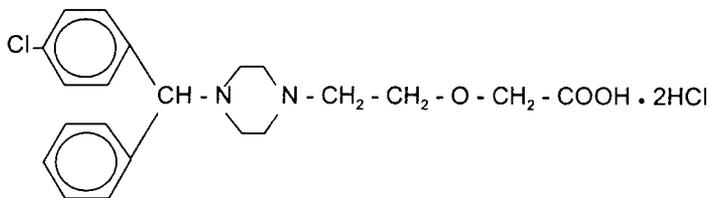


70-4573-00-5

**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>25</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 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

**Interaction Studies**

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

**Special Populations**

**Pediatric Patients:** When pediatric patients aged 7 to 12 years received a single, 5-mg oral cetirizine capsule, the mean 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. In pediatric patients aged 6 to 23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3 mg), the mean C<sub>max</sub> was 390 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304% greater and the elimination half-life was 63% shorter in this pediatric population compared to adults. The

average AUC(0-t) in children 6 months to < 2 years of age receiving the maximum dose of cetirizine solution (2.5mg twice a day) is expected to be two-fold higher than that observed in adults receiving a dose of 10 mg cetirizine tablets once a day.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

alter pulmonary function. These studies support the safety of administering ZYRTEC to pediatric and adult allergic rhinitis patients with mild to moderate asthma.

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

#### **INDICATIONS AND USAGE**

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

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

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

#### **CONTRAINDICATIONS**

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

## PRECAUTIONS

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

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

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m<sup>2</sup> basis, or approximately 7 times the maximum recommended daily oral dose in infants 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 3 times the maximum recommended daily oral dose in infants 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 equivalent to the maximum recommended daily oral dose in infants 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:** Of the total number of patients in clinical studies of ZYRTEC, 186 patients were 65 years and older, and 39 patients were 75 years and older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical studies of ZYRTEC for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients.

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

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

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

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

### ADVERSE REACTIONS

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

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

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

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

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

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

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

Pediatric studies were also conducted with ZYRTEC. More than 1300 pediatric patients aged 6 to 11 years with more than 900 treated with ZYRTEC at doses of 1.25 to 10 mg per day were

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

The majority of adverse reactions reported in pediatric patients aged 2 to 11 years with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in pediatric patients receiving up to 10 mg of ZYRTEC was uncommon (0.4% on ZYRTEC vs. 1.0% on placebo).

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

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

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

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

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

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

**Cardiovascular:** cardiac failure, hypertension, palpitation, tachycardia.

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

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

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

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

**Metabolic/Nutritional:** dehydration, diabetes mellitus, thirst.

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

**Psychiatric:** abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, 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, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

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

In foreign marketing experience 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 40 times the maximum recommended daily oral dose in infants 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 190 times the maximum recommended daily oral dose in infants 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.

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

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

### HOW SUPPLIED

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

5 mg tablets are engraved with “ZYRTEC” on one side and “5” on the other.

Bottles of 100: NDC 0069-5500-66

10 mg tablets are engraved with “ZYRTEC” on one side and “10” on the other.

Bottles of 100: NDC 0069-5510-66

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

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

120 mL amber glass bottles

NDC 0069-5530-47

1 pint amber glass bottles

NDC 0069-5530-93

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

Cetirizine is licensed from UCB Pharma, Inc.

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**Pfizer Labs**

Division of Pfizer Inc, NY, NY 10017

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Revised



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BUSULFEX is intended for dilution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP prior to intravenous infusion.

## CLINICAL PHARMACOLOGY

### Mechanism of Action:

Busulfan is a bifunctional alkylating agent in which two labile methanesulfonate groups are attached to opposite ends of a four-carbon alkyl chain. In aqueous media, busulfan hydrolyzes to release the methanesulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is thought to be responsible for much of the cytotoxicity of busulfan.

### Pharmacokinetics:

The pharmacokinetics of BUSULFEX were studied in 59 patients participating in a prospective trial of a BUSULFEX-cyclophosphamide preparatory regimen prior to allogeneic hematopoietic progenitor stem cell transplantation. Patients received 0.8 mg/kg BUSULFEX every six hours, for a total of 16 doses over four days. Fifty-five of fifty-nine patients (93%) administered BUSULFEX maintained AUC values below the target value (<1500  $\mu\text{M}\cdot\text{min}$ ).

Table 1: Steady State Pharmacokinetic Parameters Following Busulfex® (busulfan) Infusion (0.8 mg/kg; N=59)

	Mean	CV(%)	Range
$C_{\text{max}}$ (ng/mL)	1222	18	496-1684
AUC ( $\mu\text{M}\cdot\text{min}$ )	1167	20	556-1673
CL (ml/min/kg)*	2.52	25	1.49-4.31

\* Clearance normalized to actual body weight for all patients.

BUSULFEX pharmacokinetics showed consistency between dose 9 and dose 13 as demonstrated by reproducibility of steady state  $C_{max}$  and a low coefficient of variation for this parameter.

In a pharmacokinetic study of Busulfex in 24 pediatric patients, the population pharmacokinetic (PPK) estimates of Busulfex for clearance (CL) and volume of distribution (V) were determined. For actual body weight, PPK estimates of CL and V were 4.04 L/hr/20 kg (3.37 ml/min/kg; inter-patient variability 23%); and 12.8 L/20 kg (0.64 L/kg; inter-patient variability 11%).

**Distribution, Metabolism, Excretion:**

Studies of distribution, metabolism, and elimination of BUSULFEX have not been done; however, the literature on oral busulfan is relevant. Additionally, for modulating effects on pharmacodynamic parameters see **Drug Interactions**.

*Distribution:* Busulfan achieves concentrations in the cerebrospinal fluid approximately equal to those in plasma. Irreversible binding to plasma elements, primarily albumin, has been estimated to be  $32.4 \pm 2.2\%$  which is consistent with the reactive electrophilic properties of busulfan.

*Metabolism:* Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione S-transferase (GST) catalysis. This conjugate undergoes further extensive oxidative metabolism in the liver.

*Excretion:* Following administration of  $^{14}C$ - labeled busulfan to humans, approximately 30% of the radioactivity was excreted into the urine over 48 hours; negligible amounts were recovered in feces. The incomplete recovery of radioactivity may be due to the formation of long-lived metabolites or due to nonspecific alkylation of macromolecules.

## **CLINICAL STUDIES**

Documentation of the safety and efficacy of busulfan as a component of a conditioning regimen prior to allogeneic hematopoietic progenitor cell reconstitution is derived from two sources: i) analysis of a prospective clinical trial of BUSULFEX that involved 61 patients diagnosed with various hematologic malignancies, and ii) the published reports of randomized, controlled trials that employed high-dose oral busulfan as a component of a conditioning regimen for transplantation, which were identified in a literature review of five established commercial databases.

The prospective trial was a single-arm, open-label study in 61 patients who received BUSULFEX as part of a conditioning regimen for allogeneic hematopoietic stem cell transplantation. The study included patients with acute leukemia past first remission (first or subsequent relapse), with high-risk first remission, or with induction failure; chronic myelogenous leukemia (CML) in chronic phase, accelerated phase, or blast crisis; primary refractory or resistant relapsed Hodgkin's disease or non-Hodgkin's lymphoma; and myelodysplastic syndrome. Forty-eight percent of patients (29/61) were heavily pretreated, defined as having at least one of the following: prior radiation,  $\geq 3$  prior chemotherapeutic regimens, or prior hematopoietic stem cell transplant. Seventy-five percent of patients (46/61) were transplanted with active disease.

Patients received 16 BUSULFEX doses of 0.8 mg/kg every 6 hours as a two-hour infusion for 4 days, followed by cyclophosphamide 60 mg/kg once per day for two days (BuCy2 regimen). All patients received 100% of their scheduled BUSULFEX regimen. No dose adjustments were made. After one rest day, allogeneic

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hematopoietic progenitor cells were infused. The efficacy parameters in this study were myeloablation (defined as one or more of the following: absolute neutrophil count [ANC] less than  $0.5 \times 10^9/L$ , absolute lymphocyte count [ALC] less than  $0.1 \times 10^9/L$ , thrombocytopenia defined as a platelet count less than  $20,000/mm^3$  or a platelet transfusion requirement) and engraftment ( $ANC \geq 0.5 \times 10^9/L$ ).

All patients (61/61) experienced myeloablation. The median time to neutropenia was 4 days. All evaluable patients (60/60) engrafted at a median of 13 days post-transplant (range 9 to 29 days); one patient was considered non-evaluable because he died of a fungal pneumonia 20 days after BMT and before engraftment occurred. All but 13 of the patients were treated with prophylactic G-CSF. Evidence of donor cell engraftment and chimerism was documented in all patients who had a chromosomal sex marker or leukemic marker (43/43), and no patient with chimeric evidence of allogeneic engraftment suffered a later loss of the allogeneic graft. There were no reports of graft failure in the overall study population. The median number of platelet transfusions per patient was 6, and the median number of red blood cell transfusions per patient was 4.

Twenty-three patients (38%) relapsed at a median of 183 days post-transplant (range 36 to 406 days). Sixty-two percent of patients (38/61) were free from disease with a median follow-up of 269 days post-transplant (range 20 to 583 days). Forty-three patients (70%) were alive with a median follow up of 288 days post-transplant (range 51 to 583 days). There were two deaths before BMT Day +28 and six additional patients died by BMT Day +100. Ten patients (16%) died after BMT Day +100, at a median of 199 days post-transplant (range 113 to 275 days).

**Oral busulfan literature review.** Four publications of randomized, controlled trials that evaluated a high-dose oral busulfan-containing conditioning regimen (busulfan 4 mg/kg/d x 4 days + cyclophosphamide 60 mg/kg/d x 2 days) for allogeneic transplantation in the setting of CML were identified. Two of the studies (Clift and Devergie) had populations confined to CML in chronic phase that were randomized between conditioning with busulfan/cyclophosphamide (BU/CY) and cyclophosphamide/total body irradiation (CY/TBI). A total of 138 patients were treated with BU/CY in these studies. The populations of the two remaining studies (Ringden and Blume) included patients with CML, acute lymphoblastic leukemia (ALL), and acute myelogenous leukemia (AML). In the Nordic BMT Group study published by Ringden, et al., 57 patients had CML, and of those, 30 were treated with BU/CY. Patients with CML in chronic phase, accelerated phase, and blast crisis were eligible for this study. The participants with CML (34/122 patients) in a SWOG study published by Blume, et al., had disease beyond first chronic phase. Twenty of those CML patients were treated with BU/CY, and the TBI comparator arm utilized etoposide instead of cyclophosphamide.

Table 2 below summarizes the efficacy analyses reported from these 4 studies.

**Table 2: Summary of efficacy analyses from the randomized, controlled trials utilizing a high dose oral busulfan-containing conditioning regimen identified in a literature review.**

Clift, 1994 CML Chronic Phase;							
3 year Overall Survival		3 year DFS (p=0.43)		Relapse		Time to Engraftment (ANC ≥ 500)	
BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI



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BU = Busulfan

CY = Cyclophosphamide

TBI = Total Body Irradiation

DFS = Disease Free Survival

ANC = Absolute Neutrophil Count

### INDICATIONS AND USAGE

BUSULFEX® (busulfan) Injection is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

### CONTRAINDICATIONS

BUSULFEX is contraindicated in patients with a history of hypersensitivity to any of its components.

### WARNINGS

BUSULFEX should be administered under the supervision of a qualified physician experienced in hematopoietic stem cell transplantation. Appropriate management of complications arising from its administration is possible only when adequate diagnostic and treatment facilities are readily available.

The following warnings pertain to different physiologic effects of BUSULFEX in the setting of allogeneic transplantation.

**Hematologic:** The most frequent serious consequence of treatment with BUSULFEX at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Frequent complete blood counts, including white blood cell differentials, and quantitative platelet counts should be monitored during treatment and until recovery is

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achieved. Absolute neutrophil counts dropped below  $0.5 \times 10^9/L$  at a median of 4 days post-transplant in 100% of patients treated in the BUSULFEX clinical trial. The absolute neutrophil count recovered at a median of 13 days following allogeneic transplantation when prophylactic G-CSF was used in the majority of patients. Thrombocytopenia ( $<25,000/mm^3$  or requiring platelet transfusion) occurred at a median of 5-6 days in 98% of patients. Anemia (hemoglobin  $<8.0$  g/dL) occurred in 69% of patients. Antibiotic therapy and platelet and red blood cell support should be used when medically indicated.

**Neurological:** Seizures have been reported in patients receiving high-dose oral busulfan at doses producing plasma drug levels similar to those achieved following the recommended dosage of BUSULFEX. Despite prophylactic therapy with phenytoin, one seizure (1/42 patients) was reported during an autologous transplantation clinical trial of BUSULFEX. This episode occurred during the cyclophosphamide portion of the conditioning regimen, 36 hours after the last BUSULFEX dose. Anti-convulsant prophylactic therapy should be initiated prior to BUSULFEX treatment. Caution should be exercised when administering the recommended dose of BUSULFEX to patients with a history of a seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs.

**Hepatic:** Current literature suggests that high busulfan area under the plasma concentration verses time curve (AUC) values ( $>1,500 \mu M \cdot min$ ) may be associated with an increased risk of developing hepatic veno-occlusive disease (HVOD). Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing HVOD with the recommended BUSULFEX dose and regimen. Based on clinical

examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three of the five patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria. The incidence of HVOD reported in the literature from the randomized, controlled trials (see CLINICAL STUDIES) was 7.7%-12%.

**Cardiac:** Cardiac tamponade has been reported in pediatric patients with thalassemia (8/400 or 2% in one series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children died and two were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. No patients treated in the BUSULFEX (busulfan) Injection clinical trials experienced cardiac tamponade.

**Pulmonary:** Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).

**Carcinogenicity, Mutagenicity, Impairment of Fertility:**

Busulfan is a mutagen and a clastogen. In *in vitro* tests it caused mutations in *Salmonella typhimurium* and *Drosophila melanogaster*. Chromosomal aberrations induced by busulfan have been reported *in vivo* (rats, mice, hamsters, and humans) and *in vitro* (rodent and human cells). The intravenous administration of busulfan (48 mg/kg given as biweekly doses of 12 mg/kg, or 30% of the total BUSULFEX dose on a mg/m<sup>2</sup> basis) has been shown to increase the



included anasarca, cleft palate, vertebral anomalies, rib anomalies, and serious anomalies of the vessels of the heart. There are no adequate and well-controlled studies of either busulfan or DMA in pregnant women. If BUSULFEX is used during pregnancy, or if the patient becomes pregnant while receiving BUSULFEX, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

### PRECAUTIONS

**Hematologic:** At the recommended dosage of BUSULFEX, profound myelosuppression is universal, and can manifest as neutropenia, thrombocytopenia, anemia, or a combination thereof. Patients should be monitored for signs of local or systemic infection or bleeding. Their hematologic status should be evaluated frequently.

**Information for Patients:** The increased risk of a second malignancy should be explained to the patient.

**Laboratory Tests:** Patients receiving BUSULFEX should be monitored daily with a complete blood count, including differential count and quantitative platelet count, until engraftment has been demonstrated.

To detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase, and bilirubin should be evaluated daily through BMT Day +28.

**Drug Interactions:** Itraconazole decreases busulfan clearance by up to 25%, and may produce  $AUC > 1500 \mu M \cdot min$  in some patients.

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Fluconazole, and the 5-HT<sub>3</sub> antiemetics odansetron (Zofran®) and granisetron (Kytril®) have all been used with BUSULFEX.

Phenytoin increases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione-S-transferase. Since the pharmacokinetics of BUSULFEX were studied in patients treated with phenytoin, the clearance of BUSULFEX at the recommended dose may be lower and exposure (AUC) higher in patients not treated with phenytoin. Because busulfan is eliminated from the body via conjugation with glutathione, use of acetaminophen prior to (<72 hours) or concurrent with BUSULFEX may result in reduced busulfan clearance based upon the known property of acetaminophen to decrease glutathione levels in the blood and tissues.

**Pregnancy:** Pregnancy Category D. See **WARNINGS**.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for busulfan in human and animal studies, 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.

**Special Populations**

**Pediatric:** The effectiveness of BUSULFEX in the treatment of CML has not been specifically studied in pediatric patients. An open-label, uncontrolled study evaluated the pharmacokinetics of BUSULFEX in 24 pediatric patients receiving BUSULFEX as part of a conditioning regimen administered prior to hematopoietic progenitor cell transplantation for a variety of malignant hematologic (N=15) or non-malignant diseases (N=9). Patients ranged in age from 5 months to 16 years (median 3 years).

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BUSULFEX dosing was targeted to achieve an area under the plasma concentration curve (AUC) of 900-1350  $\mu\text{M}\cdot\text{min}$  with an initial dose of 0.8 mg/kg or 1.0 mg/kg (based on ABW) if the patient was  $> 4$  or  $\leq 4$  years, respectively. The dose was adjusted based on plasma concentration after completion of dose 1.

Patients received BUSULFEX doses every six hours as a two-hour infusion over four days for a total of 16 doses, followed by cyclophosphamide 50 mg/kg once daily for four days. After one rest day, hematopoietic progenitor cells were infused. All patients received phenytoin as seizure prophylaxis. The target AUC (900-1350  $\pm 5\%$   $\mu\text{M}\cdot\text{min}$ ) for BUSULFEX was achieved at dose 1 in 71% (17/24) of patients. Steady state pharmacokinetic testing was performed at dose 9 and 13. BUSULFEX levels were within the target range for 21 of 23 evaluable patients.

All 24 patients experienced neutropenia (absolute neutrophil count  $< 0.5 \times 10^9/\text{L}$ ) and thrombocytopenia (platelet transfusions or platelet count  $< 20,000/\text{mm}^3$ ). Seventy-nine percent (19/24) of patients experienced lymphopenia (absolute lymphocyte count  $< 0.1 \times 10^9$ ). In 23 patients, the ANC recovered to  $> 0.5 \times 10^9/\text{L}$  (median time to recovery = BMT day +13; range = BMT day +9 to +22). One patient who died on day +28 had not recovered to an ANC  $> 0.5 \times 10^9/\text{L}$ .

