11 years,[132] headache, pharyngitis, abdominal pain, increased coughing, somnolence and epistaxis were among the most commonly reported adverse experiences in both cetirizine 5 or 10 mg/day and placebo recipients (figure 2). The incidence of discontinuations due to adverse experiences was low (0.4% with cetirizine ≤10 mg/day and 1.0% with placebo).[132]

In paediatric patients aged 6–11 years, adverse experiences were more common in recipients of cetirizine 5 and 10 mg/day than placebo (as reported in the US manufacturer's prescribing information; statistical analysis not provided)[132] In paediatric patients aged 2–6 years in placebo-controlled trials, the nature and frequency of adverse events was generally similar to that in children aged 6–11 years.[132]

In infants aged 6–24 months,[108,109] the tolerability profile of cetirizine was similar to that of placebo. In the large, 18-month ETAC study in infants aged 12–24 months, [108] at least one adverse symptom or event was reported in 98.5% of cetirizine recipients and 98.7% of placebo recipients. The mean number of adverse symptoms/events per patient during the study was 15 in both groups. Most events/symptoms were mild and were not considered to be related to medication. Similarly, in a 1-week study in 87 evaluable infants with allergic disorders aged 6–11 months, treatment-related adverse events occurred in 45% of cetirizine and 63% of placebo recipients (statistical analysis not reported).[109]

In placebo-controlled trials in children aged 6–11 years conducted in the US, the incidence of somnolence was dose-related.[132] The incidence of somnolence with cetirizine 5 or 10 mg/day was 2% and 4%, and that with placebo was 1% (figure 2). The incidence of somnolence was similar with cetirizine or placebo in infants aged 12–24 months enrolled in the ETAC study (2% vs 2%, p = 1.00),[108] and was 19% and 28% in infants aged 6–11 months.[109]

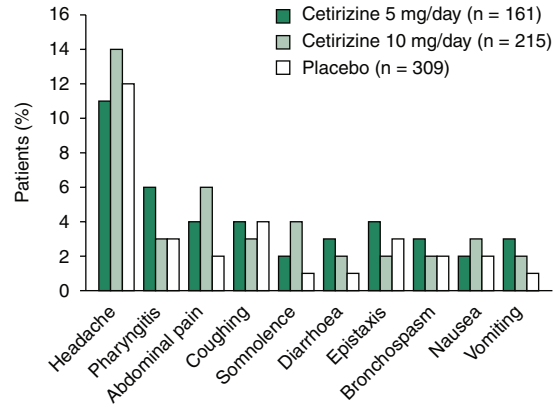

Fig. 2. Adverse events reported in ≥2% of paediatric patients treated with cetirizine 5 or 10 mg/day.[132] Pooled data were from placebo-controlled studies conducted in the US in paediatric patients aged 6–11 years. Treatment duration was 2–12 weeks.[132]

Cetirizine was not associated with clinically relevant cardiac abnormalities in the clinical trials outlined in section 4 (see also section 2). Cetirizine was not associated with any significant changes in the QT interval or QTc interval in paediatric patients (aged 5–12 years) with atopic disease,[161,244] in infants aged 12–24 months with atopic dermatitis[108] or in infants aged 6–11 months with a history of treatment for allergic diseases.[109]

In the clinical studies reported in section 4, the adverse event profile of cetirizine in paediatric patients was similar to that of oxatomide,[171,173,202] chlorphenamine,[163] ketotifen[173] or loratadine.[162,174]

Overdose has been reported in two infants in the ETAC study,[108,245] in a case-report of a 4-year-old boy[246] and in 146 patients aged 4 months to 50 years (mean 5.4 years) reported in a retrospective case-series study.[232] In the individual case reports and the larger case series, cetirizine did not produce clinically significant CNS or cardiovascular toxici-

Table XI. Recommended dosages of oral cetirizine in paediatric patients and adults or adolescents (tablet or syrup/solution formulations) for the treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) or chronic idiopahtic urticaria (CIU)

	US[132]		UK[247,248]	
	recommended dosage[a]	indications	recommended dosage[a]	indications
Adults and adolescents aged ≥12y	5 or 10mg od	SAR, PAR, CIU	10mg od	SAR, PAR, CIU
Children aged 6–11y	5 or 10mg od (1–2 tsps of syrup)	SAR, PAR, CIU	10mg od or 5mg bid	SAR, PAR, CIU
Children aged 2–5y	2.5mg od (½ tsp syrup) increased prn to 5mg od or as 2 divided doses q12h	SAR, PAR, CIU	5mg od or 2.5mg bid (syrup formulation)	SAR
Children aged 6–23mo	2.5mg od (½ tsp of syrup) increased prn in infants 12–23 mo of age to 5mg given as 2 divided doses q12h	PAR, CIU	Not recommended	
Special populations				
Aged ≥12y with renal impairment (CL_{CR} 11–31 mL/min; 0.66–1.86 L/h)	5mg od		5mg od	
Aged ≥12y and on haemodialysis (CL_{CR} <7 mL/min; <0.42 L/h)	5mg od		5mg od	
Aged 6–11y with renal or hepatic impairment	2.5mg od		2.5mg od; no specific recommendations in those with hepatic impairment	
Aged ≥12y of age with hepatic impairment	5mg od		No specific recommendations	
Aged <6y with renal or hepatic impairment	Not recommended		No specific recommendations	

a Dosage adjusted depending on symptom severity.

