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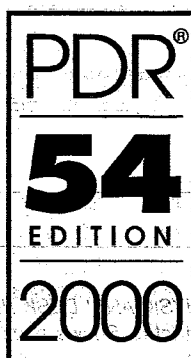
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DESK

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REFERENCE®

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# PHYSICIANS' DESK REFERENCE®

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Printed on recycled paper

ISBN: 1-56363-330-2

# 1772 CARDIZEM® Tablets, 60 mg (diltiazem hydrochloride)

ALLEGRA® 60-mg capsules are imprinted in black ink, with "60 mg" on the cap and "1102" on the body, or "allegra" on the cap and "60 mg" on the body.

ALLEGRA-D® extended-release tablets are engraved with "Allegra-D".

AMARYL® (glimepiride) Tablets 1 mg, 2 mg, and 4 mg are imprinted with "AMARYL" on one side and the Hoechst logo on both sides of the bisect on the other side.

ANZEMET® 50 mg tablets are imprinted with "ANZEMET 50" on one side.

ANZEMET® 100 mg tablets are imprinted with "100" on one side and "ANZEMET" on the other.

ARAVA™ (leflunomide) Tablets, 10 mg, are embossed with "ZBN" on one side.

ARAVA™ Tablets, 20 mg, are embossed with "ZBO" on one side.

ARAVA™ Tablets, 100 mg, are embossed with "ZBP" on one side.

BENTYL® Capsules, 10 mg (dicyclomine hydrochloride USP) is imprinted BENTYL 10.

BENTYL® Tablets, 20 mg (dicyclomine hydrochloride USP) is debossed BENTYL 20.

CANTIL® Tablets, 25 mg (mepenzolate bromide USP) is debossed MERRELL 37.

CARAFATE® Tablets, 1 g (sucralfate) is identified by the brand name CARAFATE embossed on one side and 1712 on the reverse side.

CARDIZEM® Tablets, 90 mg (diltiazem hydrochloride) is imprinted with the brand name CARDIZEM on one side and 90 mg on the reverse side.

CARDIZEM® Tablets, 120 mg (diltiazem hydrochloride) is imprinted with the brand name CARDIZEM on one side and 120 mg on the reverse side.

CARDIZEM® SR Capsules, 60 mg (diltiazem hydrochloride) is imprinted with the Cardizem logo on one end and Cardizem SR 60 mg on the other.

CARDIZEM® SR Capsules, 90 mg (diltiazem hydrochloride) is imprinted with the Cardizem logo on one end and Cardizem SR 90 mg on the other.

CARDIZEM® SR Capsules, 120 mg (diltiazem hydrochloride) is imprinted with the Cardizem logo on one end and Cardizem SR 120 mg on the other.

CARDIZEM® CD Capsules, 120 mg (diltiazem hydrochloride) is imprinted with Cardizem CD and 120 mg on one end.

CARDIZEM® CD Capsules, 180 mg (diltiazem hydrochloride) is imprinted with CARDIZEM CD and 180 mg on one end.

CARDIZEM® CD Capsules, 240 mg (diltiazem hydrochloride) is imprinted with CARDIZEM CD and 240 mg on one end.

CARDIZEM® CD Capsules, 300 mg (diltiazem hydrochloride) is imprinted with CARDIZEM CD and 300 mg on one end.

CLOMID® Tablets, 50 mg (clomiphene citrate) is debossed CLOMID 50.

DIAPETA® (glyburide) Tablets 1.25 mg, 2.5 mg, and 5 mg are imprinted with "Hoechst" on one side and "DiaP" on the other side.

RIPEX® Tablets, 1 g (methenamine hippurate) is debossed MERRELL 277.

LASIX® (furosemide) Tablets 20 mg are imprinted with "Lasix" on one side and "HOECHST" on the other.

LASIX® (furosemide) Tablets 40 mg are imprinted with "Lasix 40" on one side and the Hoechst logo on the other.

LASIX® (furosemide) Tablets 80 mg are imprinted with "Lasix 80" on one side and the Hoechst logo on the other.

NILANDRON® Tablets have a triangular logo on one face and an internal reference number (168) on the other.

NORPRAMIN® Tablets, 10 mg (desipramine hydrochloride USP) is imprinted 68-7.

NORPRAMIN® Tablets, 25 mg (desipramine hydrochloride USP) is imprinted NORPRAMIN 25.

NORPRAMIN® Tablets, 50 mg (desipramine hydrochloride USP) is imprinted NORPRAMIN 50.

NORPRAMIN® Tablets, 75 mg (desipramine hydrochloride USP) is imprinted NORPRAMIN 75.

NORPRAMIN® Tablets, 100 mg (desipramine hydrochloride USP) is imprinted NORPRAMIN 100.

NORPRAMIN® Tablets, 150 mg (desipramine hydrochloride USP) is imprinted NORPRAMIN 150.

NOVAFED® A Capsules, 120 mg pseudoephedrine hydrochloride and 8 mg chlorpheniramine maleate is imprinted NOVAFED A.

RIFADIN® Capsules, 150 mg (rifampin) is imprinted RIFADIN 150.

RIFADIN® Capsules, 300 mg (rifampin) is imprinted RIFADIN 300.

RIFAMATE® Capsules, 300 mg rifampin and 150 mg isoniazid is imprinted RIFAMATE.

RIFATER® Tablets, 120 mg rifampin, 50 mg isoniazid, and 300 mg pyrazinamide is imprinted RIFATER.

TECZEM™ extended-release tablets are coded "TECZEM 5180".

TENUATE® Tablets, 25 mg (diethylpropion hydrochloride USP) is debossed TENUATE 25.

TENUATE® DOSPAN® Controlled-Release Tablets, 75 mg (diethylpropion hydrochloride USP) is debossed TENUATE 75.

TIAMATE 120 mg extended-release tablets are coded "TIAMATE 120".

TIAMATE 180 mg extended-release tablets are coded "TIAMATE 180".

TIAMATE 240 mg extended-release tablets are coded "TIAMATE 240".

TRENTAL® (pentoxifylline) Tablets are imprinted "TRENTAL".