Four (17%) patients died during the study. Two patients died within 28 days of transplant; one with pneumonia and capillary leak syndrome, and the other with pneumonia and veno-occlusive disease. Two patients died prior to day 100; one due to progressive disease and one due to multi-organ failure.

Adverse events were reported in all 24 patients during the study period (BMT day -10 through BMT day +28) or post-study surveillance period (day +29 through +100). These included

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vomiting (100%), nausea (83%;), stomatitis (79%;), hepatic veno-occlusive disease (HVOD) (21%), graft-versus host disease (GVHD) (25%;), and pneumonia (21%).

Based on the results of this 24-patient clinical trial, a suggested dosing regimen of BUSULFEX in pediatric patients is shown in the following dosing nomogram:

**BUSULFEX Dosing Nomogram**

<b>Patient's Actual Body Weight (ABW)</b>	<b>BUSULFEX Dosage</b>
≤ 12 kgs	1.1 (mg/kg)
> 12 kgs	0.8 (mg/kg)

Simulations based on a pediatric population pharmacokinetic model indicate that approximately 60% of pediatric patients will achieve a target BUSULFEX exposure (AUC) between 900 to 1350  $\mu\text{M}\cdot\text{min}$  with the first dose of BUSULFEX using this dosing nomogram. Therapeutic drug monitoring and dose adjustment following the first dose of BUSULFEX is recommended.

**Dose Adjustment Based on Therapeutic Drug Monitoring**

Instructions for measuring the AUC of busulfan at dose 1 (see **Blood Sample Collection for AUC Determination**), and the formula for adjustment of subsequent doses to achieve the desired target AUC (1125  $\mu\text{M}\cdot\text{min}$ ), are provided below.

Adjusted dose (mg) = Actual Dose (mg) x Target AUC ( $\mu\text{M}\cdot\text{min}$ ) / Actual AUC ( $\mu\text{M}\cdot\text{min}$ )

For example, if a patient received a dose of 11 mg busulfan and if the corresponding AUC measured was 800  $\mu\text{M}\cdot\text{min}$ , for a target AUC of 1125  $\mu\text{M}\cdot\text{min}$ , the target mg dose would be:

Mg dose = 11 mg x 1125  $\mu\text{M}\cdot\text{min}$  / 800  $\mu\text{M}\cdot\text{min}$  = 15.5 mg

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Busulfex dose adjustment may be made using this formula and instructions below.

***Blood Sample Collection for AUC Determination:***

Calculate the AUC ( $\mu\text{M}\cdot\text{min}$ ) based on blood samples collected at the following time points:

For dose 1: 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled Busulfex administration). Actual sampling times should be recorded.

For doses other than dose 1: Pre-infusion (baseline), 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled Busulfex administration).

AUC calculations based on fewer than the three specified samples may result in inaccurate AUC determinations.

For each scheduled blood sample, collect one to three mL of blood into heparinized (Na or Li heparin) Vacutainer® tubes. The blood samples should be placed on wet ice immediately after collection and should be centrifuged (at 4°C) within one hour. The plasma, harvested into appropriate cryovial storage tubes, is to be frozen immediately at -20°C. All plasma samples are to be sent in a frozen state (i.e., on dry ice) to the assay laboratory for the determination of plasma busulfan concentrations.

**Calculation of AUC:**

Busulfex AUC calculations may be made using the following instructions and appropriate standard pharmacokinetic formula:

Dose 1 AUC<sub>infinity</sub> Calculation:  $\text{AUC}_{\text{infinity}} = \text{AUC}_{0-6\text{hr}} + \text{AUC}_{\text{extrapolated}}$ ,

where  $\text{AUC}_{0-6\text{hr}}$  is to be estimated using the linear trapezoidal rule and  $\text{AUC}_{\text{extrapolated}}$  can be computed by taking the ratio of the busulfan concentration at Hour 6 and the terminal elimination rate constant,  $\lambda_z$ . The  $\lambda_z$  must be calculated from the terminal elimination phase of the busulfan concentration vs. time curve. A "0" pre-dose busulfan concentration should be assumed, and used in the calculation of AUC.

If AUC is assessed subsequent to Dose 1, steady-state AUC<sub>ss</sub> ( $\text{AUC}_{0-$

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<sup>6hr</sup>) is to be estimated from the trough, 2 hr, 4 hr and 6 hr concentrations using the linear trapezoidal rule.

***Instructions for Drug Administration and Blood Sample Collection for Therapeutic Drug Monitoring:***

An administration set with minimal residual hold up (priming) volume (1-3 mL) should be used for drug infusion to ensure accurate delivery of the entire prescribed dose and to ensure accurate collection of blood samples for therapeutic drug monitoring and dose adjustment.

Prime the administration set tubing with drug solution to allow accurate documentation of the start time of Busulfex infusion. Collect the blood sample from a peripheral IV line to avoid contamination with infusing drug. If the blood sample is taken directly from the existing central venous catheter (CVC), **DO NOT COLLECT THE BLOOD SAMPLE WHILE THE DRUG IS INFUSING** to ensure that the end of infusion sample is not contaminated with any residual drug. At the end of infusion (2 hr), disconnect the administration tubing and flush the CVC line with 5 cc of normal saline prior to the collection of the end of infusion sample from the CVC port. Collect the blood samples from a different port than that used for the Busulfex infusion. When recording the Busulfex infusion stop time, do not include the time required to flush the indwelling catheter line. Discard the administration tubing at the end of the two-hour infusion.

See Preparation for Intravenous Administration section for detailed instructions on drug preparation.

**Geriatric:** Five of sixty-one patients treated in the Busulfex clinical trial were over the age of 55 (range 57-64). All achieved myeloablation and engraftment.

**Gender, Race:** Adjusting BUSULFEX dosage based on gender or race has not been adequately studied.

**Renal Insufficiency:** BUSULFEX has not been studied in patients with renal impairment.

**Hepatic Insufficiency:** BUSULFEX has not been administered to patients with hepatic insufficiency.

**Other:** Busulfan may cause cellular dysplasia in many organs. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes, pancreas, thyroid, adrenal glands, liver, lungs and bone marrow. This cytologic dysplasia may be severe enough to cause difficulty in interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix.

**ADVERSE REACTIONS:**

Dimethylacetamide (DMA), the solvent used in the BUSULFEX formulation, was studied in 1962 as a potential cancer chemotherapy drug. In a Phase 1 trial, the maximum tolerated dose (MTD) was 14.8 g/m<sup>2</sup>/d for four days. The daily recommended dose of BUSULFEX contains DMA equivalent to 42% of the MTD on a mg/m<sup>2</sup> basis. The dose-limiting toxicities in the Phase 1 study were hepatotoxicity as evidenced by increased liver transaminase (SGOT) levels and neurological symptoms as evidenced by hallucinations. The hallucinations had a pattern of onset at one day post completion of DMA administration and were associated with EEG changes. The lowest dose at which hallucinations were recognized was equivalent to 1.9 times that delivered in a conditioning regimen utilizing BUSULFEX 0.8 mg/kg every 6 hours x 16 doses. Other neurological toxicities included somnolence, lethargy, and confusion. The relative contribution of DMA and/or

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other concomitant medications to neurologic and hepatic toxicities observed with BUSULFEX is difficult to ascertain.

Treatment with BUSULFEX at the recommended dose and schedule will result in profound myelosuppression in 100% of patients, including granulocytopenia, thrombocytopenia, anemia, or a combined loss of formed elements of the blood.

Adverse reaction information is primarily derived from the clinical study (N=61) of BUSULFEX and the data obtained for high-dose oral busulfan conditioning in the setting of randomized, controlled trials identified through a literature review.

**BUSULFEX Clinical Trials:** In the BUSULFEX allogeneic stem cell transplantation clinical trial, all patients were treated with BUSULFEX 0.8 mg/kg as a two-hour infusion every six hours for 16 doses over four days, combined with cyclophosphamide 60 mg/kg x 2 days. Ninety three percent (93%) of evaluable patients receiving this dose of BUSULFEX maintained AUC less than 1,500  $\mu\text{M}\cdot\text{min}$  for dose 9, which has generally been considered the level that minimizes the risk of HVOD.

**Table 4: Summary of the Incidence (>20%) of Non-Hematologic Adverse Events through BMT Day +28 in Patients who Received BUSULFEX Prior to Allogeneic Hematopoietic Progenitor Cell Transplantation**

NON-HEMATOLOGICAL ADVERSE EVENTS*	PERCENT INCIDENCE
BODY AS A WHOLE	
Fever	80
Headache	69
Asthenia	51
Chills	46
Pain	44
Edema General	28
Allergic Reaction	26
Chest Pain	26
Inflammation at Inj Site	25
Pain Back	23

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CARDIOVASCULAR SYSTEM	
Tachycardia	44
Hypertension	36
Thrombosis	33
Vasodilation	25
DIGESTIVE SYSTEM	
Nausea	98
Stomatitis (Mucositis)	97
Vomiting	95
Anorexia	85
Diarrhea	84
Abdominal Pain	72
Dyspepsia	44
Constipation	38
Dry Mouth	26
Rectal Disorder	25
Abdominal Enlargement	23
METABOLIC AND NUTRITIONAL SYSTEM	
Hypomagnesemia	77
Hyperglycemia	66
Hypokalemia	64
Hypocalcemia	49
Hyperbilirubinemia	49
Edema	36
SGPT Elevation	31
Creatinine Increased	21
NERVOUS SYSTEM	
Insomnia	84
Anxiety	72
Dizziness	30
Depression	23
RESPIRATORY SYSTEM	
Rhinitis	44
Lung Disorder	34
Cough	28
Epistaxis	25
Dyspnea	25
SKIN AND APPENDAGES	
Rash	57
Pruritus	28

\* Includes all reported adverse events regardless of severity (toxicity grades 1-4)

The following sections describe clinically significant events occurring in the BUSULFEX clinical trials, regardless of drug attribution. For pediatric information, see Special Populations -Pediatric section.

**Hematologic:** At the indicated dose and schedule, BUSULFEX produced profound myelosuppression in 100% of patients. Following hematopoietic progenitor cell infusion, recovery of

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neutrophil counts to  $\geq 500$  cells/mm<sup>3</sup> occurred at median day 13 when prophylactic G-CSF was administered to the majority of participants on the study. The median number of platelet transfusions per patient on study was 6, and the median number of red blood cell transfusions on study was 4. Prolonged prothrombin time was reported in one patient (2%).

**Gastrointestinal:** Gastrointestinal toxicities were frequent and generally considered to be related to the drug. Few were categorized as serious. Mild or moderate nausea occurred in 92% of patients in the allogeneic clinical trial, and mild or moderate vomiting occurred in 95% through BMT day +28; nausea was severe in 7%. The incidence of vomiting during BUSULFEX administration (BMT Day -7 to -4) was 43% in the allogeneic clinical trial. Grade 3-4 stomatitis developed in 26% of the participants, and grade 3 esophagitis developed in 2%. Grade 3-4 diarrhea was reported in 5% of the allogeneic study participants, while mild or moderate diarrhea occurred in 75%. Mild or moderate constipation occurred in 38% of patients; ileus developed in 8% and was severe in 2%. Forty-four percent (44%) of patients reported mild or moderate dyspepsia. Two percent (2%) of patients experienced mild hematemesis. Pancreatitis developed in 2% of patients. Mild or moderate rectal discomfort occurred in 24% of patients. Severe anorexia occurred in 21% of patients and was mild/moderate in 64%.

**Hepatic:** Hyperbilirubinemia occurred in 49% of patients in the allogeneic BMT trial. Grade 3/4 hyperbilirubinemia occurred in 30% of patients within 28 days of transplantation and was considered life-threatening in 5% of these patients. Hyperbilirubinemia was associated with graft-versus-host disease in six patients and with hepatic veno-occlusive disease in 5 patients. Grade 3/4 SGPT elevations occurred in 7% of patients. Alkaline phosphatase increases were mild or moderate in 15% of

patients. Mild or moderate jaundice developed in 12% of patients, and mild or moderate hepatomegaly developed in 6%.

**Hepatic veno-occlusive disease:** Hepatic veno-occlusive disease (HVOD) is a recognized potential complication of conditioning therapy prior to transplant. Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three of the five patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria.

**Graft-versus-host disease:** Graft-versus-host disease developed in 18% of patients (11/61) receiving allogeneic transplants; it was severe in 3%, and mild or moderate in 15%. There were 3 deaths (5%) attributed to GVHD.

**Edema:** Seventy-nine percent (79%) of patients exhibited some form of edema, hypervolemia, or weight increase; all events were reported as mild or moderate.

**Infection/Fever:** Fifty-one percent (51%) of patients experienced one or more episodes of infection. Pneumonia was fatal in one patient (2%) and life-threatening in 3% of patients. Fever was reported in 80% of patients; it was mild or moderate in 78% and severe in 3%. Forty-six percent (46%) of patients experienced chills.

**Cardiovascular:** Mild or moderate tachycardia was reported in 44% of patients. In 7 patients (11%) it was first reported during BUSULFEX administration. Other rhythm abnormalities, which were

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all mild or moderate, included arrhythmia (5%), atrial fibrillation (2%), and ventricular extrasystoles (2%). Mild or moderate thrombosis occurred in 33% of patients, and all episodes were associated with the central venous catheter. Hypertension was reported in 36% of patients and was Grade 3/4 in 7%. Hypotension occurred in 11% of patients and was Grade 3/4 in 3%. Mild vasodilation (flushing and hot flashes) was reported in 25% of patients. Other cardiovascular events included cardiomegaly (5%), mild ECG abnormality (2%), grade 3/4 left-sided heart failure in one patient (2%), and moderate pericardial effusion (2%). These events were reported primarily in the post-cyclophosphamide phase.

**Pulmonary:** Mild or moderate dyspnea occurred in 25% of patients and was severe in 2%. One patient (2%) experienced severe hyperventilation; and in 2 (3%) additional patients it was mild or moderate. Mild rhinitis and mild or moderate cough were reported in 44% and 28% of patients, respectively. Mild epistaxis events were reported in 25%. Three patients (5%) on the allogeneic study developed documented alveolar hemorrhage. All required mechanical ventilatory support and all died. Non-specific interstitial fibrosis was found on wedge biopsies performed with video assisted thoracoscopy in one patient on the allogeneic study who subsequently died from respiratory failure on BMT Day +98. Other pulmonary events, reported as mild or moderate, included pharyngitis (18%), hiccup (18%), asthma (8%), atelectasis (2%), pleural effusion (3%), hypoxia (2%), hemoptysis (3%), and sinusitis (3%).

**Neurologic:** The most commonly reported adverse events of the central nervous system were insomnia (84%), anxiety (75%), dizziness (30%), and depression (23%). Severity was mild or moderate except for one patient (1%) who experienced severe insomnia. One patient (1%) developed a life-threatening cerebral

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hemorrhage and a coma as a terminal event following multi-organ failure after HVOD. Other events considered severe included delirium (2%), agitation (2%), and encephalopathy (2%). The overall incidence of confusion was 11%, and 5% of patients were reported to have experienced hallucinations. The patient who developed delirium and hallucination on the allogeneic study had onset of confusion at the completion of BUSULFEX (busulfan) Injection. The overall incidence of lethargy in the allogeneic BUSULFEX clinical trial was 7%, and somnolence was reported in 2%. One patient (2%) treated in an autologous transplantation study experienced a seizure while receiving cyclophosphamide, despite prophylactic treatment with phenytoin.

**Renal:** Creatinine was mildly or moderately elevated in 21% of patients. BUN was increased in 3% of patients and to a grade 3/4 level in 2%. Seven percent of patients experienced dysuria, 15% oliguria, and 8% hematuria. There were 4 (7%) Grade 3/4 cases of hemorrhagic cystitis in the allogeneic clinical trial.

**Skin:** Rash (57%) and pruritus (28%) were reported; both conditions were predominantly mild. Alopecia was mild in 15% of patients and moderate in 2%. Mild vesicular rash was reported in 10% of patients and mild or moderate maculopapular rash in 8%. Vesiculo-bullous rash was reported in 10%, and exfoliative dermatitis in 5%. Erythema nodosum was reported in 2%, acne in 7%, and skin discoloration in 8%.

**Metabolic:** Hyperglycemia was observed in 67% of patients and Grade 3/4 hyperglycemia was reported in 15%. Hypomagnesemia was mild or moderate in 77% of patients; hypokalemia was mild or moderate in 62% and severe in 2%; hypocalcemia was mild or moderate in 46% and severe in 3%; hypophosphatemia was mild or moderate in 17%; and hyponatremia was reported in 2%.



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Death ≤100d =4.1% (3/73)	No Report	Acute ≥ Grade 2 = 35%  Chronic = 41% (30/73)	1 death from Idiopathic Interstitial Pneumonitis and 1 death from pulmonary fibrosis	No Report	No Report
Devergie CML Chronic Phase					
TRM	VOD	GVHD	Pulmonary	Hemorrhagic Cystitis	Seizure
38%	7.7% (5/65) Deaths=4.6% (3/65)	Acute ≥ Grade 2 = 41% (24/59 at risk)	Interstitial Pneumonitis = 16.9% (11/65)	10.8% (7/65)	No report
Ringden CML, AML, ALL					
TRM	VOD	GVHD	Pulmonary	Hemorrhagic Cystitis	Seizure
28%	12%	Acute ≥ Grade 2 GVHD = 26%  Chronic GVHD = 45%	Interstitial pneumonitis = 14%	24%	6%
Blume CML, AML, ALL					
TRM	VOD	GVHD	Pulmonary	Hemorrhagic Cystitis	Seizure
No Report	Deaths = 4.9%	Acute ≥ Grade 2 GVHD = 22% (13/58 at risk)  Chronic GVHD = 31% (14/45 at risk)	No Report	No Report	No Report

\*TRM = Transplantation Related Mortality

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\*\*VOD = Veno-Occlusive Disease of the liver

\*\*\*GVHD = Graft versus Host Disease

**OVERDOSAGE:** There is no known antidote to BUSULFEX other than hematopoietic progenitor cell transplantation. In the absence of hematopoietic progenitor cell transplantation, the recommended dosage for BUSULFEX would constitute an overdose of busulfan. The principal toxic effect is profound bone marrow hypoplasia/aplasia and pancytopenia but the central nervous system, liver, lungs, and gastrointestinal tract may be affected. The hematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated. Survival after a single 140 mg dose of Myleran® Tablets in an 18 kg, 4-year old child has been reported. Inadvertent administration of a greater than normal dose of oral busulfan (2.1 mg/kg; total dose of 23.3 mg/kg) occurred in a 2-year old child prior to a scheduled bone marrow transplant without sequelae. An acute dose of 2.4 g was fatal in a 10-year old boy. There is one report that busulfan is dialyzable, thus dialysis should be considered in the case of overdose. Busulfan is metabolized by conjugation with glutathione, thus administration of glutathione may be considered.