bid = twice daily; **CL_{CR}** = creatinine clearance; **od** = once daily; **prn** = as required; **q12h** = once every 12 hours; **tsp(s)** = teaspoon(s).

ty, despite a mean dose ingestion >4 times the maximum recommended daily dose.

6. Dosage and Administration

Oral cetirizine, available as a syrup/solution or tablet formulation, is indicated in adults and children for the symptomatic treatment of SAR, PAR for the relief of symptoms and for the treatment of uncomplicated skin manifestations in those with CIU.[132,247,248] Recommended dosages and approved indications vary from country to country; those for the US[132] and UK[247,248] are summarised in table XI. The drug may be taken without regard for food.[132,247,248]

Cetirizine should be given to pregnant women only if clearly indicated (pregnancy category B rating in the US). It was not teratogenic in animal studies,[132] and a small, prospective, matched-case control study found no between-group differences in pregnancy outcomes in women treated with hydroxyzine or cetirizine and the control group (section 5).[243]

Dosage adjustments are recommended for patients with hepatic and/or renal impairment (section 3.1).[132,247,248]

7. Place of Cetirizine in the Management of Selected Allergic Disorders

The prevalence of allergic disorders, such as SAR, PAR, CIU, allergic asthma and atopic dermatitis has increased remarkably in recent years.[141,205,214,249-251] Allergic disorders significantly impair the quality of life of affected patients,[214,252,253] and have an enormous economic impact, including the costs of physician visits, medication and lost productivity.[254,255] In paediatric patients, allergic disorders can cause significant

morbidity, and may result in complications, such as sinusitis, otitis media or asthma, and lead to learning impairments.[141,256]

Avoidance of allergy triggers is recommended as an important first step in obtaining symptomatic relief of allergic disorders.[141,214,249,254] However, avoidance of allergens is often impractical, and pharmacological therapy may be required.

Pharmacological intervention in allergic disorders has generally focused on blocking the effect of a major mediator involved in the allergic response, namely histamine. The earlier first generation H_1 receptor antagonists (e.g. chlorphenamine, diphenhydramine or hydroxyzine) have been available for over 50 years.[9,257] However, these drugs are associated with features that limit their usefulness, including their association with sedation, impaired cognitive function and short half-life, which necessitates more frequent administration.[9] In addition, the sedative effects of these agents are accentuated in the presence of alcohol or other CNS depressants. Moreover, the anticholinergic activity associated with many of these first-generation antihistamines may be manifest as adverse effects such as dry mouth, urinary problems and impotence.[258] The newer second-generation H_1 receptor antagonists include cetirizine, loratadine, fexofenadine, mizolastine and ebastine.[9] These drugs retain the antiallergic efficacy of the first generation agents, but with minimal sedating effects when given at their recommended dosages.[9] This is because of the greater receptor selectivity and reduced penetration of the blood-brain barrier of the second-generation agents. Notably however, two of the newer H_1 receptor antagonists (astemizole and terfenadine) have been associated with isolated instances of QTc interval prolongation and torsades de pointes,[141,142] and have been withdrawn from US and other markets.[259,260]

The recent evidence-based ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines have recommended treatment for seasonal (reclassified as intermittent) and perennial (reclassified as persistent) rhinitis.[214] Oral or intranasal H_1 receptor antagonists are recommended as first-line pharmacotherapy in patients with mild intermittent allergic rhinitis.[214] Oral or nasal decongestants may be used to reduce nasal decongestion in these patients. Oral H_1 receptor antagonists, with or without decongestants, are also recommended for moderate/severe, intermittent and mild, persistent allergic rhinitis. However, for moderate/severe persistent allergic rhinitis, intranasal corticosteroids (with or without H_1 receptor antagonists and decongestants) are recommended.[214] Similarly, H_1 receptor antagonists are the drugs of choice for the treatment and prevention of the symptoms of CIU.[261-263] Although H_1 receptor antagonists are not first-line therapy for allergic asthma *per se*, some of these compounds may have a useful management function in patients

