PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

REACTINE® COMPLETE

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

Extended-Release Tablets, 5 mg Cetirizine Hydrochloride and 120 mg Pseudoephedrine Hydrochloride, Oral

McNeil Standard

Histamine H_1 Receptor Antagonist/Sympathomimetic Amine

McNeil Consumer Healthcare
division of Johnson & Johnson Inc.
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Markham, Canada
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RECENT MAJOR LABEL CHANGES

Section 7: Warnings and Precautions	05/2019

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Adults and children 12 years of age and over: REACTINE COMPLETE (Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets) are indicated

- for the relief of symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis. Symptoms treated effectively include: sneezing, rhinorrhea, post nasal discharge, tearing and redness of the eyes and nasal congestion.

1.1 Pediatrics

Pediatrics - Children < 12 years of age: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of REACTINE COMPLETE Extended Release Tablets in children below 12 years of age has not been established; therefore, Health Canada has not authorized an indication for this age group. Refer to WARNINGS AND PRECAUTIONS for additional information regarding pediatric patients.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections (See WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

REACTINE COMPLETE (Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets) are contraindicated in those patients with a known hypersensitivity to cetirizine, to its parent compound, hydroxyzine, to piperazine derivatives, those with a known hypersensitivity or idiosyncrasy to pseudoephedrine hydrochloride, to adrenergic agents, to other drugs of similar chemical structures, or to any of the ingredients in the formulation or components of the container. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias. For a complete listing, see the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.

Due to its pseudoephedrine hydrochloride component, REACTINE COMPLETE is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within 14 days of stopping such treatment. It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in patients with hyperthyroidism.

The use of cetirizine/pseudoephedrine should be avoided in children under 12 years of age.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Do not exceed recommended dose. Prolonged use only as directed by a physician.

4.2 Recommended Dose and Dosage Adjustment

REACTINE COMPLETE may be given with or without food. The tablets should be swallowed with liquid and should not be divided, chewed or crushed.

Adults and children 12 years of age and over: The recommended dose of REACTINE COMPLETE (cetirizine hydrochloride/pseudoephedrine hydrochloride) is one tablet every 12 hours.

Adults 65 years of age and over: In patients with moderate hepatic and/or renal impairment, a dose of one tablet once daily is recommended.

4.4 Administration

See Recommended Dose and Dosage Adjustment above in 4.2

4.5 Missed Dose

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time. Do not exceed the maximum daily dose.

5 OVERDOSAGE

Acute overdosage with cetirizine/pseudoephedrine may produce tachycardia, arrhythmia, hypertension, signs of CNS depression (sedation, apnea, unconsciousness, cyanosis and cardiovascular collapse) or stimulation (insomnia, hallucinations, tremor, seizures), which could be fatal. Treatment, preferably in a hospital setting, should be symptomatic and supportive, taking into account any concomitantly ingested medications. Should vomiting not occur spontaneously, it should be induced. Gastric lavage is recommended.

There are no known antidotes. Sympathomimetic amines should not be used. Hypertension can be controlled with alpha-blockers and tachycardia with beta-blockers. Seizures can be treated with intravenous diazepam (or diazepam given rectally in the case of children).

Cetirizine and pseudoephedrine are poorly eliminated by hemodialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of	Dosage Form /	Non-medicinal Ingredients

Administration	Strength/Composition	
Oral	Nonprescription tablet containing 5 mg cetirizine hydrochloride in an immediate release layer and 120 mg pseudoephedrine hydrochloride in an extended release layer	croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide

Description

REACTINE COMPLETE (Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets) 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: croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

REACTINE COMPLETE tablets are white round, biconvex tablets containing 5 mg cetirizine hydrochloride in an immediate release layer and 120 mg pseudoephedrine hydrochloride in an extended release layer. Tablets are debossed with “REACTINE +” on one side.

PVC film and aluminum foil blister packages of 10 and 30.

7 WARNINGS AND PRECAUTIONS

General

Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) have been reported very rarely with cetirizine and pseudoephedrine-containing products. This acute pustular eruption may exhibit an early or delayed onset with numerous small, mostly non-follicular pustules arising on a widespread edematous erythema mainly localized on the skin folds, trunk, and upper extremities, which may be accompanied by fever. Patients should be carefully monitored.

If symptoms persist or get worse, or if new symptoms occur, the patient should discontinue use and consult a physician.

Sympathomimetics should be used with caution in patients with stenosing peptic ulcer, pyloroduodenal obstruction, prostatic hypertrophy, or bladder neck obstruction, cardiovascular disease, arrhythmia, tachycardia, hypertension, hyperthyroidism, increased intraocular pressure, renal or hepatic insufficiency or diabetes mellitus. Sympathomimetics should be used with caution in patients receiving decongestants, appetite suppressants, psychostimulants (such as amphetamines), tricyclic antidepressants, and digitalis. Sympathomimetics may cause central nervous system (CNS) stimulation and convulsions or cardiovascular collapse with accompanying hypotension.

Activities Requiring Mental Alertness: Studies using objective measurements have shown no effect of cetirizine hydrochloride on cognitive function, motor performance or sleep latency in healthy volunteers.

However, in clinical trials the appearance of some CNS effects, particularly somnolence, have been observed. If drowsiness occurs, do not drive or operate machinery.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Until such data become available, REACTINE COMPLETE (cetirizine hydrochloride/pseudoephedrine hydrochloride) should not be used during pregnancy, unless advised otherwise by a physician.

7.1.2 Breast-feeding

Nursing Women: Cetirizine has been reported to be excreted in human breast milk. For pseudoephedrine hydrochloride administered alone, about 0.5% of the dose has been reported to be excreted in human breast milk. Because cetirizine and pseudoephedrine are excreted in milk, use of REACTINE COMPLETE in nursing mothers is not recommended.

7.1.3 Pediatrics

REACTINE COMPLETE contains a fixed dose of pseudoephedrine hydrochloride 120 mg in an extended release formulation. This dose of pseudoephedrine hydrochloride is not recommended for pediatric patients under 12 years of age. The safety and effectiveness of REACTINE COMPLETE in pediatric patients under the age of 12 years have not been established.

7.1.4 Geriatrics

In elderly patients, sympathomimetics are more likely to cause adverse reactions such as confusion, hallucination, convulsions, and/or CNS depression.

Cetirizine hydrochloride was well tolerated by patients aged 65 and over. Clearance of cetirizine hydrochloride is reduced in proportion to creatinine clearance. In patients whose creatinine clearance is reduced (i.e., those with moderate renal impairment), a starting dose of 5 mg/day (one REACTINE COMPLETE tablet) is recommended (see Human Pharmacokinetics).

Pseudoephedrine is incompletely metabolized (less than 1%) in the liver by N-demethylation to an inactive metabolite. The drug and its metabolite are excreted in urine; 55-96% of a dose is excreted unchanged. Therefore, pseudoephedrine may accumulate in patients with renal insufficiency.

Occasional instances of liver function test (transaminase) elevations have occurred during cetirizine hydrochloride therapy. This incidence was 1.6% in the short-term trials and 4.4% in the 6 month trials. These liver enzyme elevations, mainly ALT, were generally reversible. There was no evidence of jaundice or hepatitis, and the clinical significance is presently unknown. Consequently, cetirizine hydrochloride should be used with caution in patients with pre-existing liver disease. In patients with moderate hepatic impairment, a starting dose of 5 mg is recommended.

The effect of hepatic impairment on pseudoephedrine hydrochloride pharmacokinetics is unknown.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In controlled clinical trials, adverse reactions reported in more than 1% of the patients receiving the combination cetirizine/pseudoephedrine, were not different from those reported for cetirizine or pseudoephedrine alone. They included: dry mouth, headache, insomnia, somnolence, asthenia, tachycardia, nervousness, dizziness, vertigo, and nausea. Sympathomimetic drugs have also been associated with certain untoward reactions, including fear, anxiety, tenseness, restlessness, tremor, weakness, pallor, respiratory difficulty, dysuria, hallucinations, convulsions, CNS depression, arrhythmias and cardiovascular collapse with hypotension.

Hypersensitivity reactions, including skin reactions and angioedema, may occur.

Cetirizine hydrochloride: In clinical development programs (domestic and international), cetirizine hydrochloride has been evaluated in more than 6000 treated patients at daily doses ranging from 5 to 20 mg. The most common adverse reactions were headache and somnolence (see paragraph below). The incidence of headache associated with cetirizine hydrochloride was not different from placebo. The incidence of somnolence associated with cetirizine hydrochloride was dose related and predominantly mild to moderate. The adverse reaction profile in children shows a lower incidence of somnolence.

Incidence of somnolence reported in placebo controlled efficacy trials with cetirizine should not be misinterpreted as these studies were not designed or powered to assess somnolence or lack of somnolence. Several placebo controlled studies involving objective and subjective tests in healthy volunteers have demonstrated that cetirizine hydrochloride at doses up to 10 mg did not significantly differ from placebo with respect to CNS impairment or task performance.

