69-5723-00-2

ZYRTEC-D 12 HOUR®

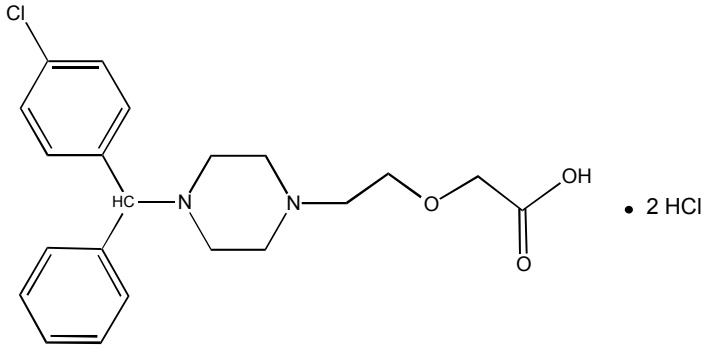
(cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets

For Oral Use

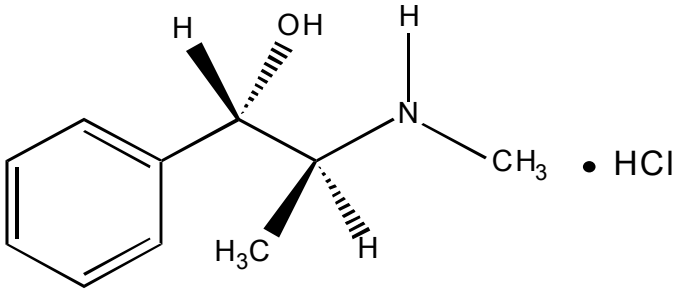
DESCRIPTION

ZYRTEC-D 12 HOUR™ (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets for oral administration contain 5 mg of cetirizine hydrochloride for immediate release and 120 mg of pseudoephedrine hydrochloride for extended release in a bilayer tablet. Tablets also contain as inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Cetirizine hydrochloride, one of the two active components of ZYRTEC-D 12 HOUR Extended Release Tablets, is an orally active and selective H_1-receptor antagonist. The chemical name is (+/-)- [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy] acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3$•2HCl. The molecular weight is 461.82. Cetirizine hydrochloride is a white, crystalline powder and is water-soluble. The chemical structure is shown below:



Pseudoephedrine hydrochloride, the other active ingredient of ZYRTEC-D 12 HOUR Extended Release Tablets, is an adrenergic (vasoconstrictor) agent with the chemical name (1S.2S)-2-methylamino-1-phenyl-1-propanol hydrochloride. The molecular weight is 201.70. The molecular formula is $C_{10}H_{15}NO$•HCl. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform. The chemical structure is shown below:



CLINICAL PHARMACOLOGY

Mechanisms of Action: Cetirizine, a metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *Ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical trials, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors**.**

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects**.**

Pharmacokinetics:
Absorption: The bioavailability of cetirizine hydrochloride and pseudoephedrine hydrochloride from ZYRTEC-D 12 HOUR Extended Release Tablets is not significantly different from that achieved with separate administration of a cetirizine 5 mg tablet and a pseudoephedrine 120 mg extended release caplet. Co-administration of cetirizine and pseudoephedrine does not significantly affect the bioavailability of either component.

Following a single dose of the ZYRTEC-D 12 HOUR Extended Release Tablet, a mean peak plasma concentration (Cmax) of 114 ng/mL at a time (Tmax) of 2.2 hours postdose was observed for cetirizine and a mean Cmax of 309 ng/mL at a Tmax of 4.4 hours postdose was observed for pseudoephedrine.

When healthy volunteers were administered multiple doses of the ZYRTEC-D 12 HOUR Extended Release Tablet to reach steady-state concentrations (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg twice daily for seven days), a mean Cmax of 178 ng/mL was observed for cetirizine and 526 ng/mL for pseudoephedrine.

Food had no significant effect on the extent of cetirizine absorption (AUC), but Tmax was delayed by 1.8 hours and Cmax was decreased by 30%. Food had no significant effect on the pharmacokinetics of pseudoephedrine. ZYRTEC-D 12 HOUR Extended Release Tablets may be given with or without food (see **DOSAGE AND ADMINISTRATION**).