Table X. Efficacy of cetirizine (CET) in patients (pts) with mild-to-moderate allergic asthma and seasonal allergic rhinitis. Studies are randomised, double-blind, parallel-group, multicentre studies

References	Treatment	Duration (wk)	No. of evaluable pts	Change from baseline in TAS[a] at endpoint (%)	Percentage of pts experiencing at least one symptom of asthma at endpoint (baseline value)[b]
Bousquet et al.[221]	CET 10mg bid	4	32		85 (100)
	CET 15mg bid		32		42 (100)†
	TER 60mg bid		33		79 (100)
Grant et al.[154]	CET 10mg od	6	93	−25[c]*	
	PL		93	+5[c]	

a Asthma symptoms rated by patients on a 10-point scale. Symptoms included chest tightness, wheezing, shortness of breath, cough, sputum production and nocturnal asthma.

b Symptoms included wheezing, dyspnoea and coughing.

c Estimated from a graph.

bid = twice daily; **od** = once daily; **PL** = placebo; **TAS** = total asthma symptom score; **TER** = terfenadine; * $p < 0.05$ vs placebo; † $p < 0.01$ vs CET 10mg bid or TER.

with concomitant allergic rhinitis and asthma,[214,264] perhaps through a direct effect on the lower airways, improved upper airways (i.e. nasal) function, or other mechanisms. Similarly, although histamine does not have a central role in the pathogenesis of atopic dermatitis, H_1 receptor antagonists have shown efficacy in the treatment of symptoms of this disease.[205,206]

Cetirizine, a second-generation H_1 receptor antagonist, possesses several pharmacological properties that make it a suitable agent for the treatment of allergic disorders. It prevents the changes induced by allergen-specific challenge, and reduces eosinophil and neutrophil infiltration at the site of the allergic reaction (section 2). Cetirizine does not readily penetrate into the CNS and is associated with less sedation than earlier generation H_1 receptor antagonists. It is not metabolised by the hepatic CYP system and is therefore unlikely to be affected by concomitantly administered drugs metabolised by hepatic isoenzymes (section 3). Cetirizine has a favourable pharmacokinetic profile (short t_{max} of 1–2 hours) and a $t_{½}$ of approximately 7–9 hours; section 3) that is is reflected in its rapid onset (section 2 and 4) and prolonged duration of action (section 2). Thus, sustained relief with once-daily administration is possible. Cetirizine inhibits histamine-induced wheal and flare responses in nonatopic and atopic adult and paediatric patients, and is generally more effective in this context (section 2) than therapeutic doses of several other antihistamine agents, including ebastine and loratadine. Such pharmacological properties translate into a favourable clinical profile for cetirizine in a number of indications.

In adults and adolescents with SAR enrolled in clinical studies (section 4.1.1), cetirizine was at least as effective as standard dosages of other H_1 receptor antagonists such as ebastine, fexofenadine and mizolastine. In studies in environmental exposure units, cetirizine was significantly more effective than loratadine in patients with SAR, with a faster onset of action. Moreover, cetirizine has a role in the relief of symptoms of SAR in paediatric patients; cetirizine, but not loratadine, was more effective than placebo, and cetirizine was as effective as chlorphenamine. Similarly, the role of cetirizine in the treatment of paediatric patients with PAR was established in clinical trials, where it proved to be at least as effective as oxatomide, loratadine and ketotifen (section 4.1.2). Cetirizine demonstrates similar efficacy to that of ebastine in adults with PAR. Head-to-head trials comparing the clinical efficacy of cetirizine with that of the H_1 receptor antagonists desloratadine or levocetirizine (the active enantiomer of cetirizine) in patients with PAR or SAR have yet to be conducted.

Promising results from small studies have indicated that combined inflammatory mediator blockade with both a H_1 receptor antagonist (cetirizine) and a leukotriene-receptor antagonist (montelukast) was as effective as topical corticosteroid therapy in improving objective and subjective measures of treatment response in SAR (section 4.1.1).

H_1 receptor antagonists are the first-choice for symptomatic treatment of patients with CIU[190,191] and, in this regard, cetirizine has a well established role in this indication (section 4.2). It was as effective as standard dosages of hydroxyzine or loratadine in adults and adolescents with CIU. Data from one study showed that cetirizine was less effective than montelukast in patients with chronic urticaria with intolerance to food additives and/or acetylsalicylic acid.[203] However, it should be noted that the patient group in this study[203] represent a unique and select group of patients with chronic urticaria. Cetirizine is also effective in paediatric patients (aged 2–6 years) with CIU, and cetirizine treatment for 18 months was effective in the prevention of acute urticaria in infants with atopic dermatitis who were aged 12–24 months at study entry.[204]