Most adverse reactions reported during cetirizine hydrochloride therapy in clinical trials were mild to moderate. The incidence of discontinuation due to adverse reactions in patients receiving cetirizine hydrochloride was not significantly different from placebo (1.0% vs 0.6%, respectively, in placebo-controlled trials). There was no difference by gender or by body weight with regard to the incidence of adverse reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse events which were reported at an incidence of greater than 1/50 (2%) in clinical trials are listed in Table 2.

Table 2

ADVERSE REACTIONS REPORTED IN PLACEBO-CONTROLLED REACTINE TRIALS (MAXIMUM DOSE OF 10 mg) AT RATES OF 2% OR GREATER (Percent Incidence)

Adverse Experience	Cetirizine HCl (n=3260)	Placebo (n=3061)	Difference of Percentage
Headache	7.42	8.07	(0.65)*
Dry Mouth	2.09	0.82	1.27
Somnolence	9.63	5.00	4.63

( )* = Higher frequency in placebo group.

The following events were observed infrequently (equal to or less than 2%), in 3982 patients who received cetirizine hydrochloride in worldwide trials, including an open study of 6 months duration; a causal relationship with cetirizine hydrochloride administration has not been established.

Autonomic Nervous System: anorexia, urinary retention, flushing, saliva increased

Cardiovascular: palpitation, tachycardia, hypertension, arrhythmia, cardiac failure

Central and Peripheral Nervous Systems: fatigue, dizziness, insomnia, nervousness, paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, cramps legs, ataxia, dysphonia, coordination abnormal, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, speech disorder, twitching, visual field defect

Endocrine: thyroid disorder

Gastrointestinal: nausea, pharnyngitis, appetite increased, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, stomatitis ulcerative, tongue disorder, tooth caries aggravated, stomatitis, tongue discoloration, tongue edema, gastritis, hemorrhage rectum, hemorrhoids, melena, hepatic function abnormal

Genitourinary: polyuria, urinary tract infection, cystitis, dysuria, hematuria, urine abnormal

Hearing and vestibular: earache, tinnitus, deafness, ototoxicity

Metabolic/Nutritional: thirst, edema, dehydration, diabetes mellitus

Musculoskeletal: myalgia, arthralgia, bone disorder, arthrosis, tendon disorder, arthritis, muscle weakness

Psychiatric: depression, emotional lability, concentration impaired, anxiety, depersonalization, paroniria, thinking abnormal, agitation, amnesia, libido decreased, euphoria

Resistance Mechanism: healing impaired, herpes simplex, infection, infection fungal, infection viral

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

Reproductive: dysmenorrhea, menstrual disorder, breast pain female, intermenstrual bleeding, leukorrhea, menorrhagia, pregnancy unintended, vaginitis, testes disorder

Reticuloendothelial: lymphadenopathy

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

Special Senses: taste perversion, taste loss, parosmia

Vision: eye abnormality, vision abnormal, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage

Body as a Whole: weight increase, back pain, malaise, pain, chest pain, fever, asthenia, edema generalized, edema periorbital, edema peripheral, rigors, edema legs, face edema, hot flushes, abdomen enlarged, allergic reaction, nasal polyps

8.3 Less Common Clinical Trial Adverse Reactions

(<1%)

Cetirizine hydrochloride: Weight gain was reported as an adverse event in 0.4% of cetirizine patients in placebo controlled trials. In an open study of 6 months duration, the mean weight gain was 2.8% after 20 weeks, with no further increase at 26 weeks.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy.

In a 6-week, placebo-controlled study of 186 patients with allergic rhinitis and mild to moderate asthma, cetirizine hydrochloride 10 mg o.d. improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine hydrochloride to allergic rhinitis patients with mild to moderate asthma.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine hydrochloride therapy, without evidence of jaundice, hepatitis or other clinical findings.

8.5 Post-Market Adverse Reactions

Additional adverse drug reactions identified during post-marketing experience include: euphoric mood, eye pain, photophobia, cough, dyspnoea, abdominal discomfort, diarrhoea, abnormal hepatic function (increased transaminases, alkaline phosphatase, y-GT, bilirubin), angioedema, pruritus, rash, urticaria, dysuria, urinary retention, erectile dysfunction, vision blurred, eye swelling, feeling abnormal, psychomotor hyperactivity (in the pediatric population), enuresis, restlessness, cerebrovascular accident, paraesthesia, tremor, myocardial infarction, colitis ischaemic, acute generalized exanthematous pustulosis, fixed drug eruption, dysgeusia, dyskinesia, dystonia, memory impairment, arthralgia, pruritus upon withdrawal and weight increased.

Cetirizine hydrochloride: In post-marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis [including Drug-induced liver injury (DILI) and other types of

non-infectious hepatitis], glomerulonephritis, stillbirth, and cholestasis. In addition, isolated cases of the following adverse drug reactions have been reported: convulsions, syncope, aggression, and hypersensitivity.

Pseudoephedrine hydrochloride: Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypertensive patients. As with other sympathomimetic amines, CNS stimulation, muscular weakness, tightness in the chest and syncope may also be encountered. 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, confusion, tenseness, tremor, Posterior Reversible Encephalopathy Syndrome, Reversible Cerebral Vasoconstriction Syndrome, hallucinations, seizures, dry mouth, difficulty in micturition, vomiting, pallor, respiratory difficulty, dysuria, fixed drug eruption, and cardiovascular collapse.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interaction studies with cetirizine hydrochloride and alcohol or diazepam indicate that cetirizine hydrochloride does not increase alcohol-induced or diazepam-induced impairment of motor and mental performance.

The drug should not be used with sedating substances such as alcohol and some other medications, including anti-anxiety medications, sleep aids, antihistamines, antidepressants, muscle relaxants or prescription analgesics due to possible interactions.

9.3 Drug-Behavioural Interactions

Interactions with lifestyle have not been established.

9.4 Drug-Drug Interactions

Cetirizine hydrochloride: No clinically significant drug interactions have been found with cetirizine hydrochloride and theophylline, pseudoephedrine hydrochloride, cimetidine, erythromycin and ketoconazole. Epidemiologic data suggests that there also would not be interaction with other macrolide antibiotics or imidazole antifungals. In clinical trials, cetirizine hydrochloride has been safely administered with beta-agonists, non-steroidal anti-inflammatory drugs, oral contraceptives, narcotic analgesics, corticosteroids, H_2-antagonists, cephalosporins, penicillins, thyroid hormones and thiazide diuretics.

Based on: (a) its relatively low level of metabolic elimination, (b) no effect on corrected QT intervals at plasma concentrations three times the maximal therapeutic levels, and (c) no apparent interactions with ketoconazole or erythromycin, cetirizine hydrochloride is unlikely to have clinically significant interactions with other macrolides such as clarithromycin or other imidazole antifungals such as itraconazole in patients with normal renal and hepatic function. Although no data with these other drugs are available at the present time, there is no epidemiological evidence (the safety database comprised 6,490 patients evaluated in U.S. and Canadian studies) of interactions between macrolide antibiotics and/or imidazole antifungals taken orally, and cetirizine hydrochloride/hydroxyzine. The epidemiologic data do not suggest an increase of adverse events, cardiac or non-cardiac, in patients treated with cetirizine hydrochloride and concomitant macrolide or imidazole antifungal medication.

Pseudoephedrine hydrochloride: Monoamine oxidase (MAO) inhibitors potentiate effects of sympathomimetic drugs such as pseudoephedrine hydrochloride. When sympathomimetic drugs are given to patients receiving MAO inhibitors, hypertensive crises may result. Pseudoephedrine hydrochloride should therefore be avoided in patients receiving drugs with MAO inhibiting activity. Pseudoephedrine hydrochloride may reduce the antihypertensive effects of methyldopa, mecamylamine, guanethidine, reserpine, and veratrum alkaloids. Beta-adrenergic blocking agents may also interact with sympathomimetics. Increased ectopic pacemaker activity can occur when pseudoephedrine hydrochloride is used concomitantly with digitalis. Therefore, use of REACTINE COMPLETE should be avoided in patients on digitalis. The antibacterial agent, furazolidone, is known to cause a dose-related inhibition of MAO. Although there are no reports of a hypertensive crisis caused by the concurrent administration of pseudoephedrine hydrochloride and furazolidone, they should not be taken together. Care should be taken in the administration of REACTINE COMPLETE concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient. (see CONTRAINDICATIONS). Antacids increase the rate of pseudoephedrine absorption; kaolin decreases it.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Cetirizine hydrochloride, an active human metabolite of hydroxyzine, is a histamine H_1 receptor antagonist anti-allergic compound; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. Cetirizine hydrochloride is distinguished from other histamine H_1 receptor antagonists by the presence of a carboxylic acid function. This difference may be partly responsible for the selectivity of cetirizine hydrochloride seen in pharmacologic models and its distinctive pharmacokinetic properties in humans.