## ALLEGRA®

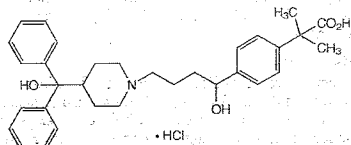
[*α*-'legra]

(fexofenadine hydrochloride) Capsules  
60 mg

Prescribing Information as of June 1998A

### DESCRIPTION

Fexofenadine hydrochloride, the active ingredient of ALLEGRA®, is a histamine H<sub>1</sub>-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]- $\alpha,\alpha$ -dimethyl benzeneacetic acid hydrochloride. It has the following chemical structure:



The molecular weight is 538.13 and the empirical formula is C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>·HCl. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

ALLEGRA is formulated as capsules for oral administration. Each capsule contains 60 mg fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H<sub>1</sub>-receptor antagonist activity. Fexofenadine inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or  $\alpha_1$ -adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

#### Pharmacokinetics

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single dose of two 60-mg capsules to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours postdose. After administration of a single 60-mg dose as an oral solution to healthy subjects, the mean plasma concentration was 209 ng/mL. Mean steady-state peak plasma concentrations of 286 ng/mL were observed when healthy volunteers were administered multiple doses of fexofenadine hydrochloride (60 mg oral solution every 12 hours for 10 doses). Fexofenadine pharmacokinetics were linear for oral doses up to 120 mg twice daily. Although the absolute bioavailability of fexofenadine hydrochloride capsules is unknown, the capsules are bioequivalent to an oral solution. The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, to steady-state in normal volunteers.

Human mass balance studies documented a recovery of approximately 80% and 11% of the [<sup>14</sup>C] fexofenadine hydrochloride dose in the feces and urine, respectively. Approximately 5% of the total dose was metabolized. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients.

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and  $\alpha_1$ -acid glycoprotein.

#### Special Populations

Special population pharmacokinetics (for age and renal and hepatic impairment), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those from normal subjects in a separate study of similar design. While subject weights were relatively uniform between studies, these special population patients were substantially older than the healthy, young volunteers. Thus, an age effect may be confounding the pharmacokinetic differences observed in some of the special populations.

**Effect of Age.** In older subjects ( $\geq 65$  years old), peak plasma levels of fexofenadine were 99% greater than those observed in normal volunteers ( $< 65$  years old). Mean elimination half-lives were similar to those observed in normal volunteers.

**Renally Impaired.** In patients with mild (creatinine clearance 41-80 mL/min) to severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance  $\leq 10$  mL/min) were 82% greater and half-life was 31% longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See DOSAGE AND ADMINISTRATION.)

**Hepatically Impaired.** The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects.

**Effect of Gender.** Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine.

#### Pharmacodynamics

**Wheal and Flare.** Human histamine skin wheal and flare studies following single and twice daily doses of 20 mg and 40 mg fexofenadine hydrochloride demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing.

**Effects on QTc.** In dogs, (10 mg/kg/day, orally for 5 days) and rabbits (10 mg/kg, intravenously over one hour) fexofenadine did not prolong QTc at plasma concentrations that were at least 28 and 63 times, respectively, the therapeutic plasma concentrations in man (based on a 60 mg twice daily fexofenadine hydrochloride dose). No effect was observed on calcium channel current, delayed K<sup>+</sup> channel current, or action potential duration in guinea pig myocytes, Na<sup>+</sup> current in rat neonatal myocytes, or on the delayed rectifier K<sup>+</sup> channel cloned from human heart at concentrations up to  $1 \times 10^{-5}$  M of fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on a 60-mg twice daily fexofenadine hydrochloride dose).

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine hydrochloride capsules in doses of 60 mg to 240 mg twice daily for two weeks or in 40 healthy volunteers given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days.

#### Clinical Studies

In three, 2-week, multi-center, randomized, double-blind, placebo-controlled trials in patients 12-68 years of age with seasonal allergic rhinitis (n=1634), fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. Statistically significant reductions in symptom scores were observed following the first 60-mg dose, with the effect maintained throughout the 12-hour interval. In general, there was no additional reduction in total symptom scores with higher doses of fexofenadine up to 240 mg twice daily. Although the number of subjects in some of the subgroups was small, there were no significant differences in the effect of fexofenadine hydrochloride across subgroups of patients defined by gender, age, and race. Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60-mg fexofenadine hydrochloride dose administered to patients with seasonal allergic rhinitis who were exposed to ragweed pollen in an environmental exposure unit.

### INDICATIONS AND USAGE

ALLEGRA is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

### CONTRAINDICATIONS

ALLEGRA is contraindicated in patients with known hypersensitivity to any of its ingredients.

### PRECAUTIONS

#### Drug Interactions

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co-administration of fexofenadine with ketoconazole and erythromycin led to increased plasma levels of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine HCl 120 mg BID (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Continued on next page

Consult 2000 PDR® supplements and future editions for revisions

**Allegra—Cont.****Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Co-Administration with Fexofenadine Hydrochloride 120 mg Every 12 Hours (twice recommended dose) in Normal Volunteers (n=24)**

Concomitant Drug	C <sub>max,ss</sub> (Peak plasma concentration)	AUC <sub>ss(0-12h)</sub> (Extent of systemic exposure)
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro*, *in situ* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. In *in vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were up to four times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

**Pregnancy**

**Teratogenic Effects: Category C.** There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose), respectively.

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nonteratogenic Effects.** Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150 mg/kg of terfenadine; at these doses the plasma AUC values of fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

**Nursing Mothers**

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of ALLEGRA in pediatric patients under the age of 12 years have not been established. Across well-controlled clinical trials in patients with seasonal allergic rhinitis, a total of 205 patients between the ages of 12 to 16 years received doses ranging from 20 mg to 240 mg twice daily for up to two weeks. Adverse events were similar in this group compared to patients above the age of 16 years.

**Geriatric Use**

In placebo-controlled trials, 42 patients, age 60 to 68 years, received doses of 20 mg to 240 mg of fexofenadine twice daily for up to two weeks. Adverse events were similar in this group to patients under age 60 years.

**ADVERSE REACTIONS**

In placebo-controlled clinical trials, which included 2461 patients receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of fexofenadine hydrochloride (60 mg twice-daily), and that were more common with fexofenadine than placebo, are listed in the following table.

**Adverse Experiences Reported in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials at Rates of Greater Than 1%**

Adverse Experience	Fexofenadine 60 mg Twice Daily (n=679)	Placebo Twice Daily (n=671)
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Adverse events occurring in greater than 1% of fexofenadine hydrochloride-treated patients (60 mg twice daily), but that were more common in the placebo-treated group, include headache and throat irritation.

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride and placebo-treated patients.

**OVERDOSAGE**

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg (6 normal volunteers at this dose level), and doses up to 690 mg twice daily for one month (3 normal volunteers at this dose level), were administered without the development of clinically significant adverse events.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine administration.

No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (170 times the maximum recommended human daily oral dose based on mg/m<sup>2</sup>) and up to 5000 mg/kg in rats (330 times the maximum recommended human daily oral dose based on mg/m<sup>2</sup>). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (450 times the maximum recommended human daily oral dose based on mg/m<sup>2</sup>).

**DOSAGE AND ADMINISTRATION**

The recommended dose of ALLEGRA is 60 mg twice daily for adults and children 12 years of age and older.