**DOSAGE AND ADMINISTRATION**

When BUSULFEX is administered as a component of the BuCy conditioning regimen prior to bone marrow or peripheral blood progenitor cell replacement, the recommended doses are as follows:

**Adults (BuCy2):** The usual adult dose is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered every six hours for four days (a total of 16 doses). For obese, or severely obese patients, BUSULFEX should be administered based

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on adjusted ideal body weight. Ideal body weight (IBW) should be calculated as follows (height in cm, and weight in kg): IBW (kg; men) =  $50 + 0.91 \times (\text{height in cm} - 152)$ ; IBW (kg; women) =  $45 + 0.91 \times (\text{height in cm} - 152)$ . Adjusted ideal body weight (AIBW) should be calculated as follows:  $AIBW = IBW + 0.25 \times (\text{actual weight} - IBW)$ . Cyclophosphamide is given on each of two days as a one-hour infusion at a dose of 60 mg/kg beginning on BMT day -3, no sooner than six hours following the 16<sup>th</sup> dose of BUSULFEX.

BUSULFEX clearance is best predicted when the BUSULFEX dose is administered based on adjusted ideal body weight. Dosing BUSULFEX based on actual body weight, ideal body weight or other factors can produce significant differences in BUSULFEX (busulfan) Injection clearance among lean, normal and obese patients.

BUSULFEX should be administered intravenously via a central venous catheter as a two-hour infusion every six hours for four consecutive days for a total of 16 doses. All patients should be premedicated with phenytoin as busulfan is known to cross the blood brain barrier and induce seizures. Phenytoin reduces busulfan plasma AUC by 15%. Use of other anticonvulsants may result in higher busulfan plasma AUCs, and an increased risk of VOD or seizures. In cases where other anticonvulsants must be used, plasma busulfan exposure should be monitored (See DRUG INTERACTIONS). Antiemetics should be administered prior to the first dose of BUSULFEX and continued on a fixed schedule through administration of BUSULFEX. Where available, pharmacokinetic monitoring may be considered to further optimize therapeutic targeting.

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**Pediatrics:** The effectiveness of BUSULFEX in the treatment of CML has not been specifically studied in pediatric patients. For additional information see Special Populations-Pediatric section.

**Preparation and Administration Precautions:**

An administration set with minimal residual hold-up volume (2-5 cc) should be used for product administration. As with other cytotoxic compounds, caution should be exercised in handling and preparing the solution of BUSULFEX. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If BUSULFEX or diluted BUSULFEX solution contacts the skin or mucosa, wash the skin or mucosa thoroughly with water.

BUSULFEX is a clear, colorless solution. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever the solution and container permit. If particulate matter is seen in the BUSULFEX ampoule the drug should not be used.

**Preparation for Intravenous Administration:**

BUSULFEX must be diluted prior to use with either 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D<sub>5</sub>W). The diluent quantity should be 10 times the volume of BUSULFEX, so that the final concentration of busulfan is approximately 0.5 mg/mL. Calculation of the dose for a 70 kg patient, would be performed as follows:

$(70\text{kg patient}) \times (0.8 \text{ mg/kg}) \div (6 \text{ mg/mL}) = 9.3 \text{ mL BUSULFEX (56 mg total dose)}$ .

To prepare the final solution for infusion, add 9.3 mL of BUSULFEX to 93 mL of diluent (normal saline or D<sub>5</sub>W) as calculated below:



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Unopened ampoules of BUSULFEX are stable until the date indicated on the package when stored under refrigeration at 2°-8°C (36°-46° F).

BUSULFEX diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is stable at room temperature (25° C) for up to 8 hours but the infusion must be completed within that time. BUSULFEX diluted in 0.9% Sodium Chloride Injection, USP is stable at refrigerated conditions (2°-8° C) for up to 12 hours but the infusion must be completed within that time.

#### **HOW SUPPLIED**

BUSULFEX is supplied as a sterile solution in 10 mL single-use clear glass ampoules each containing 60 mg of busulfan at a concentration of 6 mg/mL for intravenous use.

NDC 62161-005-38            10mL (6mg/mL) in packages of eight ampoules including eight compatible 25mm 5.0 micron Nylon Membrane syringe filters.

Unopened ampoules of BUSULFEX must be stored under refrigerated conditions between 2°-8°C (36°-46°F).

#### **HANDLING AND DISPOSAL**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.<sup>1,2,3,4,5,6</sup> There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**Distributed by:**

Orphan Medical Inc.  
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United States Patent numbers 5,430,057 and 5,559,148. Patents pending in Canada and European Union.

Revision Date: February 2000 Part No. 4040290

**References**

1. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, National Institutes of Health; 1983. US Department of Health and Human Services, Public Health Service publication NIH 83-2621.
2. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA* 1985; 253:1590-1591.
3. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
4. Clinical Oncology Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1983; 1:426-428.
5. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA-A Cancer J for Clin* 1983; 33:258-263.
6. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

For questions of a medical nature call 1-888-867-7426  
(1-888-8ORPHAN).

To order BUSULFEX call 1-800-359-4304.

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## COZAAR® (LOSARTAN POTASSIUM TABLETS)

### USE IN PREGNANCY

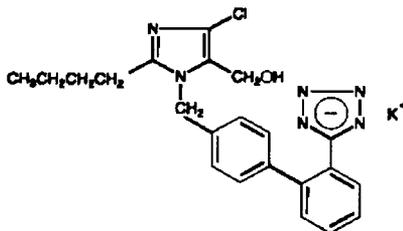
**When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.**

When pregnancy is detected, COZAAR should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

### DESCRIPTION

COZAAR\* (losartan potassium) is an angiotensin II receptor (type AT<sub>1</sub>) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is C<sub>22</sub>H<sub>22</sub>ClKN<sub>6</sub>O, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available as tablets for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg, 50 mg and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT<sub>1</sub> receptor and have much greater affinity (about 1000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT<sub>1</sub> receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT<sub>1</sub> receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

#### *Pharmacokinetics*

##### *General*

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its  $C_{max}$  but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of  $^{14}C$ -labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral  $^{14}C$ -labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of  $^{14}C$ -labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

##### *Special Populations*

*Pediatric:* Losartan pharmacokinetics have not been investigated in patients <18 years of age.

*Geriatric and Gender:* Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

*Race:* Pharmacokinetic differences due to race have not been studied. (see also PRECAUTIONS, *Race* and CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race*).

*Renal Insufficiency:* Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, *Hypotension — Volume-Depleted Patients* and DOSAGE AND ADMINISTRATION).

*Hepatic Insufficiency:* Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

##### *Drug Interactions*

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and

cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

#### *Pharmacodynamics and Clinical Effects*

**Hypertension:** Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. COZAAR was effective in reducing blood pressure regardless of race, although the effect was somewhat less in Black patients (usually a low-renin population).

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

**Reduction in the Risk of Stroke:** The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a multinational, double-blind study comparing COZAAR and atenolol in 9193 hypertensive patients with ECG-documented left ventricular hypertrophy. Patients with myocardial infarction or stroke within six months prior to randomization were excluded. Patients were randomized to receive once daily COZAAR 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of COZAAR or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure.

Of the randomized patients, 4963 (54%) were female and 533 (6%) were Black. The mean age was 67 with 5704 (62%) age  $\geq$ 65. At baseline, 1195 (13%) had diabetes, 1326 (14%) had isolated systolic hypertension, 1469 (16%) had coronary heart disease, and 728 (8%) had cerebrovascular disease. Baseline mean blood pressure was 174/98 mmHg in both treatment groups. The mean length of follow-up was 4.8 years. At the end of study or at the last visit before a primary endpoint, 77% of the group treated with COZAAR and 73% of the group treated with atenolol were still taking study medication. Of the patients still taking study medication, the mean doses of COZAAR and atenolol were both about 80 mg/day, and 15% were taking atenolol or losartan as monotherapy, while 77% were also receiving hydrochlorothiazide (at a mean dose of 20 mg/day in each group). Blood pressure reduction measured

at trough was similar for both treatment groups but blood pressure was not measured at any other time of the day. At the end of study or at the last visit before a primary endpoint, the mean blood pressures were 144.1/81.3 mmHg for the group treated with COZAAR and 145.4/80.9 mmHg for the group treated with atenolol [the difference in SBP of 1.3 mmHg was significant ( $p < 0.001$ ), while the difference of 0.4 mmHg in DBP was not significant ( $p = 0.098$ )].

The primary endpoint was the first occurrence of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Patients with non-fatal events remained in the trial, so that there was also an examination of the first event of each type even if it was not the first event (e.g., a stroke following an initial myocardial infarction would be counted in the analysis of stroke). Treatment with COZAAR resulted in a 13% reduction ( $p = 0.021$ ) in risk of the primary endpoint compared to the atenolol group (see Figure 1 and Table 1); this difference was primarily the result of an effect on fatal and nonfatal stroke. Treatment with COZAAR reduced the risk of stroke by 25% relative to atenolol ( $p = 0.001$ ) (see Figure 2 and Table 1).

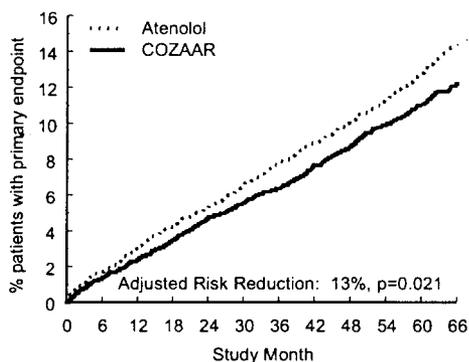


Figure 1. Kaplan-Meier estimates of the primary endpoint of time to cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction in the groups treated with COZAAR and atenolol. The Risk Reduction is adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy.

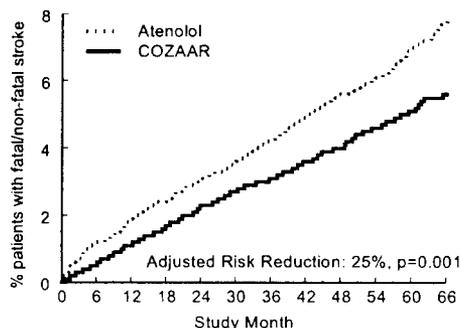


Figure 2. Kaplan-Meier estimates of the time to fatal/nonfatal stroke in the groups treated with COZAAR and atenolol. The Risk Reduction is adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy.

Table 1 shows the results for the primary composite endpoint and the individual endpoints. The primary endpoint was the first occurrence of stroke, myocardial infarction or cardiovascular death, analyzed using an intention-to-treat (ITT) approach. The table shows the number of events for each component in two different ways. The Components of Primary Endpoint (as a first event) counts only the events that define the primary endpoint, while the Secondary Endpoints count all first events of a particular type, whether or not they were preceded by a different type of event.

Table 1. Incidence of Primary Endpoint Events

	COZAAR		Atenolol		Risk Reduction†	95% CI	p-Value
	N (%)	Rate*	N (%)	Rate*			
Primary Composite Endpoint	508 (11)	23.8	588 (13)	27.9	13%	2% to 23%	0.021
Components of Primary Composite Endpoint (as a first event)							
Stroke (nonfatal‡)	209 (5)		286 (6)				
Myocardial infarction (nonfatal‡)	174 (4)		168 (4)				
Cardiovascular mortality	125 (3)		134 (3)				
Secondary Endpoints (any time in study)							
Stroke (fatal/nonfatal)	232 (5)	10.8	309 (7)	14.5	25%	11% to 37%	0.001
Myocardial infarction (fatal/nonfatal)	198 (4)	9.2	188 (4)	8.7	-7%	-13% to 12%	0.491
Cardiovascular mortality	204 (4)	9.2	234 (5)	10.6	11%	-7% to 27%	0.206
Due to CHD	125 (3)	5.6	124 (3)	5.6	-3%	-32% to 20%	0.839
Due to Stroke	40 (1)	1.8	62 (1)	2.8	35%	4% to 67%	0.032
Other§	39 (1)	1.8	48 (1)	2.2	16%	-28% to 45%	0.411

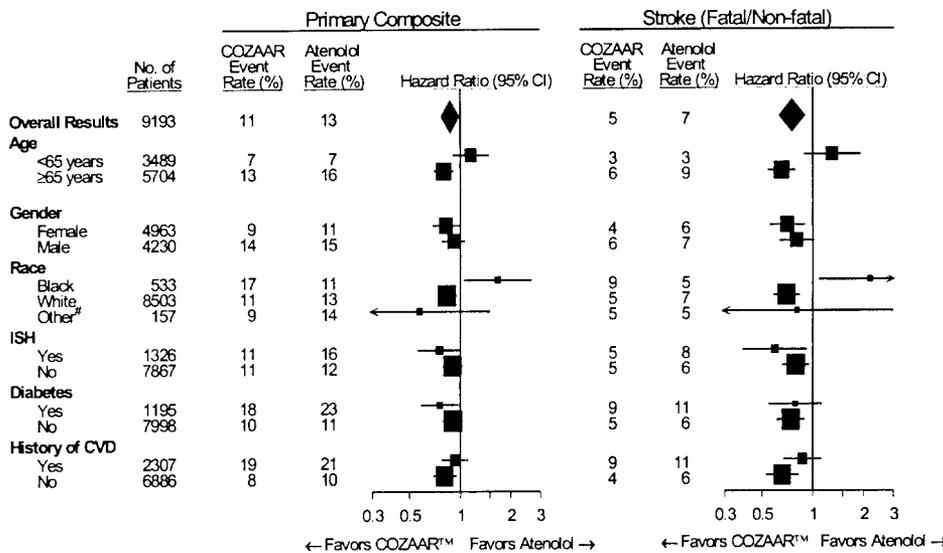
\* Rate per 1000 patient years of follow up  
 † Adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy  
 ‡ First report of an event, in some cases the patient died subsequently to the event reported  
 § Death due to heart failure, non-coronary vascular disease, pulmonary embolism, or a cardiovascular cause other than stroke or coronary heart disease

Although the LIFE study favored COZAAR over atenolol with respect to the primary endpoint (p=0.021), this result is from a single study and, therefore, is less compelling than the difference between COZAAR and placebo. Although not measured directly, the difference between COZAAR and placebo is compelling because there is evidence that atenolol is itself effective (vs. placebo) in reducing cardiovascular events, including stroke, in hypertensive patients.

Other clinical endpoints of the LIFE study were: total mortality, hospitalization for heart failure or angina pectoris, coronary or peripheral revascularization procedures, and resuscitated cardiac arrest. There were no significant differences in the rates of these endpoints between the COZAAR and atenolol groups.

For the primary endpoint and stroke, the effects of COZAAR in patient subgroups defined by age, gender, race and presence or absence of isolated systolic hypertension (ISH), diabetes, and history of cardiovascular disease (CVD) are shown in Figure 3 below. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Figure 3 Primary Endpoint Events† within Demographic Subgroups



Symbols are proportional to sample size.

#Other includes Asian, Hispanic, Asiatic, Multi-race, Indian, Native American, European.

†Adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy.

**Race:** In the LIFE study, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with COZAAR. In the subgroup of Black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 26 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 42 per 1000 patient-years) on COZAAR. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In addition, blood pressure reductions in both treatment groups were consistent between Black and non-Black patients. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study provides no evidence that the benefits of COZAAR on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients.

**Nephropathy in Type 2 Diabetic Patients:** The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a randomized, placebo-controlled, double-blind, multicenter study conducted worldwide in 1513 patients with type 2 diabetes with nephropathy (defined as serum creatinine 1.3 to 3.0 mg/dl in females or males ≤60 kg and 1.5 to 3.0 mg/dl in males >60 kg and proteinuria [urinary albumin to creatinine ratio ≥300 mg/g]).

Patients were randomized to receive COZAAR 50 mg once daily or placebo on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. After one month, investigators were instructed to titrate study drug to 100 mg once daily if the trough blood pressure goal (140/90 mmHg) was not achieved. Overall, 72% of patients received the 100 mg daily dose more than 50% of the time they were on study drug. Because the study was designed to achieve equal blood pressure control in both groups, other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for a mean duration of 3.4 years.

The study population was diverse with regard to race (Asian 16.7%, Black 15.2%, Hispanic 18.3%, White 48.6%). Overall, 63.2% of the patients were men, and 66.4% were under the age of 65 years. Almost all of the patients (96.6%) had a history of hypertension, and the patients entered the trial with a mean serum creatinine of 1.9 mg/dl and mean proteinuria (urinary albumin/creatinine) of 1808 mg/g at baseline.

The primary endpoint of the study was the time to first occurrence of any one of the following events: doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. Treatment with COZAAR resulted in a 16% risk reduction in this endpoint (see Figure 4 and Table 2). Treatment with COZAAR also reduced the occurrence of sustained doubling of serum creatinine by 25% and ESRD by 29% as separate endpoints, but had no effect on overall mortality (see Table 2).

The mean baseline blood pressures were 152/82 mmHg for COZAAR plus conventional antihypertensive therapy and 153/82 mmHg for placebo plus conventional antihypertensive therapy. At the end of the study, the mean blood pressures were 143/76 mmHg for the group treated with COZAAR and 146/77 mmHg for the group treated with placebo.