10.2 Pharmacodynamics

The antihistaminic activity of cetirizine hydrochloride has been well documented in a variety of animal and human models. *In vivo* animal models have shown negligible anticholinergic or antiserotonergic activity. *In vitro* receptor binding studies have detected no measurable affinity for other than H_1 receptors. Autoradiographic studies have shown negligible penetration into the brain. Systemically administered cetirizine does not significantly occupy cerebral H_1 receptors. Several studies involving objective and subjective tests in healthy volunteers have demonstrated that cetirizine hydrochloride at doses up to 10 mg did not significantly differ from placebo with respect to CNS impairment, daytime drowsiness, reaction times, mental alertness, task performance, objective CNS depression and various other tests of cognitive function.

Cetirizine hydrochloride does not exacerbate asthma and is effective in a variety of histamine mediated disorders. In adults, oral doses of 5-20 mg in humans strongly inhibit the skin wheal and flare response caused by the intradermal injection of histamine. The onset of activity occurs within 20 (50% of subjects) to 60 (95% of subjects) minutes and persists for at least 24 hours following a single dose. The effects of intradermal injection of various other mediators or histamine releasers as well as components of the allergic inflammatory response to cutaneous antigen challenge are also inhibited.

Studies in normal volunteers show that cetirizine hydrochloride at doses of 5 to 20 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of activity corresponds with the occurrence of maximal plasma levels, and significant blockade persists for at least 24 hours after a single dose. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine hydrochloride, as is cold-induced urticaria.

In mildly asthmatic subjects, cetirizine hydrochloride at 5 to 20 mg is highly effective in blocking bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose; a modest reduction of resting bronchial tone is also seen.

Studies in normal subjects using objective assessments of psychomotor performances showed that cetirizine hydrochloride at doses up to 20 mg did not produce significant changes in the Multiple Sleep Latency test, a measure of daytime drowsiness, in comparison with placebo. However, hydroxyzine 25 mg caused a statistically significant decrease in time to sleep onset. When the Flicker Fusion Threshold was used to measure mental alertness, cetirizine hydrochloride did not produce significant change but hydroxyzine significantly reduced the mental alertness. In this study, cetirizine hydrochloride 10 and 20 mg and hydroxyzine 25 mg had equipotent antihistaminic activity as determined by the suppression of skin wheal response to histamine.

Several combined placebo and positive control studies in normal subjects using a multiple crossover design with objective and subjective assessments of CNS and performance impairment showed that Reactine (cetirizine hydrochloride) 10 mg did not differ from placebo. Positive controls i.e. sedating antihistamines, e.g. diphenhydramine, hydroxyzine, triprolidine, were included in these trials to verify that the tests were able to detect impairment. Objective tests included: Multiple Sleep Latency Test (EEG monitoring), Critical Flicker-Fusion (CFF), Choice Reaction Time (CRT), Continuous Tracking Test (CTT), word testing, simulated driving tests and assembly line tests (SALT), actual road-driving tests. Subjective tests included: Visual Analog Scale (VAS) reporting, Stanford Sleepiness Scale (SSS) by the subject as well as subjective assessments by driving instructors.

Due to the association of torsades and QT prolongation with newer antihistamines, and the metabolic/pharmacokinetic interaction of antihistamines with erythromycin and ketoconazole, three studies were performed to evaluate the pharmacokinetic effects and ECG effects of cetirizine, and the possible interactions of cetirizine with ketoconazole and erythromycin. These studies show that cetirizine, alone or in combination with erythromycin or ketoconazole, does not cause clinically significant QTc prolongation. Furthermore, no effects on the pharmacokinetics of erythromycin or ketoconazole and no effects of these two compounds on the pharmacokinetics of cetirizine were seen.

Protocol 90CK16-0497: There were no statistically significant differences among the treatments in mean QTc prior to daily dosing, indicating that multiple dosing with cetirizine at both the maximal clinically studied daily dose (20 mg) or three times the maximal clinically studied dose (60 mg once daily) has no effect on QTc relative to a placebo effect. Furthermore, cetirizine did not have any

statistically significant effect on QT (uncorrected) or on heart rate as measured by RR interval. This finding was consistent over all dose days as indicated by no statistically significant treatment-by-day interaction for each of the three parameters. This suggests that, within the first 7 days of treatment, cetirizine produces neither an early transient effect nor a late-appearing cumulative effect. Also, there were no significant differences with respect to the mean changes in QTc, QT, and RR from pre-dosing to 1, 2, 4, and 6 hours after dosing indicating that a dose of cetirizine has no acute effect on QT interval or heart rate relative to placebo at any of the post-dose hours for up to 7 days of treatment. The plasma cetirizine concentration-time profiles were dose proportional.

Four subjects (19.1%) during cetirizine 20 mg treatment and 6 subjects (28.6%) during cetirizine 60 mg experienced at least one 10% prolongation of QTc as compared to 6 subjects (28.6%) on placebo. These incidence rates were not significantly different. The largest prolongations observed were 15.6%, 19.0%, and 15.4% over baseline for placebo, cetirizine 20 mg, and cetirizine 60 mg, respectively.

Protocol 92KC16-0604: The objectives of this study were to determine whether cetirizine, in the presence of erythromycin, induces a prolongation of the QT interval and to determine whether there are pharmacokinetic interactions between cetirizine and erythromycin in young, healthy males. This was a randomized, multiple dose, open (the cardiologist was blinded), two-way crossover study with a washout period. The two treatment regimens administered in the study were the following:

Regimen 1	Day 1:	placebo o.d.
	Days 2-6:	20 mg cetirizine o.d.
	Days 7-16:	500 mg erythromycin q8h and 20 mg cetirizine o.d.
Regimen 2	Day 1:	placebo o.d.
	Days 2-6:	500 mg erythromycin q8h
	Days 7-16:	500 mg erythromycin q8h and 20 mg cetirizine o.d.

The mean change from baseline Hodges QTc after 5 days of dosing with cetirizine alone and erythromycin alone was -5, 10 msec and 3.01 msec, respectively. After an additional 10 days of dosing with combination treatment, the mean change from baseline was -3.71 msec for combination treatment following cetirizine alone and -0.39 msec for combination treatment following erythromycin alone. Using these mean changes, the drug interaction effect was estimated to be 0.03 msec, which is not statistically significantly different from zero. This result indicates that any possible effect on changes in Hodges QTc attributable to either drug alone is not altered by the presence of the other, and that the effect on Hodges QTc of combination dosing is the sum of the individual effects. The estimated effect of cetirizine is -5.08 msec which is a statistically significant reduction from baseline. The estimated erythromycin effect of 3.03 msec was not statistically significant. These results indicate that cetirizine did not induce a mean prolongation of Hodges QTc, and since the effect of combination dosing was just the sum of each component (estimated to be -2.05), there was no significant mean prolongation associated with combination treatment.

No subject experienced a 10% prolongation of Hodges QTc over baseline during cetirizine alone treatment. Eight subjects experienced at least 1 prolongation of 10% or greater. Two subjects (13.3%) had a 10% or greater increase during treatment with erythromycin alone, 2 subjects (14.3%) during combination treatment following cetirizine and 4 subjects (26.7%) had an occurrence during combination treatment following erythromycin. The maximum prolongation in any subject in the study was 17.8% which occurred during erythromycin treatment alone. There was no significant pharmacokinetic interaction between cetirizine and erythromycin when administered concomitantly in therapeutic dosages and regimens.

Protocol 92CK16-0603: The objectives of this study were to determine whether cetirizine, in the presence of ketoconazole, induces a prolongation of the QT interval and to determine whether there are pharmacokinetic interactions between cetirizine and ketoconazole in young, healthy males. This was a randomized, multiple dose, open (the cardiologist was blinded), two-way crossover study. The two treatment regimens administered in the study were the following:

Regimen 1	Day 1:	placebo o.d.
	Days 2-6:	400 mg ketoconazole o.d.
	Days 7-16:	400 mg ketoconazole o.d. and 20 mg cetirizine o.d.
Regimen 2	Day 1:	placebo o.d.
	Days 2-6:	placebo o.d.
	Days 7-16:	20 mg cetirizine o.d.

There was no statistically significant drug interaction effect on the change in Hodges QTc from baseline. This indicates that the effect of the combination on changes in Hodges QTc is equal to the sum of the individual component effects. The effects of each drug alone on change in Hodges QTc from baseline were statistically significant, with a mean increase from baseline of 8.16 msec and 8.32 msec for cetirizine and ketoconazole, respectively. Based on these findings, the effect of combination treatment on changes in Hodges QTc is estimated to be 16.48 msec.

No subject experienced a 10% or greater QTc prolongation during the 5 days placebo treatment. Two subjects (13.3%) experienced an increase in QTc of 10% or greater during the 10 day cetirizine treatment, 1 subject (6.3%) during the 5 day ketoconazole treatment and 5 subjects (31.3%) had an occurrence during combination treatment (2 in study phase 1 and 3 in study phase II). The maximum prolongation in any subject in the study was 14.3%, which occurred during combination treatment. Cetirizine did not significantly affect ketoconazole plasma pharmacokinetics.