Histamine is an important mast cell- and basophil-derived mediator that has been implicated in the pathogenesis of asthma thorough its ability to increase smooth muscle contraction, mucus secretion, and vascular permeability.[217,265] Moreover, airway inflammation in asthma is also characterised by eosinophil recruitment and is associated with ICAM-1 up-regulation in the respiratory epithelium, the endothelium and many inflammatory cells. Ce-

tirizine not only possesses antihistaminic effects, but also inhibits *in vivo* ICAM-1 expression and eosinophil recruitment (section 2 and table I). In this regard, it has the potential to relieve asthma symptoms and delay or prevent the development of the disease.[217,266] Indeed, cetirizine was effective in the relief of symptoms of asthma in several well designed trials (section 4.4). Moreover, the ETAC trial (section 4.4) showed that cetirizine was significantly more effective than placebo in the prevention of asthma in a subgroup of infants with atopic dermatitis who were sensitised to grass pollen or to house dust mite. Because the intention-to-treat population (all infants with normal or elevated total or specific IgE) showed no significant difference in the number of cetirizine or placebo recipients who developed asthma, future studies will need to focus on the specific subgroups of patients with atopic dermatitis who clearly benefited from pharmacological intervention. Moreover, future studies should include a longer follow-up period in order to determine whether the asthma has been merely delayed or truly prevented.

Cetirizine provided relief of symptoms of atopic dermatitis in both adults and paediatric patients, according to data from a limited number of studies (section 4.3). However, at the end of treatment, its effect was not significantly different from that of placebo, except in recipients of cetirizine 40 mg/day (higher than the recommended dosage; section 6). The role of cetirizine in these patients, especially in infants with severe atopic dermatitis, may be that of sparing the use of corticosteroids, the current mainstays in atopic dermatitis treatment.[205,206] However, further large, well designed trials, with the treatment of atopic dermatitis as the primary endpoint, are still required to fully establish the exact role of cetirizine in the treatment of this disease.

A small number of trials in a limited number of patients have also indicated a potential role for cetirizine in the treatment of mosquito bites (section 4.6) and allergic cough (section 4.5).

Cetirizine was generally well tolerated in adult and adolescent patients (section 5). The incidence of somnolence associated with cetirizine was dose-related (section 5) and was significantly lower than that with a first-generation H_1 receptor antagonists, but generally similar to that of other second-generation H_1 receptor antagonists in most large randomised trials. Nevertheless, somnolence was more apparent with cetirizine than with fexofenadine in some clinical trials and than with loratadine or fexofenadine in a postmarketing surveillance study (section 5). Objective assessments of sedation in pharmacological studies showed that cetirizine was associated with no or mild impairment of driving and psychometric test performance (section 2). Moreover, an analysis of studies that assessed impairment of the cognitive and psychomotor abilities of healthy adult volunteers by H_1 receptor antagonists (see section 2) found that the sedative effect (assessed by proportional impairment ratios using both objective and subjective tests) of cetirizine was similar to that of other second-generation H_1 receptor antagonists, with the exception of fexofenadine or terfenadine (which showed no sedation with respect to second-generation H_1 receptor antagonists) or mizolastine (greater sedative effects).[120] Unlike terfenadine or astemizole, cetirizine has not been associated with any clinically relevant cardiotoxicity (section 2 and 5).

Cetirizine is also well tolerated in paediatric patients aged 6 months to 12 years (section 5). Although adverse experiences were more common in cetirizine than placebo recipients aged 2–11 years, the tolerability profile of cetirizine was similar to that of placebo in younger infants aged 6–24 months. Cetirizine did not effect cognitive function in adult or paediatric patients (section 2) nor behaviour and psychomotor milestones in paediatric patients (section 2) Cetirizine was not associated with any clinically relevant cardiotoxicity (section 5).

As in adolescents or adults, overdose of cetirizine in paediatric patients, cetirizine did not produce clinically significant CNS or cardiovascular toxicity, despite a mean dose ingestion >4 times the maximum recommended daily dose (section 5). Moreover, given its low potential for drug interactions with other agents metabolised in the liver (such as macrolide antibiotics; section 3.4) and its lack of

effect on ECG parameters when combined with macrolides (section 2.4), cetirizine offers a therapeutic option in children who are commonly prescribed these agents.

In conclusion, cetirizine is a second generation H_1 receptor antagonist that has a well established role in the treatment of symptoms of SAR, PAR or CIU in adult, adolescent and paediatric patients. It demonstrated a corticosteroid-sparing effect and reduced the relative risk of developing asthma in infants with atopic dermatitis sensitised to grass pollen or house dust mite allergens. Cetirizine was effective in the treatment of allergic cough and mosquito bites in adults; however, its precise role in these indications has yet to be clearly established. Given its efficacy, favourable tolerability profile (especially in infants) and rapid onset of action, cetirizine is an important option for use in the treatment of allergic disorders.

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