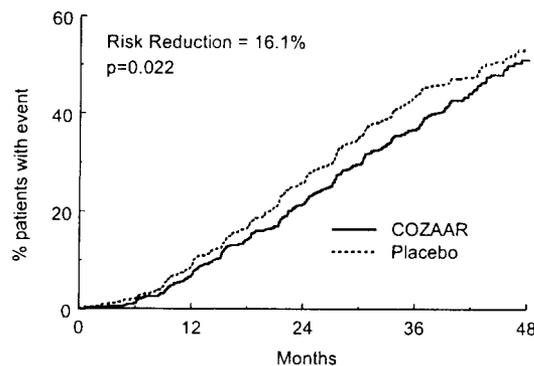


FIGURE 4: Kaplan-Meier curve for the primary composite endpoint of doubling of serum creatinine, end stage renal disease (need for dialysis or transplantation) or death.

Table 2 Incidence of Primary Endpoint Events

	Incidence		Risk Reduction	95% C.I.	p-Value
	Losartan	Placebo			
Primary Composite Endpoint	43.5%	47.1%	16.1%	2.3% to 27.9%	0.022
Doubling of Serum Creatinine, ESRD and Death Occurring as a First Event					
Doubling of Serum Creatinine	21.6%	26.0%			
ESRD	8.5%	8.5%			
Death	13.4%	12.6%			
Overall Incidence of Doubling of Serum Creatinine, ESRD and Death					
Doubling of Serum Creatinine	21.6%	26.0%	25.3%	7.8% to 39.4%	0.006
ESRD	19.6%	25.5%	28.6%	11.5% to 42.4%	0.002
Death	21.0%	20.3%	-1.7%	-26.9% to 18.6%	0.884

The secondary endpoints of the study were change in proteinuria, change in the rate of progression of renal disease, and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina, or cardiovascular death). Compared with placebo, COZAAR significantly reduced proteinuria by an average of 34%, an effect that was evident within 3 months of starting therapy, and significantly reduced the rate of decline in glomerular filtration rate during the study by 13%, as measured by the reciprocal of the serum creatinine concentration. There was no significant difference in the incidence of the composite endpoint of cardiovascular morbidity and mortality.

The favorable effects of COZAAR were seen in patients also taking other anti-hypertensive medications (angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors were not allowed), oral hypoglycemic agents and lipid-lowering agents.

For the primary endpoint and ESRD, the effects of COZAAR in patient subgroups defined by age, gender and race are shown in Table 3 below. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Table 3 Efficacy Outcomes within Demographic Subgroups

	No. of Patients	Primary Composite Endpoint			ESRD		
		COZAAR Event Rate %	Placebo Event Rate %	Hazard Ratio (95% CI)	COZAAR Event Rate %	Placebo Event Rate %	Hazard Ratio (95% CI)
Overall Results	1513	43.5	47.1	0.839 (0.721, 0.977)	19.6	25.5	0.714 (0.576, 0.885)
Age							
<65 years	1005	44.1	49.0	0.784 (0.653, 0.941)	21.1	28.5	0.670 (0.521, 0.863)
≥65 years	508	42.3	43.5	0.978 (0.749, 1.277)	16.5	19.6	0.847 (0.560, 1.281)
Gender							
Female	557	47.8	54.1	0.762 (0.603, 0.962)	22.8	32.8	0.601 (0.436, 0.828)
Male	956	40.9	43.3	0.892 (0.733, 1.085)	17.5	21.5	0.809 (0.605, 1.081)
Race							
Asian	252	41.9	54.8	0.655 (0.453, 0.947)	18.8	27.4	0.625 (0.367, 1.066)
Black	230	40.0	39.0	0.983 (0.647, 1.495)	17.6	21.0	0.831 (0.456, 1.516)
Hispanic	277	55.0	54.0	1.003 (0.728, 1.380)	30.0	28.5	1.024 (0.661, 1.586)
White	735	40.5	43.2	0.809 (0.645, 1.013)	16.2	23.9	0.596 (0.427, 0.831)

**INDICATIONS AND USAGE**

*Hypertension*

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, including diuretics.

*Hypertensive Patients with Left Ventricular Hypertrophy*

COZAAR is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients. (See PRECAUTIONS, Race and CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race.)

#### *Nephropathy in Type 2 Diabetic Patients*

COZAAR is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio  $\geq 300$  mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, COZAAR reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation) (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

#### **CONTRAINDICATIONS**

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

#### **WARNINGS**

##### *Fetal/Neonatal Morbidity and Mortality*

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAAR as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m<sup>2</sup> basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk. *Hypotension — Volume-Depleted Patients*

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

## PRECAUTIONS

### *General*

*Hypersensitivity:* Angioedema. See ADVERSE REACTIONS, *Post-Marketing Experience*.

### *Impaired Hepatic Function*

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

### *Impaired Renal Function*

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with COZAAR; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with COZAAR; in some patients, these effects were reversible upon discontinuation of therapy.

### *Electrolyte Imbalance*

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated with COZAAR as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see ADVERSE REACTIONS).

### *Information for Patients*

*Pregnancy:* Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

*Potassium Supplements:* A patient receiving COZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see PRECAUTIONS, *Drug Interactions*).

### *Drug Interactions*

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

### *Carcinogenesis, Mutagenesis, Impairment of Fertility*

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ( $p < 0.05$ ) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

#### *Pregnancy*

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

#### *Nursing Mothers*

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

#### *Pediatric Use*

Safety and effectiveness in pediatric patients have not been established.

#### *Use in the Elderly*

Of the total number of patients receiving COZAAR in controlled clinical studies for hypertension, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. In a controlled clinical study for renal protection in type 2 diabetic patients with proteinuria, 248 patients (33%) were 65 years and over. In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

#### *Race*

In the LIFE study, Black patients with hypertension and left ventricular hypertrophy had a lower risk of stroke on atenolol than on COZAAR. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study does not provide evidence that the benefits of COZAAR on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects; Reduction in the Risk of Stroke*.)

## **ADVERSE REACTIONS**

### *Hypertension*

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well-tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo-controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The adverse experiences reported in  $\geq 1\%$  of patients treated with COZAAR and more commonly than placebo are shown in the table below.

	Losartan (n=1075) Incidence %	Placebo (n=334) Incidence %
<i>Musculoskeletal</i>		
Cramp, muscle	1	0
Pain, back	2	1
Pain, leg	1	0
<i>Nervous System/Psychiatric</i>		
Dizziness	3	2
<i>Respiratory</i>		
Congestion, nasal	2	1
Infection, upper respiratory	8	7
Sinusitis	1	0

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis, diarrhea, dyspepsia, myalgia, insomnia, cough, sinus disorder.

Adverse events occurred at about the same rates in men and women, older and younger patients, and Black and non-Black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan: *Body as a Whole*: facial edema, fever, orthostatic effects, syncope; *Cardiovascular*: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; *Digestive*: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; *Hematologic*: anemia; *Metabolic*: gout; *Musculoskeletal*: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric*: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; *Respiratory*: dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; *Skin*: alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; *Special Senses*: blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital*: impotence, nocturia, urinary frequency, urinary tract infection.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1†	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2††	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

† Demographics = (89% caucasian, 64% female)

†† Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

#### *Hypertensive Patients with Left Ventricular Hypertrophy*

In the LIFE study, adverse events with COZAAR were similar to those reported previously for patients with hypertension.

#### *Nephropathy in Type 2 Diabetic Patients*

In the RENAAL study involving 1513 patients treated with COZAAR or placebo, the overall incidences of reported adverse experiences were similar for the two groups. COZAAR was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo (19% for COZAAR, 24% for placebo). The adverse experiences regardless of drug relationship, reported with an incidence of  $\geq 4\%$  of patients treated with COZAAR and occurring more commonly than placebo, on a background of conventional antihypertensive therapy are shown in the table below.

	Losartan and Conventional Antihypertensive Therapy Incidence % (n=751)	Placebo and Conventional Antihypertensive Therapy Incidence % (n=762)
<i>Body as a Whole</i>		
Asthenia/Fatigue	14	10
Chest Pain	12	8
Fever	4	3
Infection	5	4
Influenza-like disease	10	9
Trauma	4	3
<i>Cardiovascular</i>		
Hypotension	7	3
Orthostatic hypotension	4	1
<i>Digestive</i>		
Diarrhea	15	10
Dyspepsia	4	3
Gastritis	5	4
<i>Endocrine</i>		
Diabetic neuropathy	4	3
Diabetic vascular disease	10	9
<i>Eyes, Ears, Nose and Throat</i>		
Cataract	7	5
Sinusitis	6	5
<i>Hemic</i>		
Anemia	14	11
<i>Metabolic and Nutrition</i>		
Hyperkalemia	7	3
Hypoglycemia	14	10
Weight gain	4	3
<i>Musculoskeletal</i>		
Back pain	12	10
Leg pain	5	4
Knee pain	5	4
Muscular weakness	7	4
<i>Nervous System</i>		
Hypesthesia	5	4
<i>Respiratory</i>		
Bronchitis	10	9
Cough	11	10
<i>Skin</i>		
Cellulitis	7	6
<i>Urogenital</i>		
Urinary tract infection	16	13

#### *Post-Marketing Experience*

The following additional adverse reactions have been reported in post-marketing experience:

*Hypersensitivity:* Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported. Anaphylactic reactions have been reported.

*Digestive:* Hepatitis (reported rarely).

*Respiratory:* Dry cough (see above).

Hyperkalemia and hyponatremia have been reported.

#### *Laboratory Test Findings*

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

*Creatinine, Blood Urea Nitrogen:* Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone (see PRECAUTIONS, *Impaired Renal Function*).

*Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

*Liver Function Tests:* Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

#### **OVERDOSAGE**

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m<sup>2</sup> basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

#### **DOSAGE AND ADMINISTRATION**

COZAAR may be administered with other antihypertensive agents, and with or without food.

##### *Hypertension*

Dosing must be individualized. The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, *Hypotension — Volume-Depleted Patients*) and patients with a history of hepatic impairment (see PRECAUTIONS, *General*). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Hypertension*).

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Hypertension*).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

##### *Hypertensive Patients with Left Ventricular Hypertrophy*

The usual starting dose is 50 mg of COZAAR once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of COZAAR should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke*).

##### *Nephropathy in Type 2 Diabetic Patients*

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Nephropathy in Type 2 Diabetic Patients*). COZAAR may be administered with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

#### **HOW SUPPLIED**

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

**NDC 0006-0951-54** unit of use bottles of 90

**NDC 0006-0951-58** unit of use bottles of 100

**NDC 0006-0951-28** unit dose packages of 100.

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No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

**NDC** 0006-0952-31 unit of use bottles of 30

**NDC** 0006-0952-54 unit of use bottles of 90

**NDC** 0006-0952-58 unit of use bottles of 100

**NDC** 0006-0952-28 unit dose packages of 100

**NDC** 0006-0952-82 bottles of 1,000.

No. 6536 — Tablets COZAAR, 100 mg, are dark green, teardrop-shaped, film-coated tablets with code 960 on one side and MRK on the other. They are supplied as follows:

**NDC** 0006-0960-31 unit of use bottles of 30

**NDC** 0006-0960-58 unit of use bottles of 100

**NDC** 0006-0960-28 unit dose packages of 100.

*Storage*

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

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Dist. by:  
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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# Nolvadex<sup>®</sup>

## TAMOXIFEN CITRATE

**WARNING - For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer:** Serious and life-threatening events associated with NOLVADEX in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see **CLINICAL PHARMACOLOGY-Clinical Studies – Reduction in Breast Cancer Incidence In High Risk Women**). Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for NOLVADEX vs 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women-years of 0.17 for NOLVADEX vs 0.0 for placebo)\*. For stroke, the incidence rate per 1,000 women-years was 1.43 for NOLVADEX vs 1.00 for placebo\*\*. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for NOLVADEX versus 0.25 for placebo\*\*.

Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.

Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering NOLVADEX to reduce their risk of developing breast cancer.

The benefits of NOLVADEX outweigh its risks in women already diagnosed with breast cancer.

\*Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See **WARNINGS: Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma**.

\*\*See Table 3 under **CLINICAL PHARMACOLOGY-Clinical Studies**.

### DESCRIPTION

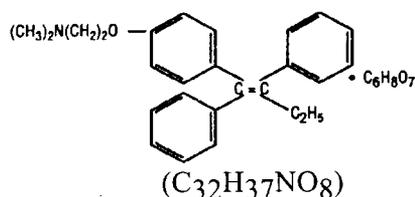
NOLVADEX<sup>®</sup> (tamoxifen citrate) Tablets, a nonsteroidal antiestrogen, are for oral administration. NOLVADEX Tablets are available as:

**10 mg Tablets.** Each tablet contains 15.2 mg of tamoxifen citrate which is equivalent to 10 mg of tamoxifen.

**20 mg Tablets.** Each tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen.

Inactive Ingredients: carboxymethylcellulose calcium, magnesium stearate, mannitol and starch.

Chemically, NOLVADEX is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z)-2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1). The structural and empirical formulas are:



Tamoxifen citrate has a molecular weight of 563.62, the pKa' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C, it is 0.2 mg/mL.

### CLINICAL PHARMACOLOGY

NOLVADEX is a nonsteroidal agent that has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.

In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

**Absorption and Distribution:** Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/mL (range 71-183 ng/mL) and 353 ng/mL (range 152-706 ng/mL), respectively. After initiation of therapy, steady-state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10 mg NOLVADEX tablets given twice a day vs. a 20 mg NOLVADEX tablet given once daily, the 20 mg NOLVADEX tablet was bioequivalent to the 10 mg NOLVADEX tablets.

**Metabolism:** Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

**Excretion:** Studies in women receiving 20 mg of <sup>14</sup>C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

**Special Populations:** The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

**Pediatric Patients:**

The pharmacokinetics of tamoxifen and N-desmethyl tamoxifen were characterized using a population pharmacokinetic analysis with sparse samples per patient obtained from 27 female pediatric patients aged 2 to 10 years enrolled in a study designed to evaluate the safety, efficacy, and pharmacokinetics of NOLVADEX in treating McCune-Albright Syndrome. Rich data from two tamoxifen citrate pharmacokinetic trials in which 59 postmenopausal women with breast cancer completed the studies were included in the analysis to determine the structural pharmacokinetic model for tamoxifen. A one-compartment model provided the best fit to the data.

In pediatric patients, an average steady state peak plasma concentration ( $C_{ss, max}$ ) and AUC were of 187 ng/mL and 4110 ng hr/mL, respectively, and  $C_{ss, max}$  occurred approximately 8 hours after dosing. Clearance (CL/F) as body weight adjusted in female pediatric patients was approximately 2.3-fold higher than in female breast cancer patients. In the youngest cohort of female pediatric patients (2-6 year olds), CL/F was 2.6-fold higher; in the oldest cohort (7-10.9 year olds) CL/F was approximately 1.9-fold higher. Exposure to N-desmethyl tamoxifen was comparable between the pediatric and adult patients. **The safety and efficacy of NOLVADEX for girls aged two to 10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond one year of treatment. The long-term effects of NOLVADEX therapy in girls have not been established.** In adults treated with NOLVADEX an increase in the incidence of uterine malignancies, stroke and pulmonary embolism has been noted (see **BOXED WARNING**).

**Drug-drug Interactions:** *In vitro* studies showed that erythromycin, cyclosporin, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent  $K_i$  of 20, 1, 45 and 30  $\mu\text{M}$ , respectively. The clinical significance of these *in vitro* studies is unknown.

Tamoxifen reduced the plasma concentration of letrozole by 37% when these drugs were co-administered. Rifampin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC and  $C_{\text{max}}$  by 86% and 55%, respectively. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

### **Clinical Studies - Metastatic Breast Cancer**

**Premenopausal Women (NOLVADEX vs. Ablation)** - Three prospective, randomized studies (Ingle, Pritchard, Buchanan) compared NOLVADEX to ovarian ablation (oophorectomy or ovarian irradiation) in premenopausal women with advanced breast cancer. Although the objective response rate, time to treatment failure, and survival were similar with both treatments, the limited patient accrual prevented a demonstration of equivalence. In an overview analysis of survival data from the 3 studies, the hazard ratio for death (NOLVADEX/ovarian ablation) was 1.00 with two-sided 95% confidence intervals of 0.73 to 1.37. Elevated serum and plasma estrogens have been observed in premenopausal women receiving NOLVADEX, but the data from the randomized studies do not suggest an adverse effect of this increase. A limited number of premenopausal patients with disease progression during NOLVADEX therapy responded to subsequent ovarian ablation.

**Male Breast Cancer** - Published results from 122 patients (119 evaluable) and case reports in 16 patients (13 evaluable) treated with NOLVADEX have shown that NOLVADEX is effective for the palliative treatment of male breast cancer. Sixty-six of these 132 evaluable patients responded to NOLVADEX which constitutes a 50% objective response rate.

### **Clinical Studies - Adjuvant Breast Cancer**

**Overview** - The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, and again in 1995. In 1998, 10-year outcome data were reported for 36,689 women in 55 randomized trials of adjuvant NOLVADEX using doses of 20-40 mg/day for 1-5+ years. Twenty-five percent of patients received 1 year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Forty-eight percent of tumors were estrogen receptor (ER) positive ( $> 10$  fmol/mg), 21% were ER poor ( $< 10$  fmol/l), and 31% were ER unknown. Among 29,441 patients with ER positive or unknown breast cancer, 58% were entered into trials comparing NOLVADEX to no adjuvant therapy and 42% were entered into trials comparing NOLVADEX in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node positive disease and 46% had node negative disease.

Among women with ER positive or unknown breast cancer and positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for NOLVADEX vs. 50.5% for control (logrank 2p < 0.00001). The recurrence-free rate at 10 years was 59.7% for NOLVADEX vs. 44.5% for control (logrank 2p<0.00001). Among women with ER positive or unknown breast cancer and negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for NOLVADEX vs. 73.3% for control (logrank 2p < 0.00001). The recurrence-free rate at 10 years was 79.2% for NOLVADEX versus 64.3% for control (logrank 2p<0.00001).

The effect of the scheduled duration of tamoxifen may be described as follows. In women with ER positive or unknown breast cancer receiving 1 year or less, 2 years or about 5 years of NOLVADEX, the proportional reductions in mortality were 12%, 17% and 26%, respectively (trend significant at 2p < 0.003). The corresponding reductions in breast cancer recurrence were 21%, 29% and 47% (trend significant at 2p < 0.00001).