Using Bazett's formula for QTc, 3 subjects had a total of 12 occurrences of a QTc >440 msec. There was 1 occurrence on placebo, 4 on cetirizine treatment and 7 on combined treatment. These occurrences of QTc >440 msec were episodic and not sustained.

The results of the study of protocol 90CK16-0497 demonstrate that cetirizine alone in multiple doses up to 60 mg (three times the maximum recommended dose of 20 mg) does not cause a prolongation of

the QTc. Cetirizine did not increase mean QTc nor increase the percentage of patients who had 10% increases or greater in post-dose QTc. The pharmacokinetics of cetirizine was linear over the dose range and no dose related increase in QTc was seen. The results of study protocols 92CK16-0603 and 0604 demonstrate there was no significant interaction of cetirizine with either ketoconazole or erythromycin on QTc. Cetirizine given at the maximum recommended dose of 20 mg daily did not prolong the QTc when given in combination with either ketoconazole 400 mg o.d. or erythromycin 500 mg q8h for 10 days. Moreover, cetirizine did not significantly alter the pharmacokinetics of either ketoconazole or erythromycin nor were the pharmacokinetics of cetirizine altered by either ketoconazole or erythromycin.

With regard to QTc effect of cetirizine alone in the interaction studies, a small clinically insignificant decrease was seen in the erythromycin-cetirizine interaction study, and a small clinically insignificant increase in QTc was seen in the cetirizine-ketoconazole study. However, this small increase may be the result of other factors. For example, in the study of protocol 0497, a small increase in QTc was seen with placebo. In order to facilitate a comparison of the data in the 20 - 60 mg cetirizine study (protocol 90CK16-0497) with that in the two interaction studies, an analysis was done using the Hodges QTc formula and statistical models similar to the interaction study analyses. Based on this analysis, QTc increases of 5.4 msec, 3.0 msec and 7.3 msec for placebo, 20 mg and 60 mg cetirizine, respectively, were observed at the end of the 7 day treatment period. A shortened RR interval was found in all treatment groups, including placebo. The increase associated with placebo treatment indicates that other factors may affect QTc such as deconditioning during confinement, which is essentially a time effect.

In one multicenter, double-blind, parallel-group, placebo-controlled 4-week study involving a total of 205 children 6-11 years of age with seasonal allergic rhinitis treated with either 5 mg (N=66) or 10 mg (N=69) cetirizine, or placebo (N=70), analysis of the available ECG data in 202 patients with regards to mean changes from baseline to either last ECG or to ECGs obtained 11-17 days after the start of the study revealed that treatment with cetirizine did not result in statistically greater mean increases in QTc compared to placebo. None of the 202 patients had an increase of 20% or more from the baseline QTc. Furthermore, the number of patients with 10-20% increase in QTc was comparable between treatment groups.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine acts directly on α-adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction which results in shrinkage of swollen nasal mucous membranes, reduction of tissue hyperemia, edema, and nasal congestion, and an increase in nasal airway patency. Drainage of sinus secretions is increased and obstructed eustachian ostia may be opened. Pseudoephedrine produces peripheral effects similar to those of ephedrine and has the potential for excitatory side effects.

Three randomized, controlled, double-blind, comparative studies in which subjects received cetirizine 5 mg and pseudoephedrine 120 mg extended release in a combination dosage form for the treatment of allergic rhinitis were conducted.

In the first study (Bertrand et al., 1996) a total of 210 patients with perennial allergic rhinitis, 97 males and 113 females aged 12 - 65 years, from eight centres, were randomized into one of three treatment groups: cetirizine 5 mg tablets, pseudoephedrine retard 120 mg capsules, or cetirizine 5 mg tablets combined with pseudoephedrine retard 120 mg capsules. The “double-dummy” technique was used to

ensure blindness. Perennial allergic rhinitis was diagnosed from reliable history and at least one year's duration and a positive allergy test.

In the second study (Grosclaude et al., 1997) a total of 687 patients, with pollen-associated allergic rhinitis, aged 9 - 66 years, were randomized in a multicentre, double-blind parallel group design to treatment with: 5 mg cetirizine alone, 120 mg pseudoephedrine retard alone, and the same doses of both agents in combination. The study was performed between March and September when pollen counts were high.

In the third study (Horak et al., 1998) a total of twenty-four patients, 10 male and 14 female, aged 18 - 32 years with a mean 10 year history of perennial allergic rhinitis due to house-dust-mite allergy were randomized to twice daily treatment with either: the formulation of cetirizine 5mg with sustained release pseudoephedrine 120 mg (cetirizine/pseudoephedrine) or a matched placebo for 1 week followed by a washout period of at least two weeks before crossover to the alternative treatment for a further week. Immediately after the first dose of each medication, nasal congestion and related symptoms were assessed during a 7 hour challenge with house-dust-mites using the Vienna Challenge Chamber.

In all of these trials, the (cetirizine/pseudoephedrine) combination treatment was more effective than, and as well tolerated as treatment with each individual agent or placebo. The combination treatment significantly reduced ($p<0.01$) individual symptom scores (nasal obstruction, sneezing, rhinorrhea, nasal pruritus and ocular pruritus) compared to cetirizine alone. When compared with placebo, the combination treatment showed a highly significant reduction ($p=0.0004$) in total nasal symptoms. The incidence of adverse effects was similar for cetirizine/pseudoephedrine and placebo.

In another study (Horak et al., 1998) a total of 36 patients with house-dust-mite induced nasal congestion and related symptoms were randomized to twice daily treatment with either cetirizine/sustained release pseudoephedrine 120 mg or intranasal budesonide 100 mcg for 4 days. Following a washout period of at least 2 weeks, patients crossed over to the alternative treatment for a further 4 days. The formulation of cetirizine/pseudoephedrine was significantly ($p<0.01$) superior to topical budesonide in relieving nasal congestion, reducing nasal secretions and improving all nasal symptoms. The combination also had a rapid onset of action and sustained efficacy throughout the challenge period.

10.3 Pharmacokinetics

Absorption: The bioavailability of cetirizine hydrochloride and pseudoephedrine hydrochloride from REACTINE COMPLETE Extended Release Tablets is not significantly different from that achieved with separate administration of cetirizine hydrochloride 5 mg tablets and pseudoephedrine hydrochloride 120 mg extended release caplets. Co-administration of cetirizine hydrochloride and pseudoephedrine hydrochloride does not significantly affect the bioavailability of either component.

Following a single dose of the REACTINE COMPLETE Tablet, cetirizine hydrochloride was rapidly absorbed and produced a mean peak plasma concentration (Cmax) of 114 ng/mL at a time (Tmax) 2.2 hours postdose. Pseudoephedrine hydrochloride produced a mean peak plasma concentration of 309 ng/mL at 4.4 hours postdose.

When healthy volunteers were administered multiple doses of the REACTINE COMPLETE Tablet to reach steady state concentrations (cetirizine hydrochloride 5 mg/pseudoephedrine hydrochloride 120 mg twice daily for seven days), a mean peak plasma concentration (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 hydrochloride 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 hydrochloride. REACTINE COMPLETE Tablets may be given with or without food.

Cetirizine hydrochloride is rapidly absorbed after oral administration. Peak plasma levels after a 10 mg dose are approximately 300 ng/mL and occur at about 1 hour. Co-administration with food slows absorption somewhat (lower Cmax and greater Tmax but does not affect bioavailability as measured by AUC. Plasma protein binding is 93%. The apparent volume of distribution is 0.45 L/kg, suggestive of significant extravascular distribution. The plasma elimination half-life is approximately 8 hours and does not change with multiple dosing. Plasma levels are proportional to the dose administered over the clinically studied range of 5 to 20 mg.

Distribution: Plasma protein binding of cetirizine hydrochloride is 93% in the concentration range observed in clinical studies.

Metabolism: In adults, cetirizine hydrochloride is less extensively metabolized than other antihistamines and approximately 60% of an administered dose is excreted unchanged in 24 hours. The high bioavailability associated with generally low inter-subject variation in blood levels is attributable primarily to low first-pass metabolism. Only one metabolite has been identified in humans - the product of oxidative dealkylation of the terminal carboxymethyl group. The antihistaminic activity of this metabolite is negligible.

Elimination: After administration of the REACTINE COMPLETE Tablet, the mean elimination half-life of cetirizine was 7.9 hours and the mean elimination half-life of pseudoephedrine was 6.0 hours.

In contrast to other known antihistamines, cetirizine hydrochloride is less extensively metabolized, and approximately 60% of an administered dose is excreted unchanged in urine. This results in high bioavailability with low inter- or intrasubject variation in blood levels. A study using 14C-labelled cetirizine hydrochloride showed that most of the plasma radioactivity is associated with the parent compound. Only one metabolite has been identified in man, the product of oxidative dealkylation of the terminal carboxymethyl group. The antihistaminic activity of this metabolite is negligible.