A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY.)

**HOW SUPPLIED**

ALLEGRA 60-mg capsules are available in: high-density polyethylene (HDPE) bottles of 60 (NDC 0088-1102-41); HDPE bottles of 100 (NDC 0088-1102-47); HDPE bottles of 500 (NDC 0088-1102-55); and aluminum-foil blister packs of 100 (NDC 0088-1102-49).

ALLEGRA capsules have a white opaque cap and a pink opaque body. The capsules are imprinted in black ink, with "60 mg" on the cap, and "1102" on the body or "allegra" on the cap and "60 mg" on the body.

Store ALLEGRA capsules at controlled room temperature 20°-25°C (68°-77°F). Foil-backed blister packs should be protected from excessive moisture.

Prescribing information as of June 1998A

Hoechst Marion Roussel, Inc.

Kansas City, MO 64137 USA

US Patents 4,254,129; 5,375,693; 5,578,610.

Shown in Product Identification Guide, page 316

**ALLEGRA-D®**

[α'-léggra-D]

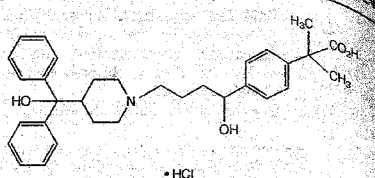
(fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg) Extended-Release Tablets

Prescribing Information as of June 1998A

**DESCRIPTION**

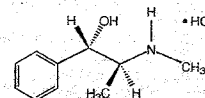
ALLEGRA-D® (fexofenadine hydrochloride and pseudoephedrine hydrochloride) Extended-Release Tablets for oral administration contain 60 mg fexofenadine hydrochloride for immediate-release and 120 mg pseudoephedrine hydrochloride for extended-release. Tablets also contain as excipients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, carnauba wax, stearic acid, silicon dioxide, hydroxypropyl methylcellulose and polyethylene glycol.

Fexofenadine hydrochloride, one of the active ingredients of ALLEGRA-D, is a histamine H<sub>1</sub>-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-(4-hydroxydiphenylmethyl)-1-piperidinyl]-butyl-α, α-dimethyl benzeneacetic acid hydrochloride and the following chemical structure: [See chemical structure at top of next column]



The molecular weight is 538.13 and the empirical formula is C<sub>28</sub>H<sub>30</sub>NO<sub>4</sub>•HCl. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

Pseudoephedrine hydrochloride, the other active ingredient of ALLEGRA-D, is an adrenergic (vasoconstrictor) agent with the chemical name [S-(R\*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride and the following chemical structure:



The molecular weight is 201.70. The molecular formula is C<sub>10</sub>H<sub>15</sub>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.

**CLINICAL PHARMACOLOGY****Mechanism of Action**

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H<sub>1</sub>-receptor antagonist activity. Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or alpha<sub>1</sub>-adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

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. At the recommended oral dose, it has little or no pressor effect in normotensive adults.

**Pharmacokinetics**

The pharmacokinetics of fexofenadine hydrochloride and pseudoephedrine hydrochloride when administered separately have been well characterized. Fexofenadine pharmacokinetics were linear for oral doses of fexofenadine hydrochloride up to 120 mg twice daily. The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg fexofenadine hydrochloride, twice daily, to steady-state in normal volunteers. Human mass balance studies documented a recovery of approximately 80% and 11% of the [<sup>14</sup>C] fexofenadine hydrochloride dose in the feces and urine, respectively. Approximately 5% of the total dose was metabolized. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component is unabsorbed drug or the result of biliary excretion. The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in healthy subjects. Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult patients. Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and α<sub>1</sub>-acid glycoprotein.

Pseudoephedrine has been shown to have a mean elimination half-life of 4-6 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8. The bioavailability of fexofenadine hydrochloride and pseudoephedrine hydrochloride from ALLEGRA-D Extended-Release Tablets is similar to that achieved with separate administration of the components. Coadministration of fexofenadine and pseudoephedrine does not significantly affect the bioavailability of either component.

Fexofenadine hydrochloride was rapidly absorbed following single-dose administration of the 60 mg fexofenadine hydrochloride/120 mg pseudoephedrine hydrochloride tablet with median time to mean maximum fexofenadine plasma concentration of 191 ng/mL occurring 2 hours postdose. Pseudoephedrine hydrochloride produced a mean single-dose pseudoephedrine peak plasma concentration of 206 ng/mL which occurred 6 hours postdose. Following multiple dosing to steady-state, a fexofenadine peak concentration of 255 ng/mL was observed 2 hours postdose. Following multiple dosing to steady-state, a pseudoephedrine peak concentration of 411 ng/mL was observed 5 hours postdose. Coadministration of ALLEGRA-D with a high-fat meal decreased fexofenadine plasma concentrations C<sub>max</sub> (-46%) and AUC (-42%). Time to maximum concentration (T<sub>max</sub>) was delayed by 50%. The rate or extent of pseudoephedrine ab-



**Zoloft—Cont.**

vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when ZOLOFT was taken alone, there were 4 deaths involving overdoses of ZOLOFT in combination with other drugs and/or alcohol. Therefore, any overdose should be treated aggressively.

**Management of Overdoses**—Establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

There are no specific antidotes for ZOLOFT.

Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

**DOSE AND ADMINISTRATION****Initial Treatment****Dosage for Adults**

**Depression and Obsessive-Compulsive Disorder**—ZOLOFT treatment should be administered at a dose of 50 mg once daily.

**Panic Disorder**—ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

While a relationship between dose and effect has not been established for depression, OCD, or panic disorder, patients were dosed in a range of 50–200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week. ZOLOFT should be administered once daily, either in the morning or evening.

**Dosage for Pediatric Population (Children and Adolescents)**  
**Obsessive-Compulsive Disorder**—ZOLOFT treatment should be initiated with a dose of 25 mg once daily in children (ages 6–12) and at a dose of 50 mg once daily in adolescents (ages 13–17).

While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25–200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for pediatric patients (6–17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

**Dosage for Hepatically or Renally Impaired Patients**

As indicated under PRECAUTIONS, a lower or less frequent dosage should be used in patients with hepatic impairment. In addition, particular care should be used in patients with renal impairment.

**Maintenance/Continuation/Extended Treatment**

**Depression**—It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of ZOLOFT has shown that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) at a dose of 50–200 mg/day (mean dose of 70 mg/day) (see Clinical Trials under CLINICAL PHARMACOLOGY).