Benefit is less clear for women with ER poor breast cancer in whom the proportional reduction in recurrence was 10% (2p=0.007) for all durations taken together, or 9% (2p=0.02) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (NS). The effects of about 5 years of NOLVADEX on recurrence and mortality were similar regardless of age and concurrent chemotherapy. There was no indication that doses greater than 20 mg per day were more effective.

**Node Positive - Individual Studies** - Two studies (Hubay and NSABP B-09) demonstrated an improved disease-free survival following radical or modified radical mastectomy in postmenopausal women or women 50 years of age or older with surgically curable breast cancer with positive axillary nodes when NOLVADEX was added to adjuvant cytotoxic chemotherapy. In the Hubay study, NOLVADEX was added to "low-dose" CMF (cyclophosphamide, methotrexate and fluorouracil). In the NSABP B-09 study, NOLVADEX was added to melphalan [L-phenylalanine mustard (P)] and fluorouracil (F).

In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50-59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while there was a nonstatistically significant trend toward adverse effect in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60-70 years, there was a trend toward a beneficial effect of NOLVADEX without any clear relationship to estrogen or progesterone receptor status.

Three prospective studies (ECOG-1178, Toronto, NATO) using NOLVADEX adjuvantly as a single agent demonstrated an improved disease-free survival following total mastectomy and axillary dissection for postmenopausal women with positive axillary nodes compared to placebo/no treatment controls. The NATO study also demonstrated an overall survival benefit.

**Node Negative - Individual Studies** - NSABP B-14, a prospective, double-blind, randomized study, compared NOLVADEX to placebo in women with axillary node-negative, estrogen-receptor positive ( $\geq 10$  fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving NOLVADEX. This benefit was apparent both in women under age 50 and in women at or beyond age 50.

One additional randomized study (NATO) demonstrated improved disease-free survival for NOLVADEX compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of NOLVADEX appeared to be independent of estrogen receptor status.

**Duration of Therapy** - In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy.

In the NSABP B-14 trial, in which patients were randomized to NOLVADEX 20 mg/day for 5 years vs. placebo and were disease-free at the end of this 5-year period were offered rerandomization to an additional 5 years of NOLVADEX or placebo. With 4 years of follow-up after this rerandomization, 92% of the women that received 5 years of NOLVADEX were alive and disease-free, compared to 86% of the women scheduled to receive 10 years of NOLVADEX ( $p=0.003$ ). Overall survivals were 96% and 94%, respectively ( $p=0.08$ ). Results of the B-14 study suggest that continuation of therapy beyond 5 years does not provide additional benefit.

A Scottish trial of 5 years of tamoxifen vs. indefinite treatment found a disease-free survival of 70% in the five-year group and 61% in the indefinite group, with 6.2 years median follow-up (HR=1.27, 95% CI 0.87-1.85).

In a large randomized trial conducted by the Swedish Breast Cancer Cooperative Group of adjuvant NOLVADEX 40 mg/day for 2 or 5 years, overall survival at 10 years was estimated to be 80% in the patients in the 5-year tamoxifen group, compared with 74% among corresponding patients in the 2-year treatment group ( $p=0.03$ ). Disease-free survival at 10 years was 73% in the 5-year group and 67% in the 2-year group ( $p=0.009$ ). Compared with 2 years of tamoxifen treatment, 5 years of treatment resulted in a slightly greater reduction in the incidence of contralateral breast cancer at 10 years, but this difference was not statistically significant.

**Contralateral Breast Cancer** - The incidence of contralateral breast cancer is reduced in breast cancer patients (premenopausal and postmenopausal) receiving NOLVADEX compared to placebo. Data on contralateral breast cancer are available from 32,422 out of 36,689 patients in the 1995 overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). In clinical trials with NOLVADEX of 1 year or less, 2 years, and about 5 years duration, the proportional reductions in the incidence rate of contralateral breast cancer among women

receiving NOLVADEX were 13% (NS), 26% (2p = 0.004) and 47% (2p < 0.00001), with a significant trend favoring longer tamoxifen duration (2p = 0.008). The proportional reductions in the incidence of contralateral breast cancer were independent of age and ER status of the primary tumor. Treatment with about 5 years of NOLVADEX reduced the annual incidence rate of contralateral breast cancer from 7.6 per 1,000 patients in the control group compared with 3.9 per 1,000 patients in the tamoxifen group.

In a large randomized trial in Sweden (the Stockholm Trial) of adjuvant NOLVADEX 40 mg/day for 2-5 years, the incidence of second primary breast tumors was reduced 40% (p<0.008) on tamoxifen compared to control. In the NSABP B-14 trial in which patients were randomized to NOLVADEX 20 mg/day for 5 years vs. placebo, the incidence of second primary breast cancers was also significantly reduced (p<0.01). In NSABP B-14, the annual rate of contralateral breast cancer was 8.0 per 1000 patients in the placebo group compared with 5.0 per 1,000 patients in the tamoxifen group, at 10 years after first randomization.

**Clinical Studies - Ductal Carcinoma in Situ:** NSABP B-24, a double-blind, randomized trial included women with ductal carcinoma in situ (DCIS). This trial compared the addition of NOLVADEX or placebo to treatment with lumpectomy and radiation therapy for women with DCIS. The primary objective was to determine whether 5 years of NOLVADEX therapy (20 mg/day) would reduce the incidence of invasive breast cancer in the ipsilateral (the same) or contralateral (the opposite) breast.

In this trial 1,804 women were randomized to receive either NOLVADEX or placebo for 5 years: 902 women were randomized to NOLVADEX 10 mg tablets twice a day and 902 women were randomized to placebo. As of December 31, 1998, follow-up data were available for 1,798 women and the median duration of follow-up was 74 months.

The NOLVADEX and placebo groups were well balanced for baseline demographic and prognostic factors. Over 80% of the tumors were less than or equal to 1 cm in their maximum dimension, were not palpable, and were detected by mammography alone. Over 60% of the study population was postmenopausal. In 16% of patients, the margin of the resected specimen was reported as being positive after surgery. Approximately half of the tumors were reported to contain comedo necrosis.

For the primary endpoint, the incidence of invasive breast cancer was reduced by 43% among women assigned to NOLVADEX (44 cases - NOLVADEX, 74 cases - placebo; p=0.004; relative risk (RR)=0.57, 95% CI: 0.39-0.84). No data are available regarding the ER status of the invasive cancers. The stage distribution of the invasive cancers at diagnosis was similar to that reported annually in the SEER data base.

Results are shown in Table 1. For each endpoint the following results are presented: the number of events and rate per 1,000 women per year for the placebo and NOLVADEX groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between NOLVADEX and

placebo. Relative risks less than 1.0 indicate a benefit of NOLVADEX therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits of NOLVADEX therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists.

**Table 1 - Major Outcomes of the NSABP B-24 Trial**

Type of Event	Lumpectomy, radiotherapy, and placebo		Lumpectomy, radiotherapy, and Nolvadex		RR	95% CI limits
	No. of events	Rate per 1000 women per year	No. of events	Rate per 1000 women per year		
<b>Invasive breast cancer (Primary endpoint)</b>	<b>74</b>	<b>16.73</b>	<b>44</b>	<b>9.60</b>	<b>0.57</b>	<b>0.39 to 0.84</b>
-Ipsilateral	47	10.61	27	5.90	0.56	0.33 to 0.91
-Contralateral	25	5.64	17	3.71	0.66	0.33 to 1.27
-Side undetermined	2	--	0	--	--	
<b>Secondary Endpoints</b>						
DCIS	56	12.66	41	8.95	0.71	0.46 to 1.08
-Ipsilateral	46	10.40	38	8.29	0.88	0.51 to 1.25
-Contralateral	10	2.26	3	0.65	0.29	0.05 to 1.13
All Breast Cancer Events	129	29.16	84	18.34	0.63	0.47 to 0.83
-All ipsilateral events	96	21.70	65	14.19	0.65	0.47 to 0.91
-All contralateral events	37	8.36	20	4.37	0.52	0.29 to 0.92
Deaths	32		28			
Uterine Malignancies <sup>1</sup>	4		9			
Endometrial Adenocarcinoma <sup>1</sup>	4	0.57	8	1.15		
Uterine Sarcoma <sup>1</sup>	0	0.0	1	0.14		
Second primary malignancies (other than endometrial and breast)	30		29			
Stroke	2		7			
Thromboembolic events (DVT, PE)	5		15			

<sup>1</sup>Updated follow-up data (median 8.1 years)

Survival was similar in the placebo and NOLVADEX groups. At 5 years from study entry, survival was 97% for both groups.

#### **Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women**

The Breast Cancer Prevention Trial (BCPT, NSABP P-1) was a double-blind, randomized, placebo-controlled trial with a primary objective to determine whether 5 years of NOLVADEX therapy (20 mg/day) would reduce the incidence of invasive breast cancer in women at high risk for the disease (See **INDICATIONS AND USAGE**). Secondary objectives included an evaluation of the incidence of ischemic heart disease; the effects on the incidence of bone fractures; and other events that might be associated with the use of NOLVADEX, including: endometrial cancer, pulmonary embolus, deep vein thrombosis, stroke, and cataract formation and surgery (See **WARNINGS**).

The Gail Model was used to calculate predicted breast cancer risk for women who were less than 60 years of age and did not have lobular carcinoma in situ (LCIS). The following risk factors were used: age; number of first-degree female relatives with breast cancer; previous breast biopsies; presence or absence of atypical hyperplasia; nulliparity; age at first live birth; and age at menarche. A 5-year predicted risk of breast cancer of  $\geq 1.67\%$  was required for entry into the trial.

In this trial, 13,388 women of at least 35 years of age were randomized to receive either NOLVADEX or placebo for five years. The median duration of treatment was 3.5 years. As of January 31, 1998, follow-up data is available for 13,114 women. Twenty-seven percent of women randomized to placebo (1,782) and 24% of women randomized to NOLVADEX (1,596) completed 5 years of therapy. The demographic characteristics of women on the trial with follow-up data are shown in Table 2.

**Table 2. Demographic Characteristics of Women in the NSABP P-1 Trial**

Characteristic	Placebo		Tamoxifen	
	#	%	#	%
Age (yrs.)				
35-39	184	3	158	2
40-49	2,394	36	2,411	37
50-59	2,011	31	2,019	31
60-69	1,588	24	1,563	24
≥70	393	6	393	6
Age at first live birth(yrs.)				
Nulliparous	1,202	18	1,205	18
12-19	915	14	946	15
20-24	2,448	37	2,449	37
25-29	1,399	21	1,367	21
≥30	606	9	577	9
Race				
White	6,333	96	6,323	96
Black	109	2	103	2
Other	128	2	118	2
Age at menarche				
≥14	1,243	19	1,170	18
12-13	3,610	55	3,610	55
≤11	1,717	26	1,764	27
# of first degree relatives with breast cancer				
0	1,584	24	1,525	23
1	3,714	57	3,744	57
2+	1,272	19	1,275	20
Prior Hysterectomy				
No	4,173	63.5	4,018	62.4
Yes	2,397	36.5	2,464	37.7
# of previous breast biopsies				
0	2,935	45	2,923	45
1	1,833	28	1,850	28
≥2	1,802	27	1,771	27
History of atypical hyperplasia in the breast				
No	5,958	91	5,969	91
Yes	612	9	575	9
History of LCIS at entry				
No	6,165	94	6,135	94
Yes	405	6	409	6
5-year predicted breast cancer risk (%)				
≤2.00	1,646	25	1,626	25
2.01-3.00	2,028	31	2,057	31
3.01-5.00	1,787	27	1,707	26
≥5.01	1,109	17	1,162	18
Total	6,570	100.0	6,544	100.0

Results are shown in Table 3. After a median follow-up of 4.2 years, the incidence of invasive breast cancer was reduced by 44% among women assigned to NOLVADEX (86 cases-NOLVADEX, 156 cases-placebo;  $p < 0.00001$ ; relative risk (RR)=0.56, 95% CI: 0.43-0.72). A reduction in the incidence of breast cancer was seen in each prospectively specified age group ( $\leq 49$ , 50-59,  $\geq 60$ ), in women with or without LCIS, and in each of the absolute risk levels specified in Table 3. A non-significant decrease in the incidence of ductal carcinoma in situ (DCIS) was seen (23-NOLVADEX, 35-placebo; RR=0.66; 95% CI: 0.39-1.11).

There was no statistically significant difference in the number of myocardial infarctions, severe angina, or acute ischemic cardiac events between the two groups (61-NOLVADEX, 59-placebo; RR=1.04, 95% CI: 0.73-1.49).

No overall difference in mortality (53 deaths in NOLVADEX group vs. 65 deaths in placebo group) was present. No difference in breast cancer-related mortality was observed (4 deaths in NOLVADEX group vs. 5 deaths in placebo group).

Although there was a non-significant reduction in the number of hip fractures (9 on NOLVADEX, 20 on placebo) in the NOLVADEX group, the number of wrist fractures was similar in the two treatment groups (69 on NOLVADEX, 74 on placebo). No information regarding bone mineral density or other markers of osteoporosis is available.

The risks of NOLVADEX therapy include endometrial cancer, DVT, PE, stroke, cataract formation and cataract surgery (See Table 3). In the NSABP P-1 trial, 33 cases of endometrial cancer were observed in the NOLVADEX group vs. 14 in the placebo group (RR=2.48, 95% CI: 1.27-4.92). Deep vein thrombosis was observed in 30 women receiving NOLVADEX vs. 19 in women receiving placebo (RR=1.59, 95% CI: 0.86-2.98). Eighteen cases of pulmonary embolism were observed in the NOLVADEX group vs. 6 in the placebo group (RR=3.01, 95% CI: 1.15-9.27). There were 34 strokes on the NOLVADEX arm and 24 on the placebo arm (RR=1.42; 95% CI 0.82-2.51). Cataract formation in women without cataracts at baseline was observed in 540 women taking NOLVADEX vs. 483 women receiving placebo (RR=1.13, 95% CI: 1.00-1.28). Cataract surgery (with or without cataracts at baseline) was performed in 201 women taking NOLVADEX vs. 129 women receiving placebo (RR=1.51, 95% CI 1.21-1.89) (See **WARNINGS**).

Table 3 summarizes the major outcomes of the NSABP P-1 trial. For each endpoint, the following results are presented: the number of events and rate per 1000 women per year for the placebo and NOLVADEX groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between NOLVADEX and placebo. Relative risks less than 1.0 indicate a benefit of NOLVADEX therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits or risks of NOLVADEX therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists.

For most participants, multiple risk factors would have been required for eligibility. This table considers risk factors individually, regardless of other co-existing risk factors, for women who developed breast cancer. The 5-year predicted absolute breast cancer risk accounts for multiple risk factors in an individual and should provide the best estimate of individual benefit (See **INDICATIONS AND USAGE**).

**Table 3: Major Outcomes of the NSABP P-1 Trial**

TYPE OF EVENT	# OF EVENTS		RATE/1000 WOMEN/YEAR		95% CI	
	PLACEBO	NOLVADEX	PLACEBO	NOLVADEX	RR	LIMITS
Invasive Breast Cancer	156	86	6.49	3.58	0.56	0.43-0.72
Age <49	59	38	6.34	4.11	0.65	0.43-0.98
Age 50-59	46	25	6.31	3.53	0.56	0.35-0.91
Age ≥60	51	23	7.17	3.22	0.45	0.27-0.74
Risk Factors for Breast Cancer						
History, LCIS						
No	140	78	6.23	3.51	0.56	0.43-0.74
Yes	16	8	12.73	6.33	0.50	0.21-1.17
History, Atypical Hyperplasia						
No	138	84	6.37	3.89	0.61	0.47-0.80
Yes	18	2	8.69	1.05	0.12	0.03-0.52
No. First Degree Relatives						
0	32	17	5.97	3.26	0.55	0.30-0.98
1	80	45	5.81	3.31	0.57	0.40-0.82
2	35	18	8.92	4.67	0.52	0.30-0.92
≥3	9	6	13.33	7.58	0.57	0.20-1.59
5-Year Predicted Breast Cancer Risk (as calculated by the Gail Model)						
≤2.00%	31	13	5.36	2.26	0.42	0.22-0.81
2.01-3.00%	39	28	5.25	3.83	0.73	0.45-1.18
3.01-5.00%	36	26	5.37	4.06	0.76	0.46-1.26
≥5.00%	50	19	13.15	4.71	0.36	0.21-0.61
DCIS	35	23	1.47	0.97	0.66	0.39-1.11
Fractures (protocol-specified sites)	92 <sup>1</sup>	76 <sup>1</sup>	3.87	3.20	0.61	0.83-1.12
Hip	20	9	0.84	0.38	0.45	0.18-1.04
Wrist <sup>2</sup>	74	69	3.11	2.91	0.93	0.67-1.29
Total Ischemic Events	59	61	2.47	2.57	1.04	0.71-1.51
Myocardial Infarction	27	27	1.13	1.13	1.00	0.57-1.78
Fatal	8	7	0.33	0.29	0.88	0.27-2.77
Nonfatal	19	20	0.79	0.84	1.06	0.54-2.09
Angina <sup>3</sup>	12	12	0.50	0.50	1.00	0.41-2.44
Acute Ischemic Syndrome <sup>4</sup>	20	22	0.84	0.92	1.11	0.58-2.13
Uterine						
Malignancies (among women with an intact uterus) <sup>10</sup>	17	57				
Endometrial Adenocarcinoma <sup>10</sup>	17	53	0.71	2.20		
Uterine Sarcoma <sup>10</sup>	0	4	0.0	0.17		
Stroke <sup>5</sup>	24	34	1.00	1.43	1.42	0.82-2.51
Transient Ischemic Attack	21	18	0.88	0.75	0.86	0.43-1.70
Pulmonary Emboli <sup>6</sup>	6	18	0.25	0.75	3.01	1.15-9.27
Deep-Vein Thrombosis <sup>7</sup>	19	30	0.79	1.26	1.59	0.86-2.98
Cataracts Developing on Study <sup>8</sup>	483	540	22.51	25.41	1.13	1.00-1.28
Underwent Cataract Surgery <sup>8</sup>	63	101	21.83	4.57	1.62	1.18-2.22
Underwent Cataract Surgery <sup>9</sup>	129	201	5.44	8.56	1.58	1.26-1.97

<sup>1</sup>Two women had hip and wrist fractures

<sup>2</sup>Includes Colles<sup>1</sup> and other lower radius fractures

<sup>3</sup>Requiring angioplasty or CABG

<sup>4</sup>New Q-wave on ECG; no angina or elevation of serum enzymes; or angina requiring hospitalization without surgery

<sup>5</sup>Seven cases were fatal; three in the placebo group and four in the NOLVADEX group

<sup>6</sup>Three cases in the NOLVADEX group were fatal

<sup>7</sup>All but three cases in each group required hospitalization

<sup>8</sup>Based on women without cataracts at baseline (6,230-Placebo, 6,199-NOLVADEX)

<sup>9</sup>All women (6,707-Placebo, 6,681-NOLVADEX)

<sup>10</sup>Updated long-term follow-up data (median 6.9 years) from NSABP P-1 study added after cut-off for the other information in this table.