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed. The apparent volume of distribution (V/F) of pseudoephedrine has been reported to be 2.6-3.3 L/kg. No plasma protein binding data in humans are available.

Metabolism: A human mass balance study of cetirizine in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting low first pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

One to seven percent of the pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after a single dose.

Elimination: After administration of the ZYRTEC-D 12 HOUR Extended Release Tablet, the mean elimination half-life of cetirizine was 7.9 hours and the mean elimination half-life of pseudoephedrine was 6.0 hours.

It was reported that 0.4-0.7% of the pseudoephedrine dose was estimated to be excreted in the breast milk over 24 hours after a single dose. The pattern of the relative milk/plasma drug concentration profile showed that pseudoephedrine concentrations in milk were 2- to 3-fold higher than those in plasma.

Drug Interactions
Pharmacokinetic interaction trials with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

Special Populations
Pediatrics: Although cetirizine pharmacokinetics have been studied in children, ZYRTEC-D 12 HOUR Extended Release Tablets contain 120 mg of pseudoephedrine hydrochloride, which exceeds the recommended dose for patients less than 12 years of age. Therefore, ZYRTEC-D 12 HOUR Extended Release Tablets are not recommended for patients under 12 years of age.

Geriatrics: Following a single, 10-mg oral dose of cetirizine, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

The pharmacokinetics of pseudoephedrine has not been adequately studied in geriatric subjects.

Gender: The effect of gender on cetirizine or pseudoephedrine pharmacokinetics has not been adequately studied.

Race: The effect of race on cetirizine or pseudoephedrine pharmacokinetics has not been adequately studied.

Renal Impairment: The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

About 55-75% of an administered dose of pseudoephedrine hydrochloride is excreted unchanged in the urine; the remainder is apparently metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal insufficiency.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

The effect of hepatic impairment on pseudoephedrine pharmacokinetics is unknown.

Dosing adjustment may be necessary in patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics: Trials in 69 adult normal volunteers (aged 20-61 years) showed that cetirizine at doses of 5 and 10 mg inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by cetirizine. In mildly asthmatic subjects, cetirizine at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose. In trials conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by cetirizine at a dose of 20 mg. The clinical significance of these findings is not known.

In four clinical trials in healthy adult males, no clinically significant mean increases in QTc were observed in cetirizine treated subjects. In the first study, a placebo-controlled crossover trial, cetirizine was given at doses up to 60 mg per day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, cetirizine 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with cetirizine alone. In the third trial, also a crossover study, cetirizine 20 mg and ketoconazole (400 mg per day) were given alone and in combination. Cetirizine caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of cetirizine and ketoconazole. In the fourth study, a placebo-controlled parallel trial, cetirizine 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by

250 mg once daily). There was no significant increase in QTc with cetirizine 20 mg alone or in combination with azithromycin.

In a six-week, placebo-controlled study of 186 patients (aged 12-64 years) with allergic rhinitis and mild to moderate asthma, cetirizine 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic rhinitis patients with mild to moderate asthma.

Clinical Trials:

ZYRTEC-D 12 HOUR Extended Release Tablets: Two multicenter, randomized, double-blind, placebo-controlled clinical trials (n = 1094 and n = 1000) comparing ZYRTEC-D 12 HOUR Extended Release Tablets (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) to active control and placebo for two weeks in patients 12 years and older with seasonal allergic rhinitis were conducted in the United States. In the two trials, 390 patients were aged 12 to 17 years. The primary efficacy measure in both trials was the mean change from baseline in the subject-rated Total Symptom Severity Complex (TSSC) score, which included the following symptoms: sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion. In both trials patients who received ZYRTEC-D showed a significant reduction in the TSSC score compared to those who received placebo.

Zyrtec Tablets: Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients 12 years and older with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration) and 2 in perennial allergic rhinitis for up to 8 weeks in duration. In general, the 10 mg dose was more effective than the 5 mg dose and the 20 mg dose gave no added effect. Some of these trials included pediatric patients aged 12 to 16 years**.**

INDICATIONS AND USAGE

ZYRTEC-D 12 HOUR Extended Release Tablets should be administered when both the antihistaminic properties of cetirizine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.

ZYRTEC-D 12 HOUR Extended Release Tablets are indicated for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older.

CONTRAINDICATIONS

ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients with a known hypersensitivity to any of its ingredients or to hydroxyzine.