The total body clearance of cetirizine hydrochloride is reduced in subjects with renal dysfunction, but below a creatinine clearance of about 30-50 mL/min, little further change occurs. Plasma levels of cetirizine hydrochloride are essentially unaffected by hemodialysis, and the plasma elimination half-life in dialysis patients is approximately 20 hours. The plasma AUC is increased about threefold in these patients.

The clearance of cetirizine hydrochloride is reduced in elderly patients, but only in proportion to the decrease in creatinine clearance. Thus, in 16 patients with a mean age of 77 years, half-life increased to 12 hours. Cetirizine hydrochloride blood levels were monitored in a clinical trial of 59 patients aged 60 to 82, who received 10 mg of cetirizine hydrochloride daily for 3 weeks and no undue accumulation of cetirizine hydrochloride was found.

The AUC and Cmax, in pediatric subjects who are administered the same doses as adults, are higher than in adults, in proportion to their lower body weights; however, the weight-normalized total body clearance is also increased at the same time and elimination half-life is reduced to 5.6 hours.

Pseudoephedrine is rapidly and almost completely absorbed from the gastrointestinal tract. The drug

is distributed to body tissues and fluids, including fetal tissue, breast milk and the central nervous system. Considerable variation in elimination half-life has been observed (from about 4.5 to 10 hours), which is attributed to individual differences in absorption and excretion. Excretion rates are also altered by urine pH, increasing with acidification and decreasing with alkalinization. Pseudoephedrine hydrochloride is incompletely metabolized (less than 1%) in the liver by N-demethylation to an inactive metabolite. The drug and its metabolite are excreted in urine; 55-96% of a dose is excreted unchanged.

Special Populations and Conditions

Hepatic Insufficiency/Renal Insufficiency: In patients with mild to moderate hepatic and renal impairment, total body clearance of cetirizine hydrochloride is reduced and AUC and half-life increased by about 2 to 3 fold. Clearance is reduced in proportion to the decline in creatinine clearance. Plasma levels are unaffected by hemodialysis. The plasma elimination half-life in dialysis patients is approximately 20 hours and the plasma AUC is increased by about threefold.

11 STORAGE, STABILITY AND DISPOSAL

Recommended storage: Store between 15°C - 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Cetirizine hydrochloride

Proper name:

- cetirizine hydrochloride

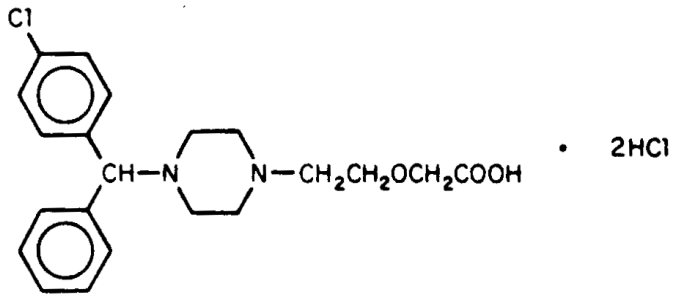
Chemical name:

- (R,S) - 2-(2-(4-((4-chlorophenyl) phenylmethyl)-1-piperazinyl) ethoxy) acetic acid, dihydrochloride

Molecular formula and molecular mass:

- $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$
- 461.8

Structural formula:



Physicochemical properties:

- Cetirizine hydrochloride is a white or practically white powder. It is freely soluble in water and practically insoluble in chloroform and acetone.

Pseudoephedrine hydrochloride

Proper name:

- pseudoephedrine hydrochloride

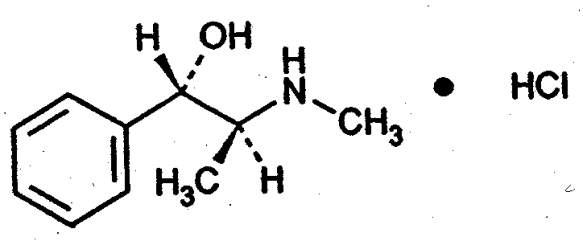
Chemical name:

- (1S.2S)-2-methylamino-1-phenyl-1-propanol hydrochloride

Molecular formula and molecular mass:

- $C_{10}H_{15}NO \cdot HCl$
- 201.70

Structural formula:



Physicochemical properties:

- Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor and a melting point range of 182 - 186 °C. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Randomized, multi-centre, double-blind, placebo-controlled clinical trials have demonstrated the effectiveness of cetirizine hydrochloride in relieving the symptoms associated with seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria. The clinical trials have shown only weak anticholinergic effects. There is no evidence that tolerance to the antihistaminic effects of cetirizine hydrochloride occurs or that cetirizine hydrochloride has any abuse potential or dependency liability.

In adults, objective measurements to evaluate the effects of cetirizine hydrochloride on the central nervous system (CNS) at doses up to 20 mg showed no significant effects on daytime drowsiness, reaction times, mental alertness, objective CNS depression and various other tests of cognitive function as compared to placebo.

Specific electrocardiographic (ECG) studies in healthy adult volunteers at doses up to 60 mg per day (three times the maximum clinically studied dose) for 1 week did not prolong QTc intervals and there was no evidence of QTc prolongation in clinical trials which included ECG evaluations.

Cetirizine given at the maximum clinically studied dose of 20 mg daily did not prolong the QTc when given in combination with either ketoconazole 400 mg o.d. or erythromycin 500 mg q8h for 10 days. Moreover, cetirizine did not significantly alter the pharmacokinetics of either ketoconazole or erythromycin nor were the pharmacokinetics of cetirizine altered by either ketoconazole or erythromycin.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity Studies

Cetirizine Hydrochloride

1. Rodents

Cetirizine hydrochloride was administered orally or intravenously to 10 fasted animals/sex/dose level. Clinical signs, food consumption, and mortality were observed for 14 days; body weights were recorded at 1 and 2 weeks, and all animals were necropsied. Results revealed no differences in clinical signs nor lethality for either sex. The oral non-lethal dose for the most sensitive sex was 250 times the expected maximal clinical dose (EMCD) of 0.4 mg/kg (20 mg/50 kg). The severity of symptoms was dose related. The main symptoms were dose related. The main symptoms were cyanosis and dyspnea. Following oral administration in rats, mortalities occurred within 24 hours; after IV administration, all deaths occurred within 10 minutes and survivors recovered within 1-3 hours. In mice, mortalities were seen in the first 3 days after oral and within 24 hours in most cases after IV administration.

The results of the rodent acute toxicity studies are summarized in Table 3.

TABLE 3

		Maximum Non-Lethal Dose mg/kg		**LD_{50} (95% Confidence Limits)**		**LD_{50}**
Species	**Sex**	**PO**	**IV**	**PO**	**IV**	**PO/IV**
Rats	M	237237	ND*	703 (305-1175)	66 (58-96)	10.65
(Wistar)	F		42	865 (553-1353)	70 (61-82)	12.36
Mice	M	237100	240240	600 (375-1391)	336 (301-476)	1.79
(NMRI)	F			752 (432-5114)	301 (264-366)	2.50

* ND = Not determined.

2. Dogs

Cetirizine hydrochloride was administered orally to groups of 2 fasted beagle dogs (1M; 1F) at doses of 40, 80, 160, or 320 mg/kg and IV in the cephalic vein at a dose of 70 mg/kg to 2 fasted beagle dogs (1M;

1F) and 125 mg/kg to 1 fasted female beagle dog. Clinical signs, food consumption, and mortality were observed daily for 14 days.

Oral: No symptoms were observed at 40 mg/kg; at 80 mg/kg an increase of heart rate was seen; at higher doses vomiting was observed; in this study the non-lethal oral dose was approximately 320 mg/kg, 800 times the EMCD.

IV: At 70 mg/kg salivation and hematuria were observed; at 125 mg/kg the treated male died, thus the maximum non-lethal IV dose in these conditions, was 70 mg/kg, 175 times the EMCD.

Administration of cetirizine pediatric solution and the corresponding vehicle to Beagle dogs at a single dose of 20 mg/kg produced no significant signs of toxicity.

Pseudoephedrine Hydrochloride

Mice injected with toxic doses of pseudoephedrine manifest increased motor activity, penile erection, mydriasis, and eventually die in respiratory exhaustion. The intravenous LD_{50} in mice is approximately 90 mg/kg. The intravenous minimum lethal dose (MLD) of pseudoephedrine in rabbits is 75 mg/kg, compared to 60 mg/kg for ephedrine. The subcutaneous MLD for pseudoephedrine in rabbits is 500 mg/kg.

The approximate oral LD_{50} values for several species are 726 mg/kg (mouse), 2,206 mg/kg (rat), 1,117 mg/kg (rabbit), 105 mg/kg (beagle dog) and 307 mg/kg (mongrel dog). Toxic effects in these species include decreased respiratory activity, salivation and lacrimation, loss of pupillary reflex reaction to light, tremor, convulsions and cardiac arrhythmias.