Table 4 describes the characteristics of the breast cancers in the NSABP P-1 trial and includes tumor size, nodal status, ER status. NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors.

**Table 4: Characteristics of Breast Cancer in NSABP P-1 Trial**

<b>Staging Parameter</b>	<b>Placebo N=156</b>	<b>Tamoxifen N=86</b>	<b>Total N=242</b>
<b>Tumor size:</b>			
T1	117	60	177
T2	28	20	48
T3	7	3	10
T4	1	2	3
Unknown	3	1	4
<b>Nodal status:</b>			
Negative	103	56	159
1-3 positive nodes	29	14	43
≥ 4 positive nodes	10	12	22
Unknown	14	4	18
<b>Stage:</b>			
I	88	47	135
II: node negative	15	9	24
II: node positive	33	22	55
III	6	4	10
IV	2 <sup>1</sup>	1	3
Unknown	12	3	15
<b>Estrogen receptor:</b>			
Positive	115	38	153
Negative	27	36	63
Unknown	14	12	26

<sup>1</sup> One participant presented with a suspicious bone scan but did not have documented metastases. She subsequently died of metastatic breast cancer.

Interim results from 2 trials in addition to the NSABP P-1 trial examining the effects of tamoxifen in reducing breast cancer incidence have been reported.

The first was the Italian Tamoxifen Prevention trial. In this trial women between the ages of 35 and 70, who had had a total hysterectomy, were randomized to receive 20 mg tamoxifen or matching placebo for 5 years. The primary endpoints were occurrence of, and death from, invasive breast cancer. Women without any specific risk factors for breast cancer were to be entered. Between 1992 and 1997, 5408 women were randomized. Hormone Replacement Therapy (HRT) was used in 14% of participants. The trial closed in 1997 due to the large number of dropouts during the first year of treatment (26%). After 46 months of follow-up there were 22 breast cancers in women on placebo and 19 in women on tamoxifen. Although no decrease in breast cancer incidence was observed, there was a trend for a reduction in breast cancer among women receiving protocol therapy for at least 1 year (19-placebo, 11- tamoxifen). The small numbers of participants along with the low level of risk in this otherwise healthy group precluded an adequate assessment of the effect of tamoxifen in reducing the incidence of breast cancer.

The second trial, the Royal Marsden Trial (RMT) was reported as an interim analysis. The RMT was begun in 1986 as a feasibility study of whether larger scale trials could be mounted. The trial was subsequently extended to a pilot trial to accrue additional participants to further assess the safety of tamoxifen. Twenty-four hundred and seventy-one women were entered between 1986 and 1996; they were selected on the basis of a family history of breast cancer. HRT was used in 40% of participants. In this trial, with a 70-month median follow-up, 34 and 36 breast cancers (8 noninvasive, 4 on each arm) were observed among women on tamoxifen and placebo, respectively. Patients in this trial were younger than those in the NSABP P-1 trial and may have been more likely to develop ER (-) tumors, which are unlikely to be reduced in number by tamoxifen therapy. Although women were selected on the basis of family history and were thought to have a high risk of breast cancer, few events occurred, reducing the statistical power of the study. These factors are potential reasons why the RMT may not have provided an adequate assessment of the effectiveness of tamoxifen in reducing the incidence of breast cancer.

In these trials, an increased number of cases of deep vein thrombosis, pulmonary embolus, stroke, and endometrial cancer were observed on the tamoxifen arm compared to the placebo arm. The frequency of events was consistent with the safety data observed in the NSABP P-1 trial.

**Clinical Studies – McCune-Albright Syndrome:** A single, uncontrolled multicenter trial of NOLVADEX 20 mg once a day was conducted in a heterogeneous group of girls with McCune-Albright Syndrome and precocious puberty manifested by physical signs of pubertal development, episodes of vaginal bleeding and/or advanced bone age (bone age of at least 12 months beyond chronological age). Twenty-eight female pediatric patients, aged 2 to 10 years, were treated for up to 12 months. Effect of treatment on frequency of vaginal bleeding, bone age advancement, and linear growth rate was assessed relative to prestudy baseline. NOLVADEX treatment was associated with a 50% reduction in frequency of vaginal bleeding episodes by patient or family report (mean annualized frequency of 3.56 episodes at baseline and 1.73 episodes on-treatment). Among the patients who reported vaginal bleeding during the pre-study period, 62% (13 out of 21 patients) reported no bleeding for a 6-month period and 33% (7 out of 21 patients) reported no vaginal bleeding for the duration of the trial. Not all patients improved on treatment and a few patients not reporting vaginal bleeding in the 6 months prior to enrollment reported menses on treatment. NOLVADEX therapy was associated with a reduction in mean rate of increase of bone age. Individual responses with regard to bone age advancement were highly heterogeneous. Linear growth rate was reduced during the course of NOLVADEX treatment in a majority of patients (mean change of 1.68 cm/year relative to baseline; change from 7.47 cm/year at baseline to 5.79 cm/year on study). This change was not uniformly seen across all stages of bone maturity; all recorded response failures occurred in patients with bone ages less than 7 years at screening.

Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. A causal relationship has not been established; however, as an increase in the incidence of endometrial adenocarcinoma and uterine sarcoma has been noted in adults treated

with NOLVADEX (see **BOXED WARNING**), continued monitoring of McCune-Albright patients treated with NOLVADEX for long-term uterine effects is recommended. **The safety and efficacy of NOLVADEX for girls aged two to 10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond one year of treatment. The long-term effects of NOLVADEX therapy in girls have not been established.**

#### **INDICATIONS AND USAGE**

**Metastatic Breast Cancer:** NOLVADEX is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, NOLVADEX is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

**Adjuvant Treatment of Breast Cancer:** NOLVADEX is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with four or more positive axillary nodes.

NOLVADEX is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

The estrogen and progesterone receptor values may help to predict whether adjuvant NOLVADEX therapy is likely to be beneficial.

NOLVADEX reduces the occurrence of contralateral breast cancer in patients receiving adjuvant NOLVADEX therapy for breast cancer.

**Ductal Carcinoma in Situ (DCIS):** In women with DCIS, following breast surgery and radiation, NOLVADEX is indicated to reduce the risk of invasive breast cancer (see **BOXED WARNING** at the beginning of the label). The decision regarding therapy with NOLVADEX for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of NOLVADEX therapy.

Current data from clinical trials support five years of adjuvant NOLVADEX therapy for patients with breast cancer.

**Reduction in Breast Cancer Incidence in High Risk Women:** NOLVADEX is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent of the participants received drug for 5 years. The longer-term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality (see **BOXED WARNING** at the beginning of the label).

NOLVADEX is indicated only for high-risk women. “High risk” is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer  $\geq 1.67\%$ , as calculated by the Gail Model.

Examples of combinations of factors predicting a 5-year risk  $\geq 1.67\%$  are:

**Age 35 or older and any of the following combination of factors:**

- One first degree relative with a history of breast cancer, 2 or more benign biopsies, and a history of a breast biopsy showing atypical hyperplasia; or
- At least 2 first degree relatives with a history of breast cancer, and a personal history of at least one breast biopsy; or
- LCIS

**Age 40 or older and any of the following combination of factors:**

- One first degree relative with a history of breast cancer, 2 or more benign biopsies, age at first live birth 25 or older, and age at menarche 11 or younger; or
- At least 2 first degree relatives with a history of breast cancer, and age at first live birth 19 or younger; or
- One first degree relative with a history of breast cancer, and a personal history of a breast biopsy showing atypical hyperplasia.

**Age 45 or older and any of the following combination of factors:**

- At least 2 first degree relatives with a history of breast cancer and age at first live birth 24 or younger; or
- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, age at menarche 11 or less and age at first live birth 20 or more.

**Age 50 or older and any of the following combination of factors:**

- At least 2 first degree relatives with a history of breast cancer; or
- History of one breast biopsy showing atypical hyperplasia, and age at first live birth 30 or older and age at menarche 11 or less; or
- History of at least two breast biopsies with a history of atypical hyperplasia, and age at first live birth 30 or more.

**Age 55 or older and any of the following combination of factors:**

- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, and age at menarche 11 or less; or
- History of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 20 or older.

**Age 60 or older and:**

- 5-year predicted risk of breast cancer  $\geq$  1.67%, as calculated by the Gail Model.

For women whose risk factors are not described in the above examples, the Gail Model is necessary to estimate absolute breast cancer risk. Health Care Professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-544-2007.

There are no data available regarding the effect of NOLVADEX on breast cancer incidence in women with inherited mutations (BRCA1, BRCA2).

After an assessment of the risk of developing breast cancer, the decision regarding therapy with NOLVADEX for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of NOLVADEX therapy. In the NSABP P-1 trial, NOLVADEX treatment lowered the risk of developing breast cancer during the follow-up period of the trial, but did not eliminate breast cancer risk (See Table 3 in **CLINICAL PHARMACOLOGY**).

**CONTRAINDICATIONS**

NOLVADEX is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.

**Reduction in Breast Cancer Incidence in High Risk Women and Women with DCIS:** NOLVADEX is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus.

**WARNINGS**

**Effects in Metastatic Breast Cancer Patients:** As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

**Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma:** An increased incidence of uterine malignancies has been reported in association with NOLVADEX treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of NOLVADEX. Most uterine malignancies seen in association with NOLVADEX are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors, have also been reported. Uterine sarcoma is generally associated with a higher FIGO stage (III/IV) at diagnosis, poorer prognosis, and shorter survival. Uterine sarcoma has been reported to occur more frequently among long-term users ( $\geq$  2 years) of NOLVADEX than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal.

In the NSABP P-1 trial, among participants randomized to NOLVADEX there was a statistically significant increase in the incidence of endometrial cancer (33 cases of invasive endometrial cancer, compared to 14 cases among participants randomized to placebo (RR=2.48, 95% CI: 1.27-4.92). The 33 cases in participants receiving NOLVADEX were FIGO Stage I, including 20 IA, 12 IB, and 1 IC endometrial adenocarcinomas. In participants randomized to placebo, 13 were FIGO Stage I (8 IA and 5 IB) and 1 was FIGO Stage IV. Five women on Nolvadex and 1 on placebo received postoperative radiation therapy in addition to surgery. This increase was primarily observed among women at least 50 years of age at the time of randomization (26 cases of invasive endometrial cancer, compared to 6 cases among participants randomized to placebo (RR=4.50, 95% CI: 1.78-13.16). Among women  $\leq$  49 years of age at the time of randomization there were 7 cases of invasive endometrial cancer, compared to 8 cases among participants randomized to placebo (RR=0.94, 95% CI: 0.28-2.89). If age at the time of diagnosis is considered, there were 4 cases of endometrial cancer among participants  $\leq$  49 randomized to NOLVADEX compared to 2 among participants randomized to placebo (RR=2.21, 95% CI: 0.4-12.0). For women  $\geq$  50 at the time of diagnosis, there were 29 cases among participants randomized to NOLVADEX compared to 12 among women on placebo (RR=2.5, 95% CI: 1.3-4.9). The risk ratios were similar in the two groups, although fewer events occurred in younger women. Most (29 of 33 cases in the NOLVADEX group) endometrial cancers were diagnosed in symptomatic women, although 5 of 33 cases in the NOLVADEX group occurred in asymptomatic women. Among women receiving NOLVADEX the events appeared between 1 and 61 months (average=32 months) from the start of treatment.

In an updated review of long-term data (median length of total follow-up is 6.9 years, including blinded follow-up) on 8,306 women with an intact uterus at randomization in the NSABP P-1 risk reduction trial, the incidence of both adenocarcinomas and rare uterine sarcomas was increased in women taking NOLVADEX. Endometrial adenocarcinoma was reported in 53 women randomized to NOLVADEX (52 cases of FIGO Stage I, and 1 Stage III endometrial adenocarcinoma) and 17 women randomized to placebo (16 cases of FIGO Stage I and 1 case of FIGO Stage II endometrial adenocarcinoma) (incidence per 1,000 women-years of 2.20 and 0.71, respectively). Some patients received post-operative radiation therapy in addition to surgery. Uterine sarcomas were reported in 4 women randomized to NOLVADEX (2 FIGO I, 1 FIGO II, 1 FIGO III. The FIGO I cases were a sarcoma and a MMMT. The FIGO II was a MMMT and the FIGO III was a sarcoma) and 0 patients randomized to placebo (incidence per 1,000 women-years of 0.17 and 0.0, respectively). A similar increased incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving NOLVADEX in five other NSABP clinical trials.

Any patient receiving or who has previously received NOLVADEX who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received NOLVADEX should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, eg, menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure.

In the P-1 trial, endometrial sampling did not alter the endometrial cancer detection rate compared to women who did not undergo endometrial sampling (0.6% with sampling, 0.5% without sampling) for women with an intact uterus. There are no data to suggest that routine endometrial sampling in asymptomatic women taking NOLVADEX to reduce the incidence of breast cancer would be beneficial.

**Non-Malignant Effects on the Uterus:** An increased incidence of endometrial changes including hyperplasia and polyps have been reported in association with NOLVADEX treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of NOLVADEX.

There have been a few reports of endometriosis and uterine fibroids in women receiving NOLVADEX. The underlying mechanism may be due to the partial estrogenic effect of NOLVADEX. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with NOLVADEX.

NOLVADEX has been reported to cause menstrual irregularity or amenorrhea.

**Thromboembolic Effects of NOLVADEX:** There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during NOLVADEX therapy. When NOLVADEX is coadministered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of NOLVADEX should be carefully considered in women with a history of thromboembolic events.

Data from the NSABP P-1 trial show that participants receiving NOLVADEX without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18-NOLVADEX, 6-placebo, RR=3.01, 95% CI: 1.15- 9.27). Three of the pulmonary emboli, all in the NOLVADEX arm, were fatal. Eighty-seven percent of the cases of pulmonary embolism occurred in women at least 50 years of age at randomization. Among women receiving NOLVADEX, the events appeared between 2 and 60 months (average=27 months) from the start of treatment.

In this same population, a non-statistically significant increase in deep vein thrombosis (DVT) was seen in the NOLVADEX group (30-NOLVADEX, 19-placebo; RR=1.59, 95% CI: 0.86-2.98). The same increase in relative risk was seen in women  $\leq 49$  and in women  $\geq 50$ , although fewer events occurred in younger women. Women with thromboembolic events were at risk for a second related event (7 out of 25 women on placebo, 5 out of 48 women on NOLVADEX) and were at risk for complications of the event and its treatment (0/25 on placebo, 4/48 on NOLVADEX). Among women receiving NOLVADEX, deep vein thrombosis events occurred between 2 and 57 months (average=19 months) from the start of treatment.

There was a non-statistically significant increase in stroke among patients randomized to NOLVADEX (24-Placebo; 34-NOLVADEX; RR=1.42; 95% CI 0.82-2.51). Six of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the NOLVADEX group were categorized as hemorrhagic. Seventeen of the 34 strokes in the NOLVADEX group were considered occlusive and 7 were considered to be of unknown etiology. Fourteen of the 24 strokes on the placebo arm were reported to be occlusive and 4 of unknown etiology. Among these strokes 3 strokes in the placebo group and 4 strokes in the NOLVADEX group were fatal. Eighty-eight percent of the strokes occurred in women at least 50 years of age at the time of randomization. Among women receiving NOLVADEX, the events occurred between 1 and 63 months (average=30 months) from the start of treatment.

**Effects on the liver: Liver cancer:** In the Swedish trial using adjuvant NOLVADEX 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the NOLVADEX-treated group vs. 1 case in the observation group (See **PRECAUTIONS-Carcinogenesis**). In other clinical trials evaluating NOLVADEX, no cases of liver cancer have been reported to date.

One case of liver cancer was reported in NSABP P-1 in a participant randomized to NOLVADEX.

**Effects on the liver: Non-malignant effects:** NOLVADEX has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to NOLVADEX is uncertain. However, some positive rechallenges and dechallenges have been reported.

In the NSABP P-1 trial, few grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on NOLVADEX). Serum lipids were not systematically collected.

**Other cancers:** A number of second primary tumors, occurring at sites other than the endometrium, have been reported following the treatment of breast cancer with NOLVADEX in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (non-uterine) cancers among patients receiving NOLVADEX. Whether an increased risk for other (non-uterine) cancers is associated with NOLVADEX is still uncertain and continues to be evaluated.

**Effects on the Eye:** Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving NOLVADEX. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving NOLVADEX.

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540-NOLVADEX; 483-placebo; RR=1.13, 95% CI: 1.00-1.28) was observed. Among these same women, NOLVADEX was associated with an increased risk of having cataract surgery (101-NOLVADEX; 63-placebo; RR=1.62, 95% CI 1.17-2.25) (See Table 3 in **CLINICAL PHARMACOLOGY**). Among all women on the trial (with or without cataracts at baseline), NOLVADEX was associated with an increased risk of having cataract surgery (201-NOLVADEX; 129-placebo; RR=1.51, 95% CI 1.21-1.89). Eye examinations were not required during the study. No other conclusions regarding non-cataract ophthalmic events can be made.

**Pregnancy Category D:** NOLVADEX may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking NOLVADEX or within 2 months of discontinuing NOLVADEX and should use barrier or nonhormonal contraceptive measures if sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups when compared to historical controls. Several pregnant marmosets were dosed with 10 mg/kg/day (about 2-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) during organogenesis or in the last half of pregnancy. No deformations were seen and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations.