Due to its pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see **PRECAUTIONS**, **Drug Interactions** section). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see **CONTRAINDICATIONS**). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension. The elderly are more likely to have adverse reactions to sympathomimetic amines.

PRECAUTIONS

Due to its pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see **WARNINGS** and **CONTRAINDICATIONS**). Patients with decreased renal function should be given a lower initial dose (one tablet per day) because they have reduced elimination of cetirizine and pseudoephedrine (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking cetirizine or ZYRTEC-D 12 HOUR Extended Release Tablets; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery after taking ZYRTEC-D 12 HOUR Extended Release Tablets. Concurrent use of ZYRTEC-D 12 HOUR Extended Release Tablets with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug Interactions: Cetirizine hydrochloride and pseudoephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly.

No clinically significant drug interactions have been found with cetirizine and theophylline at a low dose, azithromycin, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.

Due to the pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients taking monoamine oxidase (MAO) inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs that interfere with sympathetic activity (e.g., methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of ZYRTEC-D 12 HOUR Extended Release Tablets concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see **WARNINGS**).

Carcinogenesis, Mutagenesis and Impairment of Fertility: There are no carcinogenicity trials of pseudoephedrine and cetirizine in combination.

Cetirizine: In a 2-year study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily dose in adults on a mg/m^2 basis). In a 2-year study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily dose in adults on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily dose in adults on a mg/m^2 basis). The clinical

significance of these findings during long-term use of ZYRTEC-D 12 HOUR Extended Release Tablets is not known.

Pseudoephedrine: Two-year studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 1/3 and 1/2, respectively, the maximum recommended daily dose of pseudoephedrine in adults on a mg/m^2 basis).

Cetirizine was not mutagenic in the Ames test or mouse lymphoma test and not clastogenic in the human lymphocyte assay or the *in vivo* rodent micronucleus test. Likewise, the combination of cetirizine and pseudoephedrine in a 1:24 ratio was not mutagenic or clastogenic in these tests. However, the Ames and mouse lymphoma assays did not strictly adhere to test standards.

In a reproductive toxicity study in rats, combination oral doses of cetirizine and pseudoephedrine up to 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis) had no effect on fertility.

Pregnancy Category C: In rats, the combination of cetirizine and pseudoephedrine caused developmental toxicity when administered orally at 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis). When rats were dosed throughout pregnancy with oral doses of cetirizine/pseudoephedrine, 6/154 mg/kg increased the number of fetal skeletal malformations (rib distortions) and variants (unossified sternebrae). When dosing was continued through lactation, 6/154 mg/kg also decreased the viability and weight gain of offspring. These effects were not observed at 1.6/38 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m^2 basis). No embryofetal toxicity was observed when rabbits were dosed throughout organogenesis with oral doses of cetirizine/pseudoephedrine of up to 6/154 mg/kg (approximately 10 times the maximum recommended daily dose in adults on a mg/m^2 basis). Because there are no adequate and well-controlled trials in pregnant women, ZYRTEC-D 12 HOUR Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In rats the combination of cetirizine/pseudoephedrine decreased the viability and weight gain of offspring when administered orally to dams throughout pregnancy and lactation at 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis). This effect was not observed at 1.6/38 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m^2 basis). For cetirizine administered alone, studies in dogs indicate that approximately 3% of the dose is excreted in milk, and cetirizine has been reported to be excreted in human breast milk. For pseudoephedrine administered alone, 0.4-0.7% of the dose has been reported to be excreted in human breast milk.

Because cetirizine and pseudoephedrine are excreted in milk, use of ZYRTEC-D 12 HOUR Extended Release Tablets in nursing mothers is not recommended.

Geriatric Use: Clinical trials of ZYRTEC-D 12 HOUR Extended Release Tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines. In general, dosing in an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

The cetirizine and pseudoephedrine components of ZYRTEC-D 12 HOUR Extended Release Tablets are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **CLINICAL PHARMACOLOGY**).

Cetirizine: Of the total number of subjects in clinical trials of cetirizine alone, 186 were 65 years and over, while 39 were 75 years and over. No overall differences in safety were observed between these subjects and younger subjects, and other reported experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical trials of cetirizine for each approved indication did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger patients.