**Obsessive-Compulsive Disorder and Panic Disorder**—Although the efficacy of ZOLOFT beyond 10–12 weeks of dosing for OCD and panic disorder has not been documented in controlled trials, both are chronic conditions, and it is reasonable to consider continuation of a responding patient for either indication. Dosage adjustments may be needed to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

**Switching Patients to or from a Monoamine Oxidase Inhibitor**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

**HOW SUPPLIED**

ZOLOFT® (sertraline hydrochloride) capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline, are packaged in bottles.

ZOLOFT® 25mg Tablets: light green film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 25 mg.

NDC 0049-4960-50 Bottles of 50

ZOLOFT® 50 mg Tablets: light blue film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 50 mg.

NDC 0049-4900-66 Bottles of 100  
NDC 0049-4900-73 Bottles of 500  
NDC 0049-4900-84 Bottles of 5000  
NDC 0049-4900-41 Unit Dose Packages of 100  
ZOLOFT® 100 mg Tablets: light yellow film coated tablets engraved on one side with ZOLOFT and on the other side scored and engraved with 100 mg.

NDC 0049-4910-66 Bottles of 100  
NDC 0049-4910-73 Bottles of 500  
NDC 0049-4910-94 Bottles of 5000  
NDC 0049-4910-41 Unit Dose Packages of 100

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

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**ZYRTEC®**

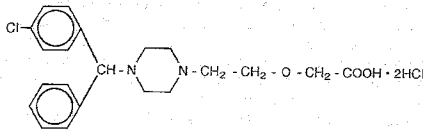
(cetirizine hydrochloride)

Tablets and Syrup

For Oral Use

**DESCRIPTION**

Cetirizine hydrochloride, the active component of ZYRTEC® tablets and syrup, is an orally active and selective H<sub>1</sub>-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<sub>21</sub>H<sub>26</sub>ClN<sub>2</sub>O<sub>3</sub>·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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> receptors.

**Pharmacokinetics:**

**Absorption:** Cetirizine was rapidly absorbed with a time to maximum concentration (T<sub>max</sub>) 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 (C<sub>max</sub>) 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 T<sub>max</sub> was delayed by 1.7 hours and C<sub>max</sub> 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 8.5 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 theophylline 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 C<sub>max</sub> 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 C<sub>max</sub> 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.

**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 **DOSE AND ADMINISTRATION**).

**Hepatic Impairment:** Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 to 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 **DOSE 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. 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 significantly increase QTc versus placebo. The effects of ZYRTEC on the QTc interval at doses higher than the 10 mg dose have not been studied in children less than 12 years of age. The effect of ZYRTEC on the QTc interval in children less than 6 years of age has not been studied.

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 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal 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 2 years 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<sup>2</sup> basis, or approximately 10 times the maximum recommended daily oral dose in children on a mg/m<sup>2</sup> 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<sup>2</sup> basis, or approximately 4 times the maximum recommended daily oral dose in children on a mg/m<sup>2</sup> 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<sup>2</sup> basis, or approximately equal to the maximum recommended daily oral dose in children on a mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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:** In placebo-controlled trials, 186 patients aged 65 to 94 years received doses of 5 to 20 mg of ZYRTEC per day. Adverse events were similar in this group to patients under age 65. Subset analysis of efficacy in this group was not done.

**Pediatric Use:** 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 effectiveness of ZYRTEC for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in pediatric patients aged 2 to 11 years is based on an extrapolation of the demonstrated efficacy of ZYRTEC in adults in these conditions and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between these two populations. 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 C<sub>max</sub> in pediatric 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 2 years have not yet 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 was 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.

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.

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, hypertension, 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, paranoia, 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, general-

Continued on next page

**Zyrtec—Cont.**

ized 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 the following additional rare, but potentially severe adverse events have been reported: anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, and thrombocytopenia.

**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<sup>2</sup> basis, or approximately 55 times the maximum recommended daily oral dose in children on a mg/m<sup>2</sup> basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 270 times the maximum recommended daily oral dose in children on a mg/m<sup>2</sup> 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, depending on symptom severity and patient response.

**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 room temperature 59° to 86°F (15° to 30°C).

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 41° to 86°F (5° to 30°C). Cetirizine is licensed from UCB Pharma, Inc.

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Manufactured/Marketed by  
**Pfizer Labs**  
Division of Pfizer Inc, NY, NY 10017  
Marketed by  
**UCB Pharma, Inc.**

Smyrna, GA 30080  
70-4578-00-3

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Shown in Product Identification Guide, page 332

**Pfizer Inc**  
**Consumer Health Care**  
**Group**  
235 E. 42nd STREET  
NY, NY 10017-5755

**DIRECT MEDICAL EMERGENCIES AND INQUIRIES TO:**

Consumer Relations Group  
(212) 733-5656  
FAX: (212) 973-7437

**BONINE®**

(Mecizine hydrochloride)  
Chewable Tablets

**ACTION**

BONINE (mecizine) is an H<sub>1</sub> histamine receptor blocker of the piperazine side chain group. It exhibits its action by an effect on the Central Nervous System (CNS), possibly by its ability to block muscarinic receptors in the brain.

**INDICATIONS**

BONINE is effective in the management of nausea, vomiting and dizziness associated with motion sickness.

**CONTRAINDICATIONS**

Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland.

**WARNINGS**

May cause drowsiness; alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Do not drive or operate dangerous machinery while taking this medication.

**Usage in Children**

Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in children under 12 years of age.

**Usage in Pregnancy**

As with any drug, if you are pregnant or nursing a baby, seek advice of a health care professional before taking this product.

**ADVERSE REACTIONS**

Drowsiness, dry mouth, and on rare occasions, blurred vision have been reported.

**DOSAGE AND ADMINISTRATION**

For motion sickness, take one or two tablets of Bonine once daily, one hour before travel starts, for up to 24 hours of protection against motion sickness. The tablet can be chewed with or without water or swallowed whole with water. Thereafter, the dose may be repeated every 24 hours for the duration of the travel.

**HOW SUPPLIED**

BONINE (mecizine HCl) is available in convenient packets of 8 chewable tablets of 25 mg. mecizine HCl.

**INACTIVE INGREDIENTS**

FD&C Red #40, Lactose, Magnesium Stearate, Purified Siliceous Earth, Raspberry Flavor, Saccharin Sodium, Starch, Talc.

**UNISOM® SleepTabs™**

[yu. 'na-som]

Nighttime Sleep Aid  
(doxylamine succinate)

**PRODUCT OVERVIEW****KEY FACTS**

Unisom is an ethanolamine antihistamine (doxylamine) which characteristically shows a high incidence of sedation. It produces a reduced latency to end of wakefulness and early onset of sleep.

**MAJOR USES**

Unisom has been shown to be clinically effective as a sleep aid when 1 tablet is given 30 minutes before retiring.