CHRONIC TOXICITY STUDIES

1. Fifteen-day Study in Mice

Fifteen-day oral studies comparing gavage dosing with diet dosing in mice (6/sex/level) at dose levels of 5, 10, 20, 40, 80, or 160 mg/kg/day revealed that similar hepatic findings, consisting of increased liver weights and periacinar hepatocytic hypertrophy, were induced by both routes of administration. The findings were similar in character, incidence and severity. Periacinar hepatocytic steatosis occurred in only 3 mice (2 male, 1 female) at 160 mg/kg by gavage dosing.

2. Four-Week Study in Mice

Dietary administration of REACTINE (cetirizine hydrochloride) to mice (16/sex/level) at dose levels of 1, 3, 9, 27 or 81 mg/kg/day for 4 weeks resulted in hepatic changes which were more pronounced in males than in female mice. In males, treatment resulted in minimal to moderate centrilobular hepatic hypertrophy at dose levels of 3 mg/kg or greater.

In females, treatment resulted in microsomal enzyme induction at dose levels of 9 mg/kg or greater, and elevated serum triglyceride levels at 27 and 81 mg/kg. Increased liver weights, hepatic hypertrophy and/or steatosis did not occur in female mice.

Electron microscopical examination of the livers of male mice revealed a moderate or minimal proliferation of smooth endoplasmic reticulum and apparent relative decrease in the amount of rough endoplasmic reticulum in centrilobular hepatocytes in all male mice receiving 27 mg/kg/day. Smooth endoplasmic reticulum proliferation was also present in 5/10 male mice receiving 9 mg/kg/day.

3. Four-Week Reversibility Study in Mice

In order to determine the reversibility of the hepatic changes in mice, REACTINE (cetirizine hydrochloride) was administered to male and female mice (36/sex/level) by dietary admixture at dose levels of 40, or 160 mg/kg/day for 4 weeks followed by recovery periods of 4 and 13 weeks. After 4 weeks of REACTINE (cetirizine hydrochloride) treatment, hepatic and/or hepatic-related changes similar to those observed in previously conducted mouse toxicity studies were induced.

Following the 4-week recovery period, the serum biochemical parameters, hepatic lipid levels, microsomal drug metabolizing enzyme activities, and liver electron microscopic results were essentially similar to controls. Although still evident at this time period, the increased liver weights, as well as the macroscopic and microscopic liver findings indicated a trend towards reversibility. By 13 weeks of recovery, the hepatic changes were no longer apparent.

4. Fifteen-day Study in Rats

Fifteen-day oral studies comparing gavage dosing with diet dosing in rats (6/sex/level) at dose levels of 5, 10, 20, 40, 80, or 160 mg/kg/day revealed that hepatic changes, consisting of liver weight increases, periacinar hepatocytic hypertrophy and large droplet hepatic steatosis, were induced by both routes of administration. However, the findings occurred more frequently and tended to be more severe with dietary dosing.

5. One-Month Gavage Study in Rats

In a preliminary study to investigate target organ toxicity, REACTINE (cetirizine hydrochloride) was administered to rats (10/sex/level) by oral gavage for 1 month at dose levels of 25, 75, and 225 mg/kg/day. At 225 mg/kg, treatment was associated with increased serum alpha-2-globulin values and increased liver weights in male and female, increased serum cholesterol values in female rats, and hepatic steatosis and necrosis in all 10 male rats. Hepatic steatosis and necrosis were also reported in 3 male rats at 75 mg/kg. There were no significant treatment-related elevations in serum enzyme levels in male rats, including alkaline phosphatase, LDH, ASAT, ALAT, and sorbitol dehydrogenase (SDH). All H&E and Oil Red O stained liver sections from male and female animals were re-evaluated. Results indicate midzonal and/or centrilobular hepatic hypertrophy in male and female rats at 75 and 225 mg/kg; hepatic steatosis in 2 males at 75 mg/kg and 10 males and 1 female rat at 225 mg/kg, and an area of centrilobular necrosis in one lobe from 1 male rat at 225 mg/kg. Centrilobular necrosis was not evident in male animals at the mid-dose or in 9/10 male rats at the high-dose.

6. Four-Week Diet Study in Rats

Dietary administration of REACTINE (cetirizine hydrochloride) to rats (16/sex/level) at dose levels of 2, 6, 18, 54, or 160 mg/kg/day for 4 weeks resulted in hepatic changes which, as in oral gavage studies, were more pronounced in males than in females. At 54 and 160 mg/kg, increased liver weights were reported in male rats, and centrilobular hepatic hypertrophy, microsomal enzyme induction, and mid-zonal/centrilobular hepatic steatosis were observed in male and female rats. Other findings included lower food consumption for females at 18 (94.3%), 54 (94.7%) and 160 (92.1%) mg/kg, and lower body weight gains in male and female rats at 160 mg/kg. A slight increase in erythropoietic activity in the spleen, characterized by increases in erythrocytic parameters and white blood cells, increased spleen weights, and a minimally increased cellularity of the splenic red pulp, was observed in male treated rats, particularly at 54 or 160 mg/kg. However, there were no associated microscopic bone marrow changes.

7. Four-Week Reversibility Study in Rats

In order to determine the reversibility of the hepatic changes in rats, REACTINE (cetirizine hydrochloride) was administered to male and female rats (30/sex/level) by dietary admixture at dose levels of 40, or 160 mg/kg/day for 4 weeks followed by recovery periods of 4 and 13 weeks. After 4 weeks of REACTINE (cetirizine hydrochloride) treatment, hepatic and/or hepatic-related changes similar to those observed in previously conducted rat toxicity studies were induced. Following the 4-week recovery period, serum biochemical parameters, hepatic lipid levels, microsomal drug metabolizing enzyme activities, liver weights, liver electron microscopic findings, and hepatic macroscopic and microscopic findings were similar to controls, indicating a reversibility of all observed liver and liver-related effects.

8. Six-Month Gavage Study in Rats

Oral administration of REACTINE (cetirizine hydrochloride) to rats (25/sex/level) by gavage at dose levels of 8, 25, or 75 mg/kg/day for 6 months produced hepatic changes consisting of hypertrophy, increased liver weights, altered serum biochemical values (after 3 months treatment) and steatosis. The modifications were less pronounced after 6 months than at 3 months and males were affected to a greater extent than females.

At the 3-month interim sacrifice, hepatic hypertrophy was observed in both sexes at all treatment levels. The degree was dose-related, ranging from minimal to moderate. Increased liver weights were reported in males at 75 mg/kg and in females at 25 and 75 mg/kg. Minimal to slight hepatic steatosis was observed in 1 male at 25 mg/kg and in 3 males and 1 female at 75 mg/kg. The steatosis was associated with slightly reduced serum triglyceride levels at 75 mg/kg. Serum SDH levels were elevated in males at all treatment levels and in females at 75 mg/kg.

After 6 months treatment, the incidence of hepatic hypertrophy was lower than reported at 3 months, and the incidence of hepatic steatosis was similar to 3-month results. Results of electron microscopic examination of livers from several control and high-dose treated animals revealed definite smooth endoplasmic reticulum (SER) proliferation in male treated rats and a slight SER proliferation in 1 female treated rat.

9. One-Month Study in Dogs

REACTINE (cetirizine hydrochloride) was administered orally (capsules) to beagle dogs (3/sex/level) at dosage levels of 15, 45 or 135 mg/kg/day for 1 month. At 15 and 45 mg/kg, REACTINE (cetirizine hydrochloride) was well tolerated with only an increased incidence of vomiting, 2.5% and 7.1%, respectively, above control incidence (0.6%) reported. At 135 mg/kg, treatment resulted in an increased incidence of vomiting (17.2%); body tremor; salivation; ataxia; body weight loss and reduced food intake in 2 female dogs at the end of the treatment period; decreased mean urine specific gravity associated with an increased urine volume; a slight increase in mean serum alkaline phosphatase and a slight increase in alpha-2-globulins for females at 4 weeks. Histopathological examination of tissues from all dogs on study revealed no treatment-related alterations.

Oral administration of cetirizine pediatric syrup for 4 weeks to groups of 6 immature male and female Beagle dogs at dose levels of 0.5 mg/kg/day and 5.0 mg/kg/day did not reveal any toxic effect in terms of clinical signs, physical and ophthalmoscopic observations, electrocardiograms, body weights, food consumption, clinical laboratory studies and results of gross and microscopic post-mortem examinations.

10. Six-Month Study in Dogs

In a 6-month study (with a 3-month interim sacrifice), REACTINE (cetirizine hydrochloride) was administered orally (capsules) to beagle dogs (5/sex/level) at dosage levels of 8, 25, or 75 mg/kg/day. At 8 mg/kg for 6 months, 20 times the EMCD, REACTINE (cetirizine hydrochloride) administration was well tolerated with only a very slight increased incidence of vomiting (0.8%) over control incidence (0.3%) reported. At 25 and 75 mg/kg, 62.5 and 187.5 times the EMCD, REACTINE (cetirizine hydrochloride) treatment resulted in an increased incidence of vomiting, 1.6% and 4.0% respectively, and decreased body weight gains in female dogs, 27% and 47% respectively, after 27 weeks of treatment. In addition, at 75 mg/kg, 1 male dog died and a 2nd male dog became moribund and was sacrificed during the study. Histopathological examination of tissues did not reveal any treatment-related lesions.