Pediatric Use: ZYRTEC-D 12 HOUR Extended Release Tablets contain 120 mg of pseudoephedrine hydrochloride in an extended release formulation. This dose of pseudoephedrine exceeds the recommended dose for pediatric patients under 12 years of age. Therefore, clinical trials of ZYRTEC-D 12 HOUR Extended Release Tablets have not been conducted in patients under 12 years of age.

ADVERSE REACTIONS

ZYRTEC-D 12 HOUR Extended Release Tablets

In two double-blind, placebo-controlled trials (n = 2094) in which 701 patients with seasonal allergic rhinitis were treated with ZYRTEC-D 12 HOUR Extended Release Tablets (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) twice daily for two weeks, the percent of patients who withdrew prematurely due to adverse events was 2.0% in the ZYRTEC-D group, compared with 1.1% in the placebo group. All adverse events that were reported by greater than 1% of patients in the ZYRTEC-D group are listed in Table 1.

TABLE 1. ADVERSE EXPERIENCES REPORTED IN PATIENTS AGED 12 YEARS AND OLDER IN SEASONAL ALLERGIC RHINITIS TRIALS OF ZYRTEC-D 12 HOUR EXTENDED RELEASE TABLETS AT RATES OF 1% OR GREATER (PERCENT INCIDENCE)

ADVERSE EXPERIENCE	ZYRTEC-D (n = 701)	PLACEBO (n = 696)
Insomnia	4.0	0.6
Dry Mouth	3.6	0.4
Fatigue	2.4	0.9
Somnolence	1.9	0.1
Pharyngitis	1.7	1.1
Epistaxis	1.1	0.9
Accidental Injury	1.1	0.4
Dizziness	1.1	0.1
Sinusitis	1.0	0.6

ZYRTEC Tablets

Controlled and uncontrolled clinical trials of cetirizine conducted in the United States and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving cetirizine at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with cetirizine were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving cetirizine 5 mg or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with cetirizine was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for cetirizine were uncommon (1.0% on cetirizine vs. 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 2 lists adverse experiences in patients aged 12 years and older that were reported for cetirizine 5 and 10 mg in controlled clinical trials in the United States and were more common with cetirizine than placebo.

TABLE 2.
ADVERSE EXPERIENCES REPORTED IN PATIENTS AGED 12 YEARS AND OLDER IN PLACEBO-CONTROLLED UNITED STATES CETIRIZINE TRIALS (MAXIMUM DOSE OF 10 MG) AT RATES OF 2% OR GREATER (PERCENT INCIDENCE)

ADVERSE EXPERIENCE	CETIRIZINE (n=2034)	PLACEBO (n=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

The following events were observed infrequently (less than 2%), in 3982 adults and children 12 years and older or in 659 pediatric (6 to 11 years) patients who received cetirizine in U.S. trials, including an open study of six months duration. A causal relationship of these infrequent events with cetirizine administration has not been established.

Autonomic Nervous System: anorexia, flushing, increased salivation, urinary retention.

Cardiovascular: cardiac failure, hypertension, palpitation, tachycardia.

Central and Peripheral Nervous Systems: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.

Gastrointestinal: abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.

Genitourinary: cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.

Hearing and Vestibular: deafness, earache, ototoxicity, tinnitus.

Metabolic/Nutritional: dehydration, diabetes mellitus, thirst.

Musculoskeletal: arthralgia, arthritis, arthrosis, muscle weakness, myalgia.

Psychiatric: abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.

Respiratory System: bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.

Reticuloendothelial: lymphadenopathy.

Skin: acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.

Special Senses: parosmia, taste loss, taste perversion.

Vision: blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.

Body as a Whole: accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine has been reported.

~~In foreign marketing experience or experience in the post market period~~From post marketing experience, the following additional rare, but potentially severe adverse events have been reported: anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, thrombocytopenia, aggressive reaction and convulsions.

Pseudoephedrine Hydrochloride

Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, nausea, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

OVERDOSAGE

Information regarding acute overdosage is limited to experience with cetirizine alone and the marketing history of pseudoephedrine hydrochloride.

Overdosage has been reported with cetirizine. In one adult patient who took 150 mg of cetirizine, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18-month-old pediatric patient who took an overdose of cetirizine (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The acute minimal lethal oral doses in mice and rats were 237 and 562 mg/kg, respectively (approximately 95 and 460 times the maximum recommended daily dose in adults on a mg/m^2 basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

In large doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma and respiratory failure.