In rodent models of fetal reproductive tract development, tamoxifen (at doses 0.002 to 2.4-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) caused changes in both sexes that are similar to those caused by estradiol, ethynylestradiol and diethylstilbestrol. Although the clinical relevance of these changes is unknown, some of these changes, especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilbestrol in utero and who have a 1 in 1000 risk of developing clear-cell adenocarcinoma of the vagina or cervix. To date, in utero exposure to tamoxifen has not been shown to cause vaginal adenosis, or clear-cell adenocarcinoma of the vagina or cervix, in young women. However, only a small number of young women have been exposed to tamoxifen in utero, and a smaller number have been followed long enough (to age 15-20) to determine whether vaginal or cervical neoplasia could occur as a result of this exposure.

There are no adequate and well-controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.

**Reduction in Breast Cancer Incidence in High Risk Women - Pregnancy Category D:** For sexually active women of child-bearing potential, NOLVADEX therapy should be initiated during menstruation. In women with menstrual irregularity, a negative B-HCG immediately prior to the initiation of therapy is sufficient (See **PRECAUTIONS-Information for Patients - Reduction in Breast Cancer Incidence in High Risk Women**).

### **PRECAUTIONS**

**General:** Decreases in platelet counts, usually to 50,000-100,000/mm<sup>3</sup>, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to NOLVADEX therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving NOLVADEX; this can sometimes be severe.

In the NSABP P-1 trial, 6 women on NOLVADEX and 2 on placebo experienced grade 3-4 drops in platelet counts ( $\leq 50,000/\text{mm}^3$ ).

#### **Information for Patients:**

**Reduction in Invasive Breast Cancer and DCIS in Women with DCIS:** Women with DCIS treated with lumpectomy and radiation therapy who are considering NOLVADEX to reduce the incidence of a second breast cancer event should assess the risks and benefits of therapy, since treatment with NOLVADEX decreased the incidence of invasive breast cancer, but has not been shown to affect survival (See Table 1 in **CLINICAL PHARMACOLOGY**).

**Reduction in Breast Cancer Incidence in High Risk Women:** Women who are at high risk for breast cancer can consider taking NOLVADEX therapy to reduce the incidence of breast cancer. Whether the benefits of treatment are considered to outweigh the risks depends on a woman's personal health history and on how she weighs the benefits and risks. NOLVADEX therapy to reduce the incidence of breast cancer may therefore not be appropriate for all women at high risk for breast cancer. Women who are considering NOLVADEX therapy should consult their health care professional for an assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer incidence (See Table 3 in **CLINICAL PHARMACOLOGY**). Women should understand that NOLVADEX reduces the incidence of breast cancer, but may not eliminate risk. NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. In women with breast cancer who are at high risk of developing a second breast cancer, treatment with

about 5 years of NOLVADEX reduced the annual incidence rate of a second breast cancer by approximately 50%.

Women who are pregnant or who plan to become pregnant should not take NOLVADEX to reduce her risk of breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking NOLVADEX and for approximately two months after discontinuing therapy if they are sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. For sexually active women of child-bearing potential, NOLVADEX therapy should be initiated during menstruation. In women with menstrual irregularity, a negative B-HCG immediately prior to the initiation of therapy is sufficient (See **WARNINGS-Pregnancy Category D**).

Two European trials of tamoxifen to reduce the risk of breast cancer were conducted and showed no difference in the number of breast cancer cases between the tamoxifen and placebo arms. These studies had trial designs that differed from that of NSABP P-1, were smaller than NSABP P-1, and enrolled women at a lower risk for breast cancer than those in P-1.

**Monitoring During NOLVADEX Therapy:** Women taking or having previously taken NOLVADEX should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take NOLVADEX.

Women taking NOLVADEX to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice. Women taking NOLVADEX as adjuvant breast cancer therapy should follow the same monitoring procedures as for women taking NOLVADEX for the reduction in the incidence of breast cancer. Women taking NOLVADEX as treatment for metastatic breast cancer should review this monitoring plan with their care provider and select the appropriate modalities and schedule of evaluation.

**Laboratory Tests:** Periodic complete blood counts, including platelet counts, and periodic liver function tests should be obtained.

**Drug Interactions:** When NOLVADEX is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

In the NSABP P-1 trial, women who required coumarin-type anticoagulants for any reason were ineligible for participation in the trial (See **CONTRAINDICATIONS**).

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with NOLVADEX.

Tamoxifen reduced letrozole plasma concentrations by 37%. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known. Tamoxifen and N-desmethyl tamoxifen plasma concentrations have been shown to be reduced when coadministered with rifampin or aminoglutethimide. Induction of CYP3A4-mediated metabolism is considered to be the mechanism by which these reductions occur; other CYP3A4 inducing agents have not been studied to confirm this effect.

One patient receiving NOLVADEX with concomitant phenobarbital exhibited a steady state serum level of tamoxifen lower than that observed for other patients (ie, 26 ng/mL vs. mean value of 122 ng/mL). However, the clinical significance of this finding is not known. Rifampin induced the metabolism of tamoxifen and significantly reduced the plasma concentrations of tamoxifen in 10 patients. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

**Drug/Laboratory Testing Interactions:** During postmarketing surveillance, T<sub>4</sub> elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given NOLVADEX.

In the postmarketing experience with NOLVADEX, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with pre-existing hyperlipidemias (See **ADVERSE REACTIONS-Postmarketing experience** section).

**Carcinogenesis:** A conventional carcinogenesis study in rats at doses of 5, 20, and 35 mg/kg/day (about one, three and seven-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) administered by oral gavage for up to 2 years) revealed a significant increase in hepatocellular carcinoma at all doses. The incidence of these tumors was significantly greater among rats administered 20 or 35 mg/kg/day (69%) compared to those administered 5 mg/kg/day (14%). In a separate study, rats were administered tamoxifen at 45 mg/kg/day (about nine-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis); hepatocellular neoplasia was exhibited at 3 to 6 months.

Granulosa cell ovarian tumors and interstitial cell testicular tumors were observed in two separate mouse studies. The mice were administered the trans and racemic forms of tamoxifen for 13 to 15 months at doses of 5, 20 and 50 mg/kg/day (about one-half, two and five-fold the daily recommended human dose on a mg/m<sup>2</sup> basis).

**Mutagenesis:** No genotoxic potential was found in a conventional battery of *in vivo* and *in vitro* tests with pro- and eukaryotic test systems with drug metabolizing systems. However, increased levels of DNA adducts were observed by <sup>32</sup>P post-labeling in DNA from rat liver and cultured human lymphocytes. Tamoxifen also has been found to increase levels of micronucleus formation *in vitro* in human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

**Impairment of Fertility:** Tamoxifen produced impairment of fertility and conception in female rats at doses of 0.04 mg/kg/day (about 0.01-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) when dosed for two weeks prior to mating through day 7 of pregnancy. At this dose, fertility and reproductive indices were markedly reduced with total fetal mortality. Fetal mortality was also increased at doses of 0.16 mg/kg/day (about 0.03-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) when female rats were dosed from days 7-17 of pregnancy. Tamoxifen produced abortion, premature delivery and fetal death in rabbits administered doses equal to or greater than 0.125 mg/kg/day (about 0.05-fold the daily maximum recommended human dose on a mg/m<sup>2</sup> basis). There were no teratogenic changes in either rats or rabbits.

**Pregnancy Category D:** See WARNINGS.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, 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.

**Pediatric Use:** The safety and efficacy of NOLVADEX for girls aged two to 10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond one year of treatment. The long-term effects of NOLVADEX therapy for girls have not been established. In adults treated with NOLVADEX, an increase in the incidence of uterine malignancies, stroke and pulmonary embolism has been noted (see **BOXED WARNING**, and **CLINICAL PHARMACOLOGY-Clinical Studies-McCune-Albright Syndrome** subsection).

**Geriatric Use:** In the NSABP P-1 trial, the percentage of women at least 65 years of age was 16%. Women at least 70 years of age accounted for 6% of the participants. A reduction in breast cancer incidence was seen among participants in each of the subsets: A total of 28 and 10 invasive breast cancers were seen among participants 65 and older in the placebo and NOLVADEX groups, respectively. Across all other outcomes, the results in this subset reflect

the results observed in the subset of women at least 50 years of age. No overall differences in tolerability were observed between older and younger patients (See **CLINICAL PHARMACOLOGY - Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women** section).

In the NSABP B-24 trial, the percentage of women at least 65 years of age was 23%. Women at least 70 years of age accounted for 10% of participants. A total of 14 and 12 invasive breast cancers were seen among participants 65 and older in the placebo and NOLVADEX groups, respectively. This subset is too small to reach any conclusions on efficacy. Across all other endpoints, the results in this subset were comparable to those of younger women enrolled in this trial. No overall differences in tolerability were observed between older and younger patients.

### **ADVERSE REACTIONS**

Adverse reactions to NOLVADEX are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with NOLVADEX as compared to placebo.

**Metastatic Breast Cancer:** Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

In patients treated with NOLVADEX for metastatic breast cancer, the most frequent adverse reaction to NOLVADEX is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.

**Premenopausal Women:** The following table summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared NOLVADEX therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

## OVARIAN

<b>Adverse Reactions*</b>	<b>NOLVADEX All Effects % of Women n = 104</b>	<b>ABLATION All Effects % of Women n = 100</b>
Flush	33	46
Amenorrhea	16	69
Altered Menses	13	5
Oligomenorrhea	9	1
Bone Pain	6	6
Menstrual Disorder	6	4
Nausea	5	4
Cough/Coughing	4	1
Edema	4	1
Fatigue	4	1
Musculoskeletal Pain	3	0
Pain	3	4
Ovarian Cyst(s)	3	2
Depression	2	2
Abdominal Cramps	1	2
Anorexia	1	2

\*Some women had more than one adverse reaction.

**Male Breast Cancer:** NOLVADEX is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of NOLVADEX in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

**Adjuvant Breast Cancer:** In the NSABP B-14 study, women with axillary node-negative breast cancer were randomized to 5 years of NOLVADEX 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of approximately 6.8 years) showing adverse events more common on NOLVADEX than on placebo. The incidence of hot flashes (64% vs. 48%), vaginal discharge (30% vs. 15%), and irregular menses (25% vs. 19%) were higher with NOLVADEX compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events; a higher incidence was seen in NOLVADEX-treated patients (through 5 years, 1.7% vs. 0.4%). Two of the patients treated with NOLVADEX who had thrombotic events died.

**NSABP B-14 Study**

<b>Adverse Effect</b>	<b>% of Women</b>	
	<b>NOLVADEX (n=1422)</b>	<b>Placebo (n=1437)</b>
Hot Flashes	64	48
Fluid Retention	32	30
Vaginal Discharge	30	15
Nausea	26	24
Irregular Menses	25	19
Weight Loss (>5%)	23	18
Skin Changes	19	15
Increased SGOT	5	3
Increased Bilirubin	2	1
Increased Creatinine	2	1
Thrombocytopenia*	2	1
Thrombotic Events		
Deep Vein Thrombosis	0.8	0.2
Pulmonary Embolism	0.5	0.2
Superficial Phlebitis	0.4	0.0

\*Defined as a platelet count of <100,000/mm<sup>3</sup>

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, NOLVADEX or placebo was administered for 2 years to women following mastectomy. When compared to placebo, NOLVADEX showed a significantly higher incidence of hot flashes (19% vs. 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for NOLVADEX was 10% vs. 3% for placebo, an observation of borderline statistical significance.

In other adjuvant studies, Toronto and NOLVADEX Adjuvant Trial Organization (NATO), women received either NOLVADEX or no therapy. In the Toronto study, hot flashes were observed in 29% of patients for NOLVADEX vs. 1% in the untreated group. In the NATO trial, hot flashes and vaginal bleeding were reported in 2.8% and 2.0% of women, respectively, for NOLVADEX vs. 0.2% for each in the untreated group.

**Ductal Carcinoma in Situ (DCIS):** The type and frequency of adverse events in the NSABP B-24 trial were consistent with those observed in the other adjuvant trials conducted with NOLVADEX.

**Reduction in Breast Cancer Incidence in High Risk Women:** In the NSABP P-1 Trial, there was an increase in five serious adverse effects in the NOLVADEX group: endometrial cancer (33 cases in the NOLVADEX group vs. 14 in the placebo group); pulmonary embolism (18 cases in the NOLVADEX group vs. 6 in the placebo group); deep vein thrombosis (30 cases in the NOLVADEX group vs. 19 in the placebo group); stroke (34 cases in the NOLVADEX group vs. 24 in the placebo group); cataract formation (540 cases in the NOLVADEX group vs. 483 in the placebo group) and cataract surgery (101 cases in the NOLVADEX group vs. 63 in the placebo group) (See **WARNINGS** and Table 3 in **CLINICAL PHARMACOLOGY**).

The following table presents the adverse events observed in NSABP P-1 by treatment arm. Only adverse events more common on NOLVADEX than placebo are shown.

	NSABP P-1 Trial: All Adverse Events	
	% of Women	
	NOLVADEX	PLACEBO
	N=6681	N=6707
<u>Self Reported Symptoms</u>	<u>N=6441<sup>1</sup></u>	<u>N=6469<sup>1</sup></u>
Hot Flashes	80	68
Vaginal Discharges	55	35
Vaginal Bleeding	23	22
<u>Laboratory Abnormalities</u>	<u>N=6520<sup>2</sup></u>	<u>N=6535<sup>2</sup></u>
Platelets decreased	0.7	0.3
<u>Adverse Effects</u>	<u>N=6492<sup>3</sup></u>	<u>N=6484<sup>3</sup></u>
<u>Other Toxicities</u>		
Mood	11.6	10.8
Infection/Sepsis	6.0	5.1
Constipation	4.4	3.2
Alopecia	5.2	4.4
Skin	5.6	4.7
Allergy	2.5	2.1

<sup>1</sup>Number with Quality of Life Questionnaires

<sup>2</sup>Number with Treatment Follow-up Forms

<sup>3</sup>Number with Adverse Drug Reaction Forms

In the NSABP P-1 trial, 15.0% and 9.7% of participants receiving NOLVADEX and placebo therapy, respectively withdrew from the trial for medical reasons. The following are the medical reasons for withdrawing from NOLVADEX and placebo therapy, respectively: Hot flashes (3.1% vs. 1.5%) and Vaginal Discharge (0.5% vs. 0.1%).

In the NSABP P-1 trial, 8.7% and 9.6% of participants receiving NOLVADEX and placebo therapy, respectively withdrew for non-medical reasons.

On the NSABP P-1 trial, hot flashes of any severity occurred in 68% of women on placebo and in 80% of women on NOLVADEX. Severe hot flashes occurred in 28% of women on placebo and 45% of women on NOLVADEX. Vaginal discharge occurred in 35% and 55% of women on placebo and NOLVADEX respectively; and was severe in 4.5% and 12.3% respectively. There was no difference in the incidence of vaginal bleeding between treatment arms.

**Pediatric Patients - McCune-Albright Syndrome:** Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. A causal relationship has not been established; however, as an increase in the incidence of endometrial adenocarcinoma and uterine sarcoma has been noted in adults treated with NOLVADEX (see **BOXED WARNING**), continued monitoring of McCune-Albright patients treated with NOLVADEX for long-term effects is recommended. **The safety and efficacy of NOLVADEX for girls aged two to 10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond one year of treatment. The long-term effects of NOLVADEX therapy in girls have not been established.**

**Postmarketing experience:** Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, skin rash and headaches. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment. Very rare reports of erythema multiforme, Stevens-Johnson syndrome, bullous pemphigoid, interstitial pneumonitis, and rare reports of hypersensitivity reactions including angioedema have been reported with NOLVADEX therapy. In some of these cases, the time to onset was more than one year. Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of NOLVADEX (see **PRECAUTIONS- Drug/Laboratory Testing Interactions** section).

#### **OVERDOSAGE**

Signs observed at the highest doses following studies to determine LD<sub>50</sub> in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3-5 days of beginning NOLVADEX and cleared within 2-5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients

were all greater than 400 mg/m<sup>2</sup> loading dose, followed by maintenance doses of 150 mg/m<sup>2</sup> of NOLVADEX given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m<sup>2</sup> loading dose, followed by maintenance doses of 80 mg/m<sup>2</sup> of NOLVADEX given twice a day. For a woman with a body surface area of 1.5 m<sup>2</sup> the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

### **DOSAGE AND ADMINISTRATION**

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the NSABP B-14 adjuvant study in women with node-negative breast cancer, one 10 mg NOLVADEX tablet was given twice a day for at least 5 years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see **CLINICAL PHARMACOLOGY**). In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy. There was no indication that doses greater than 20 mg per day were more effective. Current data from clinical trials support 5 years of adjuvant NOLVADEX therapy for patients with breast cancer.

**Ductal Carcinoma in Situ (DCIS):** The recommended dose is NOLVADEX 20 mg daily for 5 years.

**Reduction in Breast Cancer Incidence in High Risk Women:** The recommended dose is NOLVADEX 20 mg daily for 5 years. There are no data to support the use of NOLVADEX other than for 5 years (See **CLINICAL PHARMACOLOGY-Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women**).

### **HOW SUPPLIED**

**10 mg Tablets** containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets, 180 tablets and 2500 tablets. NDC 0310-0600.

**20 mg Tablets** containing tamoxifen as the citrate in an amount equivalent to 20 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 30 tablets, 90 tablets and 1250 tablets. NDC 0310-0604.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Dispense in a well-closed, light-resistant container.

**Patient Information about  
NOLVADEX<sup>®</sup> (tamoxifen citrate) Tablets**

for Breast Cancer Treatment and Reduction in the Incidence of Breast Cancer

Brand Name: **NOLVADEX<sup>®</sup>** (Nol 'va dex)

Generic Name: Tamoxifen (ta-MOX-i-fen)

Please read this information carefully before you begin taking NOLVADEX. It is important to read this information each time your prescription is filled or refilled in case new information is available. This summary does not tell you everything about NOLVADEX. Your health care professional is the best source of information about this medicine. You should talk with him or her before you begin taking NOLVADEX and at regular checkups. In addition, the professional package insert contains more detailed information on NOLVADEX.