**SAFETY INFORMATION**

Unisom is contraindicated in pregnancy and nursing mothers. It is also contraindicated in patients with asthma, glaucoma, and enlargement of the prostate. Caution should be used if taken when alcohol is being consumed. Caution is also indicated when taken concurrently with other medications due to the anticholinergic properties of antihistamines.

**DESCRIPTION**

Pale blue oval scored tablets containing 25 mg. of doxylamine succinate, 2- $\alpha$ -(2-dimethylaminoethoxy)- $\alpha$ -methylbenzylpyridine succinate.

**INACTIVE INGREDIENTS**

Dibasic Calcium Phosphate, FD&C Blue #1 Aluminum Lake, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate.

**ADMINISTRATION AND DOSAGE**

One tablet 30 minutes before going to bed. Take once daily or as directed by a doctor. Not for children under 12 years of age.

**WARNINGS**

Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Do not take this product if pregnant or nursing a baby.

- If sleeplessness persists continuously for more than two weeks, consult your doctor. Insomnia may be a symptom of a serious underlying medical illness.
- Do not take this product if presently taking any other drug, without consulting your doctor or pharmacist.
- Take this product with caution if alcohol is being consumed.
- For adults only. Do not give to children under 12 years of age.
- Keep this and all medications out of the reach of children. This product contains an antihistamine and will cause drowsiness. It should be used only at bedtime.

**SIDE EFFECTS**

Occasional anticholinergic effects may be seen.

**ATTENTION**

Use only if tablet blister seals are unbroken.

**HOW SUPPLIED**

Boxes of 8, 16, 32 or 48 tablets.

**MAXIMUM STRENGTH**  
**UNISOM® SLEEPGELS™**  
Nighttime Sleep Aid

**DESCRIPTION**

Maximum Strength Unisom SleepGels are liquid-filled, blue soft gelatin capsules.

**ACTIVE INGREDIENT**

Diphenhydramine Hydrochloride 50 mg.

**INACTIVE INGREDIENTS**

FD&C Blue No. 1, Gelatin, Glycerin, Pharmaceutical Glaze, Polyethylene Glycol, Propylene Glycol, Purified Water, Sorbitol, Titanium Dioxide.

**INDICATIONS**

Helps to reduce difficulty falling asleep.

**ACTION**

Diphenhydramine Hydrochloride is an ethanolamine antihistamine with anticholinergic and sedative effects.

**ADMINISTRATION AND DOSAGE**

Adults and children 12 years of age and over: Oral dosage is one softgel (50 mg) at bedtime if needed, or as directed by a doctor.

**WARNINGS**

Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland. Do not take this product if pregnant or nursing a baby.

- Do not give to children under 12 years of age.
- If sleeplessness persists continuously for more than two weeks, consult your doctor. Insomnia may be a symptom of serious underlying medical illness.
- Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor.
- **Do Not Use:** with any other product containing diphenhydramine, including one applied topically.
- Keep this and all drugs out of the reach of children.
- In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

**DRUG INTERACTION**

Monoamine oxidase (MAO) inhibitors prolong and intensify the anticholinergic effects of antihistamines. The CNS depressant effect is heightened by alcohol and other CNS depressant drugs.

**SYMPTOMS OF ORAL OVERDOSAGE**

Antihistamine overdose reactions may vary from central nervous system depression to stimulation. Stimulation is particularly likely in children. Atropine-like signs and symptoms, such as dry mouth, fixed and dilated pupils, flushing, and gastrointestinal symptoms, may also occur.

**ATTENTION**

Use only if softgel blister seals are unbroken.

**HOW SUPPLIED**

Boxes of 16 liquid filled softgels in child resistant blisters and boxes of 8 with non-child resistant packaging. Also in a 32 count easy to open child resistant bottle. Store between 15° and 30°C (59° and 86°F)



tion and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

The use of CELESTONE SOLUSPAN Injectable Suspension in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

**Usage in pregnancy:** Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

## PRECAUTIONS

### Information for Patients

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

**General:** Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed. The following additional precautions also apply for parenteral corticosteroids. Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided.

Corticosteroids should not be injected into unstable joints. The slower rate of absorption by intramuscular administration should be recognized.

## ADVERSE REACTIONS

**Fluid and electrolyte disturbances:** sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

**Musculoskeletal:** muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones.

**Gastrointestinal:** peptic ulcer with possible subsequent perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis.

**Dermatologic:** impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests.

**Neurological:** convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache.

**Endocrine:** menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics.

**Ophthalmic:** posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

**Metabolic:** negative nitrogen balance due to protein catabolism.

The following additional adverse reactions are related to parenteral corticosteroid therapy: rare instances of blindness associated with intralesional therapy around the face and head, hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, post-injection flare (following intra-articular use), charcot-like arthropathy.

## DOSEAGE AND ADMINISTRATION

The initial dosage of CELESTONE SOLUSPAN Injectable Suspension may vary from 0.5 to 9.0 mg per day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. Usually the parenteral dosage ranges are one-third to one-half the oral dose given every 12 hours. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, CELESTONE SOLUSPAN Injectable Suspension should be discontinued and the patient transferred to other appropriate therapy. *It Should Be Emphasized That Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient.* After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of CELESTONE SOLUSPAN Injectable Suspension for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

If coadministration of a local anesthetic is desired, CELESTONE SOLUSPAN Injectable Suspension may be mixed with 1% or 2% lidocaine hydrochloride, using the formulations which do not contain parabens. Similar local anesthetics may also be used. Diluents containing methylparaben, propylparaben, phenol, etc., should be avoided since these compounds may cause flocculation of the steroid. The required dose of CELESTONE SOLUSPAN Injectable Suspension is first withdrawn from the vial into the syringe. The local anesthetic is then drawn in, and the syringe shaken briefly. **Do not inject local anesthetics into the vial of CELESTONE SOLUSPAN Injectable Suspension.**

**Bursitis, tenosynovitis, peritendinitis.** In acute subdeltoid, subacromial, olecranon, and prepatellar bursitis, one intrabursal injection of 1.0 mL CELESTONE SOLUSPAN Injectable Suspension can relieve pain and restore full range of movement. Several intrabursal injections of corticosteroids are usually required in recurrent acute bursitis and in acute exacerbations of chronic bursitis. Partial relief of pain and some increase in mobility can be expected in both conditions after one or two injections. Chronic bursitis may be treated with reduced dosage once the acute condition is controlled. In tenosynovitis and tendinitis, three or four local injections at intervals of 1 to 2 weeks between injections are given in most cases. Injections should be made into the affected tendon sheaths rather than into the tendons themselves. In ganglions of joint capsules and tendon sheaths, injection of 0.5 mL directly into the ganglion cysts has produced marked reduction in the size of the lesions.