DOSAGE AND ADMINISTRATION

Adults and Children 12 Years of Age and Older: The recommended dose of ZYRTEC-D 12 HOUR Extended Release Tablets is one tablet twice daily for adults and children 12 years of age and older. ZYRTEC-D 12 HOUR Extended Release Tablets may be given with or without food.

Dose Adjustment for Renal and Hepatic Impairment: In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of one tablet once daily is recommended (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

ZYRTEC-D 12 HOUR Extended Release Tablets should be swallowed whole, and should not be broken or chewed.

HOW SUPPLIED

ZYRTEC-D 12 HOUR™ Extended Release Tablets are white, round, biconvex, bilayer tablets containing 5 mg cetirizine hydrochloride in an immediate release layer and 120 mg pseudoephedrine hydrochloride in an extended release layer. ZYRTEC-D 12 HOUR Extended Release Tablets are supplied in high-density polyethylene bottles of 100 tablets fitted with polypropylene child-resistant closures (NDC 0069-1630-66).

ZYRTEC-D 12 HOUR Extended Release Tablets are engraved with ZYRTEC-D on one side.

STORAGE: ***Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]***

Cetirizine is licensed from UCB Pharma, Inc.

Manufactured/Distributed by

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

Marketed by

UCB Pharma, Inc.
Smyrna, GA 30080

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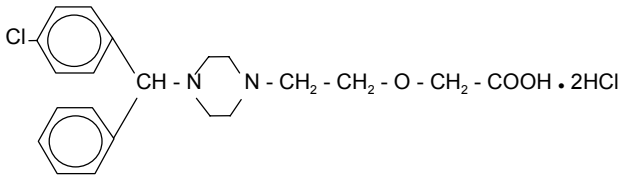
ZYRTEC®
(cetirizine hydrochloride)
Tablets and Syrup
For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC® tablets and syrup, is an orally active and selective H_1-receptor antagonist. The chemical name is (±) - [2- [4- [(4-chlorophenyl)phenylmethyl] -1- piperazinyl] ethoxy]acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. The molecular weight is 461.82 and the chemical structure is shown below:



Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5 and 10 mg strengths. Inactive ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

ZYRTEC syrup is a colorless to slightly yellow syrup containing cetirizine hydrochloride at a concentration of 1 mg/mL (5 mg/5 mL) for oral administration. The pH is between 4 and 5. The inactive ingredients of the syrup are: banana flavor; glacial acetic acid; glycerin; grape flavor; methylparaben; propylene glycol; propylparaben; sodium acetate; sugar syrup; and water.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

Pharmacokinetics:
Absorption: Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (Cmax) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but Tmax was delayed by 1.7 hours and Cmax was decreased by 23% in the presence of food.

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

Metabolism: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Elimination: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

Interaction Studies
Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

Special Populations
Pediatric Patients: When pediatric patients aged 7 to 12 years received a single, 5-mg oral cetirizine capsule, the mean Cmax was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years who received 5 mg of cetirizine, the mean Cmax was 660 ng/mL. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults. In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3 mg), the mean Cmax was 390 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304% greater and the

elimination half-life was 63% shorter in this pediatric population compared to adults. The average AUC(0-t) in children 6 months to <2 years of age receiving the maximum dose of cetirizine solution (2.5 mg twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine tablets once a day.

Geriatric Patients: Following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

Effect of Gender: The effect of gender on cetirizine pharmacokinetics has not been adequately studied.

Effect of Race: No race-related differences in the kinetics of cetirizine have been observed.

Renal Impairment: The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

Dosing adjustment may be necessary in patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics: Studies in 69 adult normal volunteers (aged 20 to 61 years) showed that ZYRTEC at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. ZYRTEC at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5 to 12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found. In 10 infants 7 to 25 months of age who received 4 to 9 days of cetirizine

in an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/mL) cutaneous wheal and 87% inhibition of the flare 12 hours after administration of the last dose. The clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.

The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by cetirizine, as was response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20-mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by ZYRTEC at a dose of 20 mg.