11. Two-Week Study in Monkeys

In a 2-week duration study, REACTINE (cetirizine hydrochloride) was administered by oral gavage to cynomolgus monkeys (1/sex/level) at dose levels of 50, 100, or 200 mg/kg/day. At 200 mg/kg, vomiting, salivation, and other signs indicative of a debilitating condition were reported. Both monkeys at this level exhibited a progressive loss in body weight and a marked reduction in food consumption during the treatment period. One monkey each at 50 (124 g) and 100 mg/kg (183 g) also exhibited a body weight loss during the treatment period. Histopathological examinations revealed minimal to moderate fatty infiltration in centrilobular hepatocytes from both monkeys at 200 mg/kg.

12. Four-Week Study in Monkeys

In a 4-week study, REACTINE (cetirizine hydrochloride) was administered by oral gavage to cynomolgus monkeys (3/sex/level) at doses of 17, 50 or 150 mg/kg/day. Vomiting, huddled posture, poor coat condition, limb tremors, abnormal scratching motions and a reduced body temperature were observed in animals treated at 150 mg/kg. One female monkey at 150 mg/kg became moribund and was sacrificed on day 22 of dosing. This animal exhibited a debilitated body condition; a marked reduction in food consumption, an overall body weight loss of 622 g; elevated serum urea, GPT and GOT levels with decreased serum calcium and triglycerides, and a slow heart rate with sinus arrhythmia noted from an ECG recording made immediately prior to sacrifice. No treatment-related microscopic findings were reported. Marked body weight losses were recorded for the majority of monkeys at 150 mg/kg. Results of laboratory investigations performed during week 4 revealed decreased Ornithine Carbomoyltransferase (OCT) and SDH levels for the groups receiving 50 or 150 mg/kg, and increased triglyceride levels for the group receiving 150 mg/kg. No changes in the activities of measured hepatic microsomal enzymes were detected and no treatment-related microscopic abnormalities were observed.

13. One-Year Study in Dogs

The oral (capsule) administration of REACTINE (cetirizine hydrochloride) to beagle dogs (5/sex/level) at dose levels of 4, 15, or 60 mg/kg/day for 52 weeks was well tolerated and did not produce any significant toxicological findings. A dose-related increased incidence of vomiting, up to 6.3% at 60 mg/kg, within 1-hour of dose administration occurred in all treatment groups. There were no other treatment-related clinical signs. At necropsy, hepatic drug metabolizing enzyme activities were evaluated for each dog. REACTINE (cetirizine hydrochloride), at dose levels up to 60 mg/kg/day, did not cause any induction of hepatic microsomal drug metabolizing enzymes, microsomal protein levels, or cytochrome P-450.

14. One-Year Study in Monkeys

The oral (gavage) administration of REACTINE (cetirizine hydrochloride) to cynomolgus monkeys (5/sex/level) at dose levels of 5, 15 or 45 mg/kg/day for 52 weeks was well tolerated and did not produce any significant toxicological findings. A dose-related increased incidence of salivation at or just after dose administration was reported in all dose groups. At necropsy, hepatic drug metabolizing enzyme activities were evaluated for each monkey. REACTINE (cetirizine hydrochloride), at dose levels up to 45 mg/kg/day, did not cause any induction of hepatic microsomal drug metabolizing enzymes, microsomal protein levels, or cytochrome P-450.

CARCINOGENICITY

1. Two-Year Cetirizine Hydrochloride Study in Mice

Dietary administration of REACTINE (cetirizine hydrochloride) to mice (52/sex/level) at dose levels of 1, 4, or 16 mg/kg/day for 104 weeks, produced no evidence of a carcinogenic potential at doses 40 times the maximum clinically studied human daily dose (20 mg).

2. Two-Year Cetirizine Hydrochloride Study in Rats

Dietary administration of REACTINE (cetirizine hydrochloride) to rats (50/sex/level) at dose levels of 3, 8, or 20 mg/kg/day for 104 weeks produced no evidence of a carcinogenic potential at doses 50 times higher than the maximum clinically studied human daily dose.

Non-neoplastic treatment-related microscopic findings consisted of a tendency towards an increased incidence of centrilobular vacuolation and fat deposition in the liver in male rats at 8 and 20 mg/kg, and of a slight, not dose-related, increased incidence of ulceration of the non-glandular stomach in female rats.

3. Two-Year Pseudoephedrine Studies in Rats and Mice

Two-year studies in rats and mice under the auspices of the US National Toxicology Program 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).

MUTAGENICITY

The mutagenic potential of REACTINE (cetirizine hydrochloride) was assessed in *in vitro* non-mammalian cell systems as well as in *in vitro* and *in vivo* mammalian cell systems. REACTINE (cetirizine hydrochloride) was not mutagenic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Cetirizine Hydrochloride

1. Reproduction and Fertility Study in Mice

REACTINE (cetirizine hydrochloride) dissolved in distilled water, was administered by oral gavage at dose levels of 0, 4, 16 and 64 mg/kg/day to groups of 20 male and 40 female COBS CD-1 mice, in a reproduction and fertility study. There were no effects on male and female fertility or reproductive performance, or on pup development through 2 generations at oral doses up to 16 mg/kg, 40 times the expected maximum clinical dose (EMCD) of 20 mg.

2. **Teratology**

a. Teratology Study in Mice: REACTINE (cetirizine hydrochloride) was administered by oral gavage at dose levels of 6, 24, and 96 mg/kg/day to groups of 30 time-mated COBS CD-1 female mice from day 6 to day 15 of gestation. REACTINE (cetirizine hydrochloride) at dose levels up to 96 mg/kg/day from gestation days 6 through 15 was not embryo-feto- toxic nor teratogenic.

b. Teratology Study in Rats: REACTINE (cetirizine hydrochloride), administered by oral gavage at dose levels of 8, 25, 75 and 225 mg/kg/day to mated Sprague Dawley female rats (25/level at 8 and 25 mg/kg; 26/level at 75 and 225 mg/kg; 26 in the control group) from day 6 to day 15 of gestation, was not teratogenic. The incidence of the major malformations was not dose-related and the 2 fetuses exhibiting these malformations were both runts, 1 at 8 mg/kg (agnathia with displacement of the eyes and ears and left microphthalmia) and 1 at 225 mg/kg (left microphthalmia). Although the limited in-house historical data on this species of rat (1225-2800 fetuses) did not report agnathia or microphthalmia (Report No. T-27), these types of malformations have been reported at a low incidence in control data for Charles River CD rats (Report No. T-28). The no-effect level for maternal toxicity was 25 mg/kg, and the no-effect level for embryo-feto-toxicity, although not clearly established, was approximately 8 mg/kg.

At 8 mg/kg, the incidence of reduced ossification of parietal, interparietal, and hyoid cranial bones was slightly higher than control incidence, but, considered to be within normal variability.

c. Teratology Study in Rabbits: REACTINE (cetirizine hydrochloride), administered by oral gavage at dose levels of 15, 45, and 135 mg/kg/day to mated New Zealand White female rabbits (16/level at 15 and 45 mg/kg; 18/level at 135 mg/kg; 17 in the control group) from day 6 to day 18 of gestation was not teratogenic. The no-effect level for maternal toxicity and embryo-feto-toxicity was 15 mg/kg, 37.5 times the EMCD. At 15 mg/kg, maternal body weight gain was slightly decreased during the post-treatment period.

d. Conclusion: The above described anomalies, irregularly found in all REACTINE (cetirizine hydrochloride) treated groups, did not occur in a dose-related fashion; moreover, these sorts of anomalies are known to occur spontaneously in untreated animal populations. In addition, many of the anomalies observed occurred in small fetuses, and at doses associated with maternal toxicity. Consequently a definitive causal relationship with REACTINE (cetirizine hydrochloride) cannot be ruled out.

3. **Peri- and Post-Natal Development Study in Mice**

REACTINE (cetirizine hydrochloride) was administered by oral gavage to groups of 32 time-mated COBS CD-1 female mice at dose levels of 0, 6, 24 or 96 mg/kg/day from day 15 of gestation and continued up to sacrifice of the dams on, or shortly after, day 21 post partum (weaning). REACTINE (cetirizine hydrochloride), at dose levels of 6 and 24 mg/kg/day, up to 60 times the EMCD, from day 15 of gestation to weaning of pups, did not produce any adverse effect on perinatal conditions or progeny development. At 96 mg/kg, REACTINE (cetirizine hydrochloride) treatment was associated with slight maternal effects and lower mean pup weights after birth, at 4 to 21 days of lactation.

Cetirizine/Pseudoephedrine Combination

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.

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).