**Rheumatoid arthritis and osteoarthritis.** Following intra-articular administration of 0.5 to 2.0 mL of CELESTONE SOLUSPAN Injectable Suspension, relief of pain, soreness, and stiffness may be experienced. Duration of relief varies widely in both diseases. Intra-articular Injection—CELESTONE SOLUSPAN Injectable Suspension is well tolerated in joints and periarticular tissues. There is virtually no pain on injection, and the "secondary flare" that sometimes occurs a few hours after intra-articular injection of corticosteroids has not been reported with CELESTONE SOLUSPAN Injectable Suspension. Using sterile technique, a 20- to 24-gauge needle on an empty syringe is inserted into the synovial cavity, and a few drops of synovial fluid are withdrawn to confirm that the needle is in the joint. The aspirating syringe is replaced by a syringe containing CELESTONE SOLUSPAN Injectable Suspension and injection is then made into the joint.

Recommended Doses for Intra-articular Injection		
Size of joint	Location	Dose (mL)
Very Large	Hip	1.0-2.0
Large	Knee, Ankle, Shoulder	1.0
Medium	Elbow, Wrist	0.5-1.0

Small (Metacarpophalangeal, interphalangeal) (Sternoclavicular)	Hand Chest	0.25-0.5
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A portion of the administered dose of CELESTONE SOLUSPAN Injectable Suspension is absorbed systemically following intra-articular injection. In patients being treated concomitantly with oral or parenteral corticosteroids, especially those receiving large doses, the systemic absorption of the drug should be considered in determining intra-articular dosage.

**Dermatologic conditions.** In intralesional treatment, 0.2 mL/sq cm of CELESTONE SOLUSPAN Injectable Suspension is injected intradermally (not subcutaneously) using a tuberculin syringe with a 25-gauge, 1/2-inch needle. Care should be taken to deposit a uniform depot of medication intradermally. A total of no more than 1.0 mL at weekly intervals is recommended.

**Disorders of the foot.** A tuberculin syringe with a 25-gauge, 3/4-inch needle is suitable for most injections into the foot. The following doses are recommended at intervals of 3 days to a week.

Diagnosis	CELESTONE SOLUSPAN Injectable Suspension Dose (mL)
Bursitis	
under heloma durum or heloma molle	0.25-0.5
under calcaneal spur over hallux rigidus or digiti quinti varus	0.5
Tenosynovitis,	
peritendinitis of cuboid	0.5
Acute gouty arthritis	0.5-1.0

## HOW SUPPLIED

CELESTONE SOLUSPAN Injectable Suspension, 5 mL multiple-dose vial; box of one (NDC 0085-0566-05).

Shake well before using.

Store between 2° and 25°C (36° and 77°F).

Protect from light.

Schering Corporation

Kenilworth, NJ 07033 USA

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Rev. 3/96

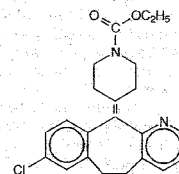
10229790

## CLARITIN®

brand of loratadine  
TABLETS, SYRUP, and  
RAPIDLY-DISINTEGRATING TABLETS

## DESCRIPTION

Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of  $C_{22}H_{25}ClN_2O_2$ ; its chemical name is ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate and has the following structural formula:



CLARITIN Tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. They also contain the following inactive ingredients: corn starch, lactose, and magnesium stearate.

CLARITIN Syrup contains 1 mg/mL micronized loratadine, an antihistamine, to be administered orally. It also contains the following inactive ingredients: citric acid, edetate sodium, artificial flavor, glycerin, propylene glycol, sodium benzoate, sugar, and water. The pH is between 2.5 and 3.1. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor.

## CLINICAL PHARMACOLOGY

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine  $H_1$ -receptor antagonistic activity.

Continued on next page

Information on Schering products appearing on these pages is effective as of August 15, 1999.

Consult 2000 PDR® supplements and future editions for revisions



**Claritin—Cont.**

Human histamine skin wheal studies following single and repeated 10 mg oral doses of CLARITIN have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with CLARITIN.

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H<sub>1</sub>-receptors indicate that there was preferential binding to peripheral versus central nervous system H<sub>1</sub>-receptors.

Repeated application of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) to the hamster cheek pouch did not cause local irritation.

**Pharmacokinetics:** Loratadine was rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult volunteers with times to maximum concentration (T<sub>max</sub>) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. Based on a cross-study comparison of single doses of loratadine syrup and tablets given to healthy adult volunteers, the plasma concentration profile of descarboethoxyloratadine for the two formulations is comparable. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10 to 40 mg and are not altered by the duration of treatment. In a single-dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration (T<sub>max</sub>) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C<sub>max</sub>) were not affected by food.

Pharmacokinetic studies showed that CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) provide plasma concentrations of loratadine and descarboethoxyloratadine similar to those achieved with CLARITIN Tablets. Following administration of 10 mg loratadine once daily for 10 days with each dosage form in a randomized crossover comparison in 24 normal adult subjects, similar mean exposures (AUC) and peak plasma concentrations (C<sub>max</sub>) of loratadine were observed. CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) mean AUC and C<sub>max</sub> were 11% and 6% greater than that of the CLARITIN Tablet values, respectively. Descarboethoxyloratadine bioequivalence was demonstrated between the two formulations. After 10 days of dosing, mean peak plasma concentrations were attained at 1.3 hours and 2.3 hours (T<sub>max</sub>) for parent and metabolite, respectively.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), food increased the AUC of loratadine by approximately 48% and did not appreciably affect the AUC of descarboethoxyloratadine. The times to peak plasma concentration (T<sub>max</sub>) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) administration. Parent and metabolite peak concentrations (C<sub>max</sub>) were not affected by food.

In a single-dose study with CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in 24 subjects, the AUC of loratadine was increased by 26% when administered without water compared to administration with water, while C<sub>max</sub> was not substantially affected. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. In nearly all patients, exposure (AUC) to the metabolite is greater than to the parent loratadine. The mean elimination half-lives in normal adult subjects (n = 54) were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. There was considerable variability in the pharmacokinetic data in all studies of CLARITIN Tablets and Syrup, probably due to the extensive first-pass metabolism.

*In vitro* studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine (see **Drug Interactions** section).

The pharmacokinetic profile of loratadine in children in the 6- to 12-year age group is similar to that of adults. In a single-dose pharmacokinetic study of 13 pediatric volunteers (aged 8-12 years) given 10 mL of CLARITIN Syrup containing 10 mg loratadine, the ranges of individual subject values of pharmacokinetic parameters (AUC and C<sub>max</sub>) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers.