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects. In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, ZYRTEC 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with ZYRTEC alone. In the third trial, also a crossover study, ZYRTEC 20 mg and ketoconazole (400 mg per day) were given alone and in combination. ZYRTEC caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of ZYRTEC and ketoconazole. In the fourth study, a placebo-controlled parallel trial, ZYRTEC 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with ZYRTEC 20 mg alone or in combination with azithromycin.

In a four-week clinical trial in pediatric patients aged 6 to 11 years, results of randomly obtained ECG measurements before treatment and after 2 weeks of treatment showed that ZYRTEC 5 or 10 mg did not increase QTc versus placebo. In a one week clinical trial (N=86) of ZYRTEC syrup (0.25 mg/kg bid) compared with placebo in pediatric patients 6 to 11 months of age, ECG measurements taken within 3 hours of the last dose did not show any ECG abnormalities or increases in QTc interval in either group compared to baseline assessments. Data from other studies where ZYRTEC was administered to patients 6-23 months of age were consistent with the findings in this study.

The effects of ZYRTEC on the QTc interval at doses higher than 10 mg have not been studied in children less than 12 years of age.

In a six-week, placebo-controlled study of 186 patients (aged 12 to 64 years) with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. In a two-week, placebo-controlled clinical trial, a subset analysis of 65 pediatric (aged 6 to 11 years) allergic rhinitis patients with asthma showed

ZYRTEC did not alter pulmonary function. These studies support the safety of administering ZYRTEC to pediatric and adult allergic rhinitis patients with mild to moderate asthma.

Clinical Studies: Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients 12 years and older with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration) and 2 in perennial allergic rhinitis for up to 8 weeks in duration. Two 4-week multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients with chronic idiopathic urticaria were also conducted and showed significant improvement in symptoms of chronic idiopathic urticaria. In general, the 10-mg dose was more effective than the 5-mg dose and the 20-mg dose gave no added effect. Some of these trials included pediatric patients aged 12 to 16 years. In addition, four multicenter, randomized, placebo-controlled, double-blind 2-4 week trials in 534 pediatric patients aged 6 to 11 years with seasonal allergic rhinitis were conducted in the United States at doses up to 10 mg.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing, and redness of the eyes.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 6 months of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients or hydroxyzine.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug-Drug Interactions: No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400-mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.

Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 7 times the maximum recommended daily oral dose in infants on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately equivalent to the maximum recommended daily oral dose in infants on a mg/m^2 basis). The clinical significance of these findings during long-term use of ZYRTEC is not known.

Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and *in vivo* micronucleus test in rats.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).

Pregnancy Category B: In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: Of the total number of patients in clinical studies of ZYRTEC, 186 patients were 65 years and older, and 39 patients were 75 years and older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical studies of ZYRTEC for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients.

ZYRTEC is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See Geriatric Patients and Renal Impairment subsections in CLINICAL PHARMACOLOGY).

Pediatric Use: The safety of ZYRTEC has been demonstrated in pediatric patients aged 6 months to 11 years. The safety of ZYRTEC, at daily doses of 5 or 10 mg, has been demonstrated in 376 pediatric patients aged 6 to 11 years in placebo-controlled trials lasting up to four weeks and in 254 patients in a non-placebo-controlled 12-week trial. The safety of cetirizine has been demonstrated in 168 patients aged 2 to 5 years in placebo-controlled trials of up to 4 weeks duration. On a mg/kg basis, most of the 168 patients received between 0.2 and 0.4 mg/kg of cetirizine HCl. The safety of cetirizine in 399 patients aged 12 to 24 months has been demonstrated in a placebo-controlled 18-month trial, in which the average dose was 0.25 mg/kg bid, corresponding to a range of 4 to 11 mg/day. The safety of ZYRTEC syrup has been demonstrated in 42 patients aged 6 to 11 months in a placebo-controlled 7-day trial. The prescribed dose was 0.25 mg/kg bid, which corresponded to a mean of 4.5 mg/day, with a range of 3.4 to 6.2 mg/day.