TOXICOLOGY SUMMARY

The principle findings in rodent subchronic oral toxicity studies were related to the liver and consisted of hypertrophy of hepatocytes, proliferation of smooth endoplasmic reticulum (SER), microsomal enzyme induction, increased liver weights, hepatic steatosis, hepatic necrosis, elevated or reduced serum triglyceride levels, and increased serum GPT, OCT and SDH values. Of these findings, the SER proliferation associated with microsomal enzyme induction and hepatic hypertrophy followed by increased liver weights are probably pharmacological responses to REACTINE (cetirizine hydrochloride) treatment rather than toxicological. The hepatotoxic findings consisting of hepatic steatosis and necrosis, and altered biochemical parameters appear to be related to the marked hepatic metabolism of REACTINE (cetirizine hydrochloride) in rodents. Significant safety margins, calculated for rodent hepatotoxicity, ranged from 20 to greater than 370 times the expected maximum human clinical dose (EMCD) of 20 mg depending on species, route of administration, and duration of treatment.

Similar liver-related findings were not evident in dogs receiving REACTINE (cetirizine hydrochloride) orally for 1 month at doses up to 338 times the EMCD or for 6 months and 1 year respectively at doses up to 188 and 150 times the EMCD, nor were liver-related changes observed in cynomolgus monkeys receiving REACTINE (cetirizine hydrochloride) for 1 month and 1 year respectively at doses up to 375 and 112.5 times the EMCD.

The dietary administration of REACTINE (cetirizine hydrochloride) to mice at doses up to 16 mg/kg/day, 40 times the EMCD, and to rats at doses up to 20 mg/kg/day, 50 times the EMCD, for 104 weeks showed no indications of carcinogenic potential.

Recent re-analysis of the data demonstrated that no adverse effects on embryo-fetal viability, body weight or morphology were produced by maternally toxic dosages in development toxicity (Segment II) studies in the rat (225 mg/kg/day, 563 times the maximum clinically studied human dose), rabbit (135 mg/kg/day, 338 times the maximum clinically studied human dose) and mouse (96 mg/kg/day, 240 times the maximum clinically study human dose.)

Cetirizine is a major human metabolite of hydroxyzine (50 mg hydroxyzine = 20 mg cetirizine). Thus, the long-term experience with hydroxyzine also provides an indication of the safety of cetirizine in pregnancy. During 30 years of clinical use, hydroxyzine has not been associated with an increase of any human congenital malformation above the expected background incidence. Thus, human exposure to cetirizine has occurred for more than 30 years without any indication that it or its parent compound, hydroxyzine, is a human teratogen. The effect of hydroxyzine on human pregnancies have been studied in a large epidemiology study [the Collaborative Perinatal Project (Heinonen, et al., 1977)]. The study did not report any increase in human congenital malformation as a consequence of the use of hydroxyzine.

The only other reported effect of hydroxyzine on pregnancy in a laboratory species was abortion in rhesus monkeys at dosages of 5 to 12 mg/kg. Steffek, et al. (1968), identified three abortions and 2 normal offspring produced after administration of 5 to 12 mg/kg dosages during organogenesis. The rhesus monkey is known to have a high incidence of abortion. The absence of expected control procedures in this old study, and the use of only 5 animals precludes drawing a causal relationship of this observation with hydroxyzine.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

REACTINE® COMPLETE
Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

Read this carefully before you start taking **REACTINE® COMPLETE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **REACTINE® COMPLETE**.

What is REACTINE® COMPLETE used for?

REACTINE® COMPLETE is indicated for the fast, long lasting relief of itchy watery eyes, sneezing, runny nose and nasal congestion caused by seasonal allergies (hay fever, trees, grass, pollen and ragweed) and perennial allergies (dust mites, animal dander and molds).

How does REACTINE® COMPLETE work?

Your allergy symptoms are simply your body's overreaction in trying to protect you from allergens such as dust, ragweed, grass and tree pollen, animal dander or mold. When allergens are detected, your body rushes a substance called histamine to histamine receptor sites in your skin and tissues. The resulting reaction causes itchy, watery eyes, sneezing and runny nose. REACTINE® (cetirizine hydrochloride) helps relieve your allergy symptoms by blocking these receptor sites before histamine binds there. The pseudoephedrine component of REACTINE® COMPLETE is recognized as an effective agent for the relief of nasal congestion caused by your allergies.

What are the ingredients in REACTINE® COMPLETE?

Medicinal ingredients: 5 mg cetirizine hydrochloride, 120 mg pseudoephedrine hydrochloride.

Non-medicinal ingredients: Croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

REACTINE® COMPLETE comes in the following dosage forms:

Tablets containing 5 mg cetirizine hydrochloride in an immediate release layer and, 120 mg pseudoephedrine hydrochloride in an extended release layer.

Do not use REACTINE® COMPLETE if:

- you are allergic to cetirizine hydrochloride, to its parent compound, hydroxyzine, or to piperazine derivatives
- you have a known hypersensitivity or history of unusual reactions to pseudoephedrine hydrochloride, to other stimulants, or to any of the ingredients in the formulation or components of the container
- you have any of the following conditions: glaucoma, problems urinating, if you are taking some antidepressant medications, or within 14 days of stopping such treatment
- you have high blood pressure, heart disease, problems with blood circulation, or an overactive thyroid gland
- in children under 12 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REACTINE® COMPLETE. Talk about any health conditions or problems you may have, including if you:

- have or have had narrow-angle glaucoma
- have or have had urinary retention due to prostate gland enlargement
- have or have had severe hypertension (high blood pressure)
- have or have had severe coronary artery disease (heart disease)
- have or have had thyroid disease
- have or have had diabetes
- are receiving a Monoamine oxidase (MAO) inhibitor or within 14 days of stopping such treatment
- are taking any prescription drugs, non-prescription drugs, or natural health products
- are pregnant or breast feeding
- have liver or kidney disease

Other warnings you should know about:

- If signs and symptoms such as formation of small pimples occur, with or without fever or redness, then treatment with REACTINE® COMPLETE should be discontinued and a doctor should be consulted
- Some people can experience drowsiness due to allergies or antihistamine use. If drowsiness does occur, do not drive or operate machinery.
- If symptoms persist or worsen, or if new symptoms occur, stop use and consult a doctor

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with REACTINE® COMPLETE:

Do not use REACTINE® COMPLETE with sedating substances such as alcohol and some other medications, including: anti-anxiety medications, sleep aids, antihistamines, antidepressants, muscle relaxants, or prescription analgesics. **Drugs that may interact with pseudoephedrine include:** Monoamine oxidase (MAO) inhibitors, methyldopa, mecamylamine, guanethidine, reserpine, veratrum alkaloids, beta-adrenergic blocking agents, digitalis, furazolidone, other sympathomimetic amines, antacids and kaolin.

How to take REACTINE® COMPLETE:

Do not exceed recommended dosage unless directed by a doctor. The tablets should be swallowed with liquid and should not be divided, chewed or crushed. May be taken with or without food. Prolonged use only as directed by a doctor.

Usual dose:

Adults and children 12 years of age and over: The recommended dose of REACTINE® COMPLETE is one tablet every 12 hours.

Adults 65 years of age and over and in patients with moderate liver and/or kidney disease: A dose of one tablet once daily is recommended.

Overdose:

Acute overdosage with REACTINE® COMPLETE may produce abnormally rapid beating of the heart, other abnormal heartbeat, high blood pressure, signs of CNS depression (for example: sleepiness, breathing disturbances, unconsciousness, bluish colouration of the skin or mucous membranes, and cardiovascular collapse) or stimulation (insomnia, hallucinations, tremor, seizures), which could be fatal.

If you think you, or a person you are caring for, have taken too much REACTINE® COMPLETE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Treatment in a hospital setting is preferred. Notify of any other medications you may have been taking. If emergency help is not available, vomiting should be induced at once by Syrup of Ipecac. VOMITING SHOULD NEVER BE INDUCED IN UNCONSCIOUS INDIVIDUALS OR IN CHILDREN UNDER 1 YEAR WITHOUT MEDICAL HELP.

Missed Dose:

If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time. Do not exceed the maximum daily dose.

What are possible side effects from using REACTINE® COMPLETE?

These are not all the possible side effects you may have when taking REACTINE® COMPLETE. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects associated with cetirizine hydrochloride use are headache, sleepiness and dry mouth. If these side effects do not go away, call your doctor or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Restlessness with increased body movement			√
Difficulty urinating			√
New rash or itching after stopping drug			√
Liver dysfunction (inflammation of the liver, appearance of jaundice, i.e. yellowing of the skin)			√

The following side effects have been reported very rarely: aggression, agitation, hallucination, memory

impairment/ amnesia, insomnia, dizziness, loss of taste, erectile dysfunction, eye pain or swelling and blurred vision.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at temperatures between 15°C and 30°C. Keep out of reach and sight of children.

If you want more information about REACTINE® COMPLETE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://www.reactine.ca, or by calling 1-877-322-8463.

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