**REPORTED ADVERSE EVENTS WITH AN INCIDENCE OF MORE THAN 2% IN PLACEBO-CONTROLLED ALLERGIC RHINITIS CLINICAL TRIALS IN PATIENTS 12 YEARS OF AGE AND OLDER**

**PERCENT OF PATIENTS REPORTING**

	LORATADINE 10 mg QD n = 1926	PLACEBO n = 2545	CLEMASTINE 1 mg BID n = 536	TERFENADINE 60 mg BID n = 684
Headache	12	11	8	8
Somnolence	8	6	22	9
Fatigue	4	3	10	2
Dry Mouth	3	2	4	3

**ADVERSE EVENTS OCCURRING WITH A FREQUENCY OF ≥2% IN LORATADINE SYRUP-TREATED PATIENTS (6-12 YEARS OLD) IN PLACEBO-CONTROLLED TRIALS, AND MORE FREQUENTLY THAN IN THE PLACEBO GROUP**

**PERCENT OF PATIENTS REPORTING**

	LORATADINE 10 mg QD n = 188	PLACEBO n = 262	CHLORPHENIRAMINE 2-4 mg BID/TID n = 170
Nervousness	4	2	2
Wheezing	4	2	5
Fatigue	3	2	5
Hyperkinesia	3	1	1
Abdominal Pain	2	0	0
Conjunctivitis	2	<1	1
Dysphonia	2	<1	0
Malaise	2	0	1
Upper Respiratory Tract Infection	2	<1	0

**Special Populations:** In a study involving twelve healthy geriatric subjects (66 to 78 years old), the AUC and peak plasma levels (C<sub>max</sub>) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies of younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11 to 38 hours) for descarboethoxyloratadine.

In a study involving 12 subjects with chronic renal impairment (creatinine clearance ≤ 30 mL/min) both AUC and C<sub>max</sub> increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to 6 subjects with normal renal function (creatinine clearance ≥ 60 mL/min). The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

In seven patients with chronic alcoholic liver disease, the AUC and C<sub>max</sub> of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in other trials enrolling normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

**Clinical Trials:** Clinical trials of CLARITIN Tablets involved over 10,700 patients, 12 years of age and older, who received either CLARITIN Tablets or another antihistamine and/or placebo in double-blind randomized controlled studies. In placebo-controlled trials, 10 mg once daily of CLARITIN Tablets was superior to placebo and similar to clemastine (1 mg BID) or terfenadine (60 mg BID) in effects on nasal and non-nasal symptoms of allergic rhinitis. In these studies somnolence occurred less frequently with CLARITIN Tablets than with clemastine and at about the same frequency as terfenadine or placebo. In studies with CLARITIN Tablets at doses 2 to 4 times higher than the recommended dose of 10 mg, a dose-related increase in the incidence of somnolence was observed. Therefore, some patients, particularly those with hepatic or renal impairment and the elderly, or those on medications that impair clearance of loratadine and its metabolites may experience somnolence. In addition, three placebo-controlled, double-blind, 2-week trials in 188 pediatric patients with seasonal allergic rhinitis aged 6 to 12 years, were conducted at doses of CLARITIN Syrup up to 10 mg once daily.

Clinical trials of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) involved over 1300 patients who received either CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), CLARITIN Tablets, or placebo. In placebo-controlled trials, one CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) once daily was superior to placebo and similar to CLARITIN Tablets in effects on nasal and non-nasal symptoms of seasonal allergic rhinitis.

Among those patients involved in double-blind, randomized, controlled studies of CLARITIN Tablets, approximately 1000 patients (age 12 and older), were enrolled in studies of chronic idiopathic urticaria. In placebo-controlled clinical trials, CLARITIN Tablets 10 mg once daily were superior to placebo in the management of chronic idiopathic urticaria, as demonstrated by reduction of associated itching, erythema, and hives. In these studies, the incidence of somnolence seen with CLARITIN Tablets was similar to that seen with placebo.

In a study in which CLARITIN Tablets were administered to adults at 4 times the clinical dose for 90 days, no clinically significant increase in the QT<sub>c</sub> was seen on ECGs.

In a single-rising dose study in which doses up to 160 mg (16 times the clinical dose) were studied, loratadine did not cause any clinically significant changes on the QT<sub>c</sub> interval in ECGs.

**INDICATIONS AND USAGE**

CLARITIN is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 6 years of age or older.

**CONTRAINDICATIONS**

CLARITIN is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

**PRECAUTIONS**

**General:** Patients with liver impairment or renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (10 mg every other day). (See **CLINICAL PHARMACOLOGY: Special Populations**.)

**Drug Interactions:** Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n = 24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT<sub>c</sub> intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in the following table:

**Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg)**

	In Normal Volunteers	
	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg Q8h)	+ 40%	+46%
Cimetidine (300 mg QID)	+103%	+ 6%
Ketoconazole (200 mg Q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** In an 18-month carcinogenicity study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined ad-

enomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of CLARITIN is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis).

**Pregnancy Category B:** There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis). There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, CLARITIN should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC<sub>0-12h</sub>/AUC<sub>0-12h</sub> plasma ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when CLARITIN is administered to a nursing woman.

**Pediatric Use:** The safety of CLARITIN Syrup at a daily dose of 10 mg has been demonstrated in 188 pediatric patients 6-12 years of age in placebo-controlled 2-week trials. The effectiveness of CLARITIN for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in this pediatric age group is based on an extrapolation of the demonstrated efficacy of CLARITIN in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparison of the pharmacokinetics of CLARITIN in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of CLARITIN in pediatric patients under 6 years of age have not been established.

## ADVERSE REACTIONS

**CLARITIN Tablets:** Approximately 90,000 patients, aged 12 and older, received CLARITIN Tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day varied from 2 weeks' to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2% in both the treated and placebo groups.

[See first table at top of previous page.]

Adverse events reported in placebo-controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of nonwhite subjects was relatively small.

**CLARITIN REDITABS (loratadine rapidly-disintegrating tablets):** Approximately 500 patients received CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with CLARITIN Tablets and placebo.

Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) did not result in an increased reporting frequency of mouth or tongue irritation.

**CLARITIN Syrup:** Approximately 300 pediatric patients 6 to 12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 8-15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg was less than 1%.

[See second table on previous page.]

In addition to those adverse events reported above (≥2%), the following adverse events have been reported in at least one patient in CLARITIN clinical trials in adult and pediatric patients:

**Autonomic Nervous System:** Altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

**Body As A Whole:** Angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, viral infection, weight gain.

**Cardiovascular System:** Hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

**Central and Peripheral Nervous System:** Blepharospasm, dizziness, dysphonia, hypertonie, migraine, paresthesia, tremor, vertigo.

**Gastrointestinal System:** Altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, nausea, stomatitis, toothache, vomiting.