The effectiveness of ZYRTEC for the treatment of allergic rhinitis and chronic idiopathic urticaria in pediatric patients aged 6 months to 11 years is based on an extrapolation of the demonstrated efficacy of ZYRTEC in adults with these conditions and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between these two populations. Efficacy is extrapolated down to 6 months of age for perennial allergic rhinitis and down to 2 years of age for seasonal allergic rhinitis because these diseases are thought to occur down to these ages in children. The recommended doses for the pediatric population are based on cross-study comparisons of the pharmacokinetics and pharmacodynamics of cetirizine in adult and pediatric subjects and on the safety profile of cetirizine in both adult and pediatric patients at doses equal to or higher than the recommended doses. The cetirizine AUC and Cmax in pediatric subjects aged 6 to 23 months who received a mean of 2.3 mg in a single dose, and in subjects aged 2 to 5 years who received a single dose of 5 mg of cetirizine syrup and in pediatric subjects aged 6 to 11 years who received a single dose of 10 mg of cetirizine syrup were estimated to be intermediate between that observed in adults who received a single dose of 10 mg of cetirizine tablets and those who received a single dose of 20 mg of cetirizine tablets.

The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials conducted in the United States and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on ZYRTEC than placebo was somnolence. The incidence of somnolence associated with ZYRTEC was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for ZYRTEC were uncommon (1.0% on ZYRTEC vs. 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 1 lists adverse experiences in patients aged 12 years and older which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States and that were more common with ZYRTEC than placebo.

Table 1.
Adverse Experiences Reported in Patients Aged 12 Years and Older in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10 mg) at Rates of 2% or Greater (Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

Pediatric studies were also conducted with ZYRTEC. More than 1300 pediatric patients aged 6 to 11 years with more than 900 treated with ZYRTEC at doses of 1.25 to 10 mg per day were included in controlled and uncontrolled clinical trials conducted in the United States. The duration of treatment ranged from 2 to 12 weeks. Placebo-controlled trials up to 4 weeks duration included 168 pediatric patients aged 2 to 5 years who received cetirizine, the majority of whom received single daily doses of 5 mg. A placebo-controlled trial 18 months in duration included 399 patients aged 12 to 24 months treated with cetirizine (0.25 mg/kg bid), and another placebo-controlled trial of 7 days duration included 42 patients aged 6 to 11 months who were treated with cetirizine (0.25 mg/kg bid).

The majority of adverse reactions reported in pediatric patients aged 2 to 11 years with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to

adverse reactions in pediatric patients receiving up to 10 mg of ZYRTEC was uncommon (0.4% on ZYRTEC vs. 1.0% on placebo).

Table 2 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in pediatric patients aged 6 to 11 years in placebo-controlled clinical trials in the United States and were more common with ZYRTEC than placebo. Of these, abdominal pain was considered treatment-related and somnolence appeared to be dose-related, 1.3% in placebo, 1.9% at 5 mg and 4.2% at 10 mg. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were qualitatively similar in nature and generally similar in frequency to those reported in trials with children aged 6 to 11 years.

In the placebo-controlled trials of pediatric patients 6 to 24 months of age, the incidences of adverse experiences, were similar in the cetirizine and placebo treatment groups in each study. Somnolence occurred with essentially the same frequency in patients who received cetirizine and patients who received placebo. In a study of 1 week duration in children 6-11 months of age, patients who received cetirizine exhibited greater irritability/fussiness than patients on placebo. In a study of 18 months duration in patients 12 months and older, insomnia occurred more frequently in patients who received cetirizine compared to patients who received placebo (9.0% v. 5.3%). In those patients who received 5 mg or more per day of cetirizine as compared to patients who received placebo, fatigue (3.6% v. 1.3%) and malaise (3.6% v. 1.8%) occurred more frequently.

Table 2.
Adverse Experiences Reported in Pediatric Patients Aged 6 to 11 Years in Placebo-Controlled United States ZYRTEC Trials (5 or 10 mg Dose) Which Occurred at a Frequency of ≥2% in Either the 5-mg or the 10-mg ZYRTEC Group, and More Frequently Than in the Placebo Group

Adverse Experiences	Placebo (N=309)	ZYRTEC	
		5 mg (N=161)	10 mg (N=215)
Headache	12.3%	11.0%	14.0%
Pharyngitis	2.9%	6.2%	2.8%
Abdominal pain	1.9%	4.4%	5.6%
Coughing	3.9%	4.4%	2.8%
Somnolence	1.3%	1.9%	4.2%
Diarrhea	1.3%	3.1%	1.9%
Epistaxis	2.9%	3.7%	1.9%
Bronchospasm	1.9%	3.1%	1.9%
Nausea	1.9%	1.9%	2.8%
Vomiting	1.0%	2.5%	2.3%

The following events were observed infrequently (less than 2%), in either 3982 adults and children 12 years and older or in 659 pediatric patients aged 6 to 11 years who received

ZYRTEC in U.S. trials, including an open adult study of six months duration. A causal relationship of these infrequent events with ZYRTEC administration has not been established.

Autonomic Nervous System: anorexia, flushing, increased salivation, urinary retention.

Cardiovascular: cardiac failure, hypertension, palpitation, tachycardia.

Central and Peripheral Nervous Systems: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.

Gastrointestinal: abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.

Genitourinary: cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.

Hearing and Vestibular: deafness, earache, ototoxicity, tinnitus.

Metabolic/Nutritional: dehydration, diabetes mellitus, thirst.

Musculoskeletal: arthralgia, arthritis, arthrosis, muscle weakness, myalgia.

Psychiatric: abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.

Respiratory System: bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.

Reticuloendothelial: lymphadenopathy.

Skin: acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.

Special Senses: parosmia, taste loss, taste perversion.

Vision: blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.

Body as a Whole: accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of ZYRTEC has been reported.

~~In foreign marketing experience or experience in the post market period~~ From post marketing experience, the following additional rare, but potentially severe adverse events have been reported: anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, thrombocytopenia, aggressive reaction and convulsions.

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one adult patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18 month old pediatric patient who took an overdose of ZYRTEC (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 40 times the maximum recommended daily oral dose in infants on a mg/m^2 basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 190 times the maximum recommended daily oral dose in infants on a mg/m^2 basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

DOSAGE AND ADMINISTRATION

Adults and Children 12 Years and Older: The recommended initial dose of ZYRTEC is 5 or 10 mg per day in adults and children 12 years and older, depending on symptom severity. Most patients in clinical trials started at 10 mg. ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

Children 6 to 11 Years: The recommended initial dose of ZYRTEC in children aged 6 to 11 years is 5 or 10 mg (1 or 2 teaspoons) once daily depending on symptom severity. The time of administration may be varied to suit individual patient needs.

Children 2 to 5 Years: The recommended initial dose of ZYRTEC syrup in children aged 2 to 5 years is 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5 mg per day given as 1 teaspoon (5 mg) once daily, or as ½ teaspoon (2.5 mg) given every 12 hours.

Children 6 months to <2 years: The recommended dose of ZYRTEC syrup in children 6 months to 23 months of age is 2.5 mg (½ teaspoon) once daily. The dose in children 12 to 23 months of age can be increased to a maximum dose of 5 mg per day, given as ½ teaspoonful (2.5 mg) every 12 hours.

Dose Adjustment for Renal and Hepatic Impairment: In patients 12 years of age and older with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg once daily is recommended. Similarly, pediatric patients aged 6 to 11 years with impaired renal or hepatic function should use the lower recommended dose. Because of the difficulty in reliably administering doses of less than 2.5 mg (½ teaspoon) of ZYRTEC syrup and in the absence of pharmacokinetic and safety information for cetirizine in children below the age of 6 years with impaired renal or hepatic function, its use in this impaired patient population is not recommended.

HOW SUPPLIED

ZYRTEC® tablets are white, film-coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with “ZYRTEC” on one side and “5” on the other.
Bottles of 100: NDC 0069-5500-66
10 mg tablets are engraved with “ZYRTEC” on one side and “10” on the other.
Bottles of 100: NDC 0069-5510-66

STORAGE: Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

ZYRTEC® syrup is colorless to slightly yellow with a banana-grape flavor. Each teaspoonful (5 mL) contains 5 mg cetirizine hydrochloride. ZYRTEC® syrup is supplied as follows:

120 mL amber glass bottles	NDC 0069-5530-47
1 pint amber glass bottles	NDC 0069-5530-93

STORAGE: Store at 20°-25°C (68°-77°F) excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]; **or Store refrigerated, 2°-8°C (36°-46°F)**.

Cetirizine is licensed from UCB Pharma, Inc.

Rx only

Manufactured/Marketed by

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

Marketed by

UCB Pharma, Inc.
Smyrna, GA 30080

70-4573-00-6

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