**Musculoskeletal System:** Arthralgia, myalgia.

**Psychiatric:** Agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria.

**Reproductive System:** Breast pain, dysmenorrhea, menorrhagia, vaginitis.

**Respiratory System:** Bronchitis, bronchospasm, coughing, dyspnea, epistaxis, hemoptysis, laryngitis, nasal dryness, pharyngitis, sinusitis, sneezing.

**Skin and Appendages:** Dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, rash, urticaria.

**Urinary System:** Altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; and seizures.

## DRUG ABUSE AND DEPENDENCE

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

## OVERDOSAGE

In adults, somnolence, tachycardia, and headache have been reported with overdoses greater than 10 mg with the Tablet formulation (40 to 180 mg). Extrapyramidal signs and palpitations have been reported in children with overdoses of greater than 10 mg of CLARITIN Syrup. In the event of overdose, general symptomatic and supportive measures should be instituted promptly and maintained for as long as necessary.

Treatment of overdose would reasonably consist of emesis (ipecac syrup), except in patients with impaired consciousness, followed by the administration of activated charcoal to absorb any remaining drug. If vomiting is unsuccessful, or contraindicated, gastric lavage should be performed with normal saline. Saline cathartics may also be of value for rapid dilution of bowel contents. Loratadine is not eliminated by hemodialysis. It is not known if loratadine is eliminated by peritoneal dialysis.

No deaths occurred at oral doses up to 5000 mg/kg in rats and mice (greater than 2400 and 1200 times, respectively, the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis). Single oral doses of loratadine showed no effects in rats, mice, and monkeys at doses as high as 10 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis.

## DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: The recommended dose of CLARITIN is 10 mg once daily.

Children 6-11 years of age: The recommended dose of CLARITIN is 10 mg (2 teaspoonsfuls) once daily.

In patients with liver failure or renal insufficiency (GFR <30 mL/min), one tablet or two teaspoonsfuls every other day should be the starting dose.

**Administration of CLARITIN REDITABS (loratadine rapidly-disintegrating tablets):** Place CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) on the tongue. Tablet disintegration occurs rapidly. Administer with or without water.

## HOW SUPPLIED

**CLARITIN Tablets:** 10 mg, white to off-white compressed tablets; impressed with the product identification number "458" on one side and "CLARITIN 10" on the other; high-density polyethylene plastic bottles of 100 (NDC 0085-0458-03) and 500 (NDC 0085-0458-06). Also available, CLARITIN Unit-of-Use packages of 14 tablets (7 tablets per blister card) (NDC 0085-0458-01) and 30 tablets (10 tablets per blister card) (NDC 0085-0458-05); and 10 x 10 tablet Unit Dose-Hospital Pack (NDC 0085-0458-04).

**Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from excessive moisture.**

**Store between 2° and 30°C (36° and 86°F).**

**CLARITIN Syrup:** Clear, colorless to light-yellow liquid, containing 1 mg loratadine per mL, amber glass bottles of 16 fluid ounces (NDC 0085-1223-01).

**Store between 2° and 25°C (36° and 77°F).**

**CLARITIN REDITABS (loratadine rapidly-disintegrating tablets):** CLARITIN REDITABS (loratadine rapidly-disintegrating tablets), 10 mg, white to off-white blister-formed tablet: Unit-of-Use polyvinyl chloride blister packages of 30 tablets (3 laminated foil pouches, each containing one blister card of 10 tablets) supplied with Patient's Instructions for Use (NDC 0085-1128-02).

**Keep CLARITIN REDITABS (loratadine rapidly-disintegrating tablets) in a dry place.**

**Store between 2° and 25°C (36° and 77°F). Use within 6 months of opening laminated foil pouch, and immediately upon opening individual tablet blister.**

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**CLARITIN REDITABS (loratadine rapidly-disintegrating tablets)** are manufactured for Schering Corporation by Scherer DDS, England.

U.S. Patent Nos. 4,282,233 and 4,371,516.

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Shown in Product Identification Guide, pages 335 and 336

## CLARITIN-D® 12 HOUR

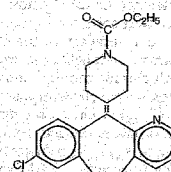
brand of loratadine and pseudoephedrine sulfate, USP  
Extended Release Tablets

**CAUTION: Federal Law Prohibits Dispensing Without Prescription**

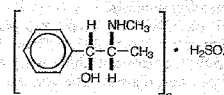
## DESCRIPTION

CLARITIN-D 12 HOUR Extended Release Tablets contain 5 mg loratadine in the tablet coating for immediate release and 120 mg pseudoephedrine sulfate, USP equally distributed between the tablet coating for immediate release and the barrier-coated extended release core.

Loratadine is a white to off-white powder, not soluble in water, but very soluble in acetone, alcohol, and chloroform. Loratadine has a molecular weight of 382.89 and empirical formula of C<sub>20</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>; the chemical name, ethyl 4-(8-chloro-5,6-dihydro-1H-benzo[5,6]cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidine-carboxylate; and has the following chemical structure:



Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is (C<sub>10</sub>H<sub>15</sub>NO)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub>; the chemical name is [S-(R\*)-R\*)-α-[1(methylamino)ethyl] benzenemethanol sulfate (2:1) (salt), and the following chemical structure:



The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

The inactive ingredients for CLARITIN-D 12 HOUR Extended Release Tablets are acacia, butylparaben, calcium sulfate, carnauba wax, corn starch, lactose, magnesium stearate, microcrystalline cellulose, neutral soap, oleic acid, povidone, rosin, sugar, talc, titanium dioxide, white wax, and zein.

## CLINICAL PHARMACOLOGY

The following information is based upon studies of loratadine alone or pseudoephedrine alone, except as indicated. Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H<sub>1</sub>-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated oral doses of loratadine have shown that the drug exhibits an antihistaminic effect beginning within 1 to 3 hours, reaching a maximum at 8 to 12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect developing after 28 days of dosing with loratadine.

Pharmacokinetic studies following single and multiple oral doses of loratadine in 115 volunteers showed that loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxyloratadine). Approximately 80% of the total dose administered can be found equally distributed between urine and feces in the form of metabolic products after 10 days. The mean elimination half-lives found in studies in normal adult subjects (n=54) were 8.4 hours (range = 3 to 20 hours) for loratadine and 23 hours (range = 8.8 to 92 hours) for the major active metabolite (descarboethoxyloratadine). In nearly all patients, exposure (AUC) to the metabolite is greater than exposure to parent loratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. The pharmacokinetics of loratadine and descarboethoxyloratadine are dose independent over the dose range of 10 to 40 mg and are not significantly altered by the duration of treatment.

*In vitro* studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by P450 CYP3A4 and, to a lesser extent, by

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Information on Schering products appearing on these pages is effective as of August 15, 1999.

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