**What are the most important things I should know about NOLVADEX?**

NOLVADEX has been shown to help women with advanced breast cancer and in clinical trials of over 30,000 women with early breast cancer it has been shown to reduce the risk of recurrence. Also in a trial of 13,000 women at high risk of breast cancer, NOLVADEX reduced the risk of developing the disease.

Like all medicines, NOLVADEX has some side effects. Most are mild and relate to its hormonal mode of action. **For all women NOLVADEX can, however, also increase the risk of some serious and potentially life-threatening events, including uterine cancer, blood clots, and stroke. Some of these events have caused death.** NOLVADEX can also increase the risk of getting cataracts or of needing cataract surgery. If you experience symptoms of any of these, tell your doctor **immediately** (see “**What should I avoid or do while taking NOLVADEX?**”).

**If you are a woman at high risk for breast cancer or a woman with DCIS considering NOLVADEX to reduce your risk of developing breast cancer, you should discuss the potential benefits versus the potential risks of these serious events with your health care provider.**

**What is NOLVADEX?**

- NOLVADEX is a prescription medicine used to reduce the risk of getting breast cancer (in women who have a high risk of getting breast cancer)

This effect was shown in the Breast Cancer Prevention Trial (BCPT, NSABP P-1), a large study where over 13,000 women at high risk for breast cancer were to take NOLVADEX or placebo (a pill without tamoxifen) for 5 years. High risk women were those who were at least 35 years old and had a combination of risks that made their chances of developing breast cancer greater than 1.67% in the next five years. The risk factors included early age at first menstrual period, late age at first pregnancy, no pregnancies, close family members with breast cancer (mother, sister, or daughter), history of previous breast biopsies, or high-risk changes in the breast seen on a biopsy. Twenty-five percent of the women in the study completed 5 years of treatment, and most women in this study have been followed for about 4 years. The study showed that NOLVADEX reduced the chance of getting breast cancer by 44%. The longer-term effects of NOLVADEX on reducing the chance of getting breast cancer are not known.

We do not know whether taking NOLVADEX for 5 years only delays the appearance of cancer, or actually decreases the number of tumors that will ever develop since long-term studies have not been completed.

Some women in this study also experienced serious side effects of NOLVADEX. They are described in detail in the section, **What are the possible side effects of NOLVADEX?**. Some of these women experienced complications related to the treatment of these side effects.

The following table of the major results from the study is intended to be an aid in weighing the potential benefit of a reduction in risk of breast cancer against the potential risk of serious side effects of NOLVADEX.

	<b>Cases per year out of 1000 women taking NOLVADEX</b>	<b>Cases per year out of 1000 women taking Placebo</b>
Breast Cancer	3.6	6.5
Endometrial Cancer*	2.3	0.9
Blood clot in the lungs	0.8	0.3
Blood clot in the veins	1.3	0.8
Stroke	1.4	1.0
Cataracts	25.4	22.5
Cataract surgery	46.6	31.4

\*In women with a uterus.

Two European trials of NOLVADEX in women with a high risk of breast cancer were also conducted. They showed no difference in the number of breast cancer cases between the women who took tamoxifen and those who got placebo. These studies had trial designs that differed from that of NSABP P-1 were smaller than P-1, and enrolled women at a lower risk for breast cancer than those in the P-1 trial.

- In women with DCIS, following breast surgery and radiation, NOLVADEX is indicated to reduce the risk of invasive breast cancer. The decision regarding therapy with NOLVADEX for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of NOLVADEX therapy.

A trial evaluated the addition of NOLVADEX to lumpectomy and radiation therapy in women with DCIS. The primary objective was to determine whether 5 years of NOLVADEX therapy would reduce the incidence of invasive breast cancer in the ipsilateral (the same) or contralateral (the opposite) breast. The incidence of invasive breast cancer was reduced by 43% among women treated with NOLVADEX.

- NOLVADEX is used to reduce the recurrence of breast cancer in women who have had surgery and/or radiation therapy to treat early breast cancer. NOLVADEX is also used in women with breast cancer who are at risk of developing a second breast cancer in the opposite breast.

The Early Breast Cancer Trialists Collaborative Group reviewed the 10-year results of studies of NOLVADEX for early breast cancer. Treatment with NOLVADEX for about 5 years reduced the risk of recurrence of breast cancer and improved overall survival. Treatment with about 5 years of NOLVADEX also reduced the chance of getting a second breast cancer in the opposite breast by approximately 50%, a result similar to that seen in the NSABP P-1 study.

- NOLVADEX is used to treat advanced breast cancer in women and men.

Three studies compared NOLVADEX to surgery or radiation to the ovaries in premenopausal women with advanced breast cancer and found that NOLVADEX was similar to surgery or radiation in causing tumor shrinkage.

Published studies have demonstrated that NOLVADEX is effective for the treatment of advanced breast cancer in men.

- NOLVADEX is a prescription tablet available in two dosage strengths: 10 mg tablets and 20 mg tablets. The active ingredient in each tablet is tamoxifen citrate.

**How does NOLVADEX work?**

NOLVADEX belongs to a group of medicines called antiestrogens. Antiestrogens work by blocking the effects of the hormone estrogen in the body. Estrogen may cause the growth of some types of breast tumors. NOLVADEX may block the growth of tumors that respond to estrogen.

**Who should not take NOLVADEX?**

- You should not take NOLVADEX to reduce the risk of getting breast cancer if you have ever had blood clots or if you develop blood clots that require medical treatment. However, if you are taking NOLVADEX for treatment of early or advanced breast cancer, the benefits of NOLVADEX may outweigh the risks associated with developing new blood clots. Your health care professional can assist you in deciding whether NOLVADEX is right for you.
- You should not take NOLVADEX to reduce the risk of getting breast cancer if you are taking medicines to thin your blood (anticoagulants) like warfarin (Coumadin®\*).
- You should not take NOLVADEX if you plan to become pregnant while taking NOLVADEX or during the two months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately and stop taking NOLVADEX if you become pregnant while taking the drug. Please talk with your doctor about birth control recommendations. If you are capable of becoming pregnant, you should start NOLVADEX during a menstrual period or if you have irregular periods have a negative pregnancy test before beginning to take NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- You should not take NOLVADEX if you are breast feeding.
- You should not take NOLVADEX if you have ever had an allergic reaction to NOLVADEX or tamoxifen citrate (the chemical name) or any of its ingredients.
- NOLVADEX is not known to reduce the risk of breast cancer in women with changes in breast cancer genes (BRCA1 or BRCA2).
- You should not take NOLVADEX to decrease the chance of getting breast cancer if you are less than age 35 because NOLVADEX has not been tested in younger women.
- You should not take NOLVADEX to reduce the risk of breast cancer unless you are at high risk of getting breast cancer. Certain conditions put women at high risk and it is possible to calculate this risk for any woman. Breast cancer risk assessment tools to help calculate your risk of breast cancer have been developed and are available to your health care professional. You should discuss your risks with your health care professional.

Girls with McCune-Albright Syndrome (a genetic condition associated with premature puberty) under the age of two and older than 10 years of age should not take NOLVADEX because treatment in this age group has not been studied. NOLVADEX has not been studied in boys.

**How should I take NOLVADEX?**

- Follow your doctor's instructions about when and how to take NOLVADEX. Read the label on the container. If you are unsure or have questions, ask your doctor or pharmacist.
- You will take NOLVADEX differently, depending on your diagnosis.
- For reduction of the risk of breast cancer, the usual dose is 20 mg a day, for five years.
- For treatment of breast cancer in adult women and men, the usual dose is 20-40 mg a day. Take the tablets once or twice a day depending on the tablet strength prescribed. If your doctor has prescribed a different dose, do not change it unless he or she tells you to do so. For women with early breast cancer, NOLVADEX should be taken for 5 years. For women with advanced cancer, NOLVADEX should be taken until your doctor feels it is no longer indicated.
- Take your medicine each day. You may find it easier to remember to take your medicine if you take it at the same time each day. If you forget to take a dose, take it as soon as you remember and then take the next dose as usual.
- Swallow the tablets whole with a drink of water.
- You can take NOLVADEX with or without food.
- Do not stop taking your tablets unless your doctor tells you to do so.

**Are there other important factors to consider before taking NOLVADEX?**

- Tell your doctor if you have ever had blood clots that required medical treatment.
- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medications, particularly if you are taking warfarin to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the two months after you stop taking it as NOLVADEX may harm your unborn child. Please contact your doctor for birth control recommendations. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX.

### **What should I avoid or do while taking NOLVADEX?**

- You should contact your doctor immediately if you notice any of the following symptoms. Some of these symptoms may suggest that you are experiencing a rare but serious side effect associated with NOLVADEX (see “**What are the possible side effects of NOLVADEX?**”).
  - new breast lumps
  - vaginal bleeding
  - changes in your menstrual cycle
  - changes in vaginal discharge
  - pelvic pain or pressure
  - swelling or tenderness in your calf
  - unexplained breathlessness (shortness of breath)
  - sudden chest pain
  - coughing up blood
  - changes in your vision

If you see a health care professional who is new to you (an emergency room doctor, another doctor in the practice), tell him or her that you take NOLVADEX or have previously taken NOLVADEX.

- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medicines. Be sure to tell your doctor if you are taking warfarin (Coumadin) to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the two months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX. Please talk with your doctor about birth control recommendations. If you are taking NOLVADEX to reduce your risk of getting breast cancer, and you are sexually active, NOLVADEX should be started during your menstrual period. If you have irregular periods, you should have a negative pregnancy test before you start NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- If you are taking NOLVADEX to reduce your risk of getting breast cancer, you should know that NOLVADEX does not prevent all breast cancers. While you are taking NOLVADEX and after you stop taking NOLVADEX and in keeping with your doctor’s recommendation, you should have annual gynecological check-ups which should include breast exams and mammograms. If breast cancer occurs, there is no guarantee that it will be detected at an early stage. This is why it is important to continue with regular check-ups.

### **What are the possible side effects of NOLVADEX?**

Like many medicines, NOLVADEX causes side effects in most patients. The majority of the side effects seen with NOLVADEX have been mild and do not usually cause breast cancer patients to stop taking the medication. In women with breast cancer, withdrawal from NOLVADEX therapy is about 5%. Approximately 15% of women who took NOLVADEX to reduce the chance of getting breast cancer stopped treatment because of side effects.

The most common side effects reported with NOLVADEX are: hot flashes; vaginal discharge or bleeding; and menstrual irregularities (these side effects may be mild or may be a sign of a more serious side effect). Women may experience hair loss, skin rashes (itching or peeling skin) or headaches; or inflammation of the lungs, which may have the same symptoms as pneumonia, such as breathlessness and cough; however, hair loss is uncommon and is usually mild.

A rare but serious side effect of NOLVADEX is a blood clot in the veins. Blood clots stop the flow of blood and can cause serious medical problems, disability, or death. Women who take NOLVADEX are at increased risk for developing blood clots in the lungs and legs. Some women may develop more than one blood clot, even if NOLVADEX is stopped. Women may also have complications from treating the clot, such as bleeding from thinning the blood too much. Symptoms of a blood clot in the lungs may include sudden chest pain, shortness of breath or coughing up blood. Symptoms of a blood clot in the legs are pain or swelling in the calves. A blood clot in the legs may move to the lungs. If you experience any of these symptoms of a blood clot, contact your doctor immediately.

NOLVADEX increases the chance of having a stroke, which can cause serious medical problems, disability, or death. If you experience any symptoms of stroke, such as weakness, difficulty walking or talking, or numbness, contact your doctor immediately.

NOLVADEX increases the chance of changes occurring in the lining (endometrium) or body of your uterus which can be serious and could include cancer. If you have not had a hysterectomy (removal of the uterus), it is important for you to contact your doctor immediately if you experience any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities; or pain or pressure in the pelvis (lower stomach). These may be caused by changes to the lining (endometrium) or body of your uterus. It is important to bring them to your doctor's attention without delay as they can occasionally indicate the start of something more serious and even life-threatening.

NOLVADEX may cause cataracts or changes to parts of the eye known as the cornea or retina. NOLVADEX can increase the chance of needing cataract surgery, and can cause blood clots in the veins of the eye. NOLVADEX can result in difficulty in distinguishing different colors. If you experience any changes in your vision, tell your doctor immediately.

Rare side effects, which may be serious, include certain liver problems such as jaundice (which may be seen as yellowing of the whites of the eyes) or hypertriglyceridemia (increased levels of fats in the blood) sometimes with pancreatitis (pain or tenderness in the upper abdomen). Stop taking NOLVADEX and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue and/or throat) even if you have been taking NOLVADEX for a long time.

If you are a woman receiving NOLVADEX for treatment of advanced breast cancer, and you experience excessive nausea, vomiting or thirst, tell your doctor immediately. This may mean that there are changes in the amount of calcium in your blood (hypercalcemia). Your doctor will evaluate this.

In patients with breast cancer, a temporary increase in the size of the tumor may occur and sometimes results in muscle aches/bone pain and skin redness. This condition may occur shortly after starting NOLVADEX and may be associated with a good response to treatment.

Many of these side effects happen only rarely. However, you should contact your doctor if you think you have any of these or any other problems with your NOLVADEX. Some side effects of NOLVADEX may become apparent soon after starting the drug, but others may first appear at any time during therapy.

This summary does not include all possible side effects with NOLVADEX. It is important to talk to your health care professional about possible side effects. If you want to read more, ask your doctor or pharmacist to give you the professional labeling.

**How should I store NOLVADEX?**

NOLVADEX Tablets should be stored at room temperature (68-77°F). Keep in a well-closed, light-resistant container. Keep out of the reach of children.

Do not take your tablets after the expiration date on the container. Be sure that any discarded tablets are out of the reach of children.

This leaflet provides you with a summary of information about NOLVADEX. Medicines are sometimes prescribed for uses other than those listed. NOLVADEX has been prescribed specifically for you by your doctor. Do not give your medicine to anyone else, even if they have a similar condition, because it may harm them.

If you have any questions or concerns, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about NOLVADEX written for health care professionals that you can ask to read. For more information about NOLVADEX or breast cancer, call 1-800-34 LIFE 4.

\*Coumadin® is a registered trademark of Bristol-Myers Squibb Pharmaceuticals.

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## Accupril® (Quinapril Hydrochloride Tablets)

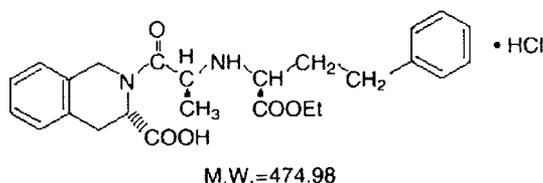
### USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

### DESCRIPTION

ACCUPRIL® (quinapril hydrochloride) is the hydrochloride salt of quinapril, the ethyl ester of a non-sulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat.

Quinapril hydrochloride is chemically described as [3S-[2[R\*(R\*)], 3R\*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. Its empirical formula is  $C_{25}H_{30}N_2O_5 \cdot HCl$  and its structural formula is:



Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents.

ACCUPRIL tablets contain 5 mg, 10 mg, 20 mg, or 40 mg of quinapril for oral administration. Each tablet also contains candelilla wax, crospovidone, gelatin, lactose, magnesium carbonate, magnesium stearate, synthetic red iron oxide, and titanium dioxide.

### CLINICAL PHARMACOLOGY

**Mechanism of Action:** Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension and in congestive heart failure (CHF) appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, norepinephrine or epinephrine. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced

aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with ACCUPRIL alone resulted in mean increases in potassium of 0.07 mmol/L (see PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. ACCUPRIL was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in nonblacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

**Pharmacokinetics and Metabolism:** Following oral administration, peak plasma quinapril concentrations are observed within one hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is at least 60%. The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when ACCUPRIL tablets are administered during a high-fat meal. Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of ACCUPRIL, there is an effective accumulation half-life of quinaprilat of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose. Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose, and has an elimination half-life in plasma of approximately 2 hours and a prolonged terminal phase with a half-life of 25 hours. The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5-80 mg doses and 40-160 mg in multiple daily doses. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic hemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. Elimination of quinaprilat may be reduced in elderly patients ( $\geq 65$  years) and in those with heart failure; this reduction is attributable to decrease in renal function (see DOSAGE AND ADMINISTRATION). Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

### **Pharmacodynamics and Clinical Effects**

**Hypertension:** Single doses of 20 mg of ACCUPRIL provide over 80% inhibition of plasma ACE for 24 hours. Inhibition of the pressor response to angiotensin I is shorter-lived, with a 20 mg dose giving 75% inhibition for about 4 hours, 50% inhibition for about 8 hours, and 20% inhibition at 24 hours. With chronic dosing, however, there is substantial inhibition of angiotensin II levels at 24 hours by doses of 20-80 mg.

Administration of 10 to 80 mg of ACCUPRIL to patients with mild to severe hypertension results in a reduction of sitting and standing blood pressure to about the same extent with minimal effect on heart rate. Symptomatic postural hypotension is infrequent although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS). Antihypertensive activity commences within 1 hour with

peak effects usually achieved by 2 to 4 hours after dosing. During chronic therapy, most of the blood pressure lowering effect of a given dose is obtained in 1-2 weeks. In multiple-dose studies, 10-80 mg per day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5-11/3-7 mm Hg. The trough effect represents about 50% of the peak effect. While the dose-response relationship is relatively flat, doses of 40-80 mg were somewhat more effective at trough than 10-20 mg, and twice daily dosing tended to give a somewhat lower trough blood pressure than once daily dosing with the same total dose. The antihypertensive effect of ACCUPRIL continues during long-term therapy, with no evidence of loss of effectiveness.

Hemodynamic assessments in patients with hypertension indicate that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction.

Use of ACCUPRIL with a thiazide diuretic gives a blood-pressure lowering effect greater than that seen with either agent alone.

In patients with hypertension, ACCUPRIL 10-40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.

Therapeutic effects appear to be the same for elderly ( $\geq 65$  years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

**Heart Failure:** In a placebo-controlled trial involving patients with congestive heart failure treated with digitalis and diuretics, parenteral quinaprilat, the active metabolite of quinapril, reduced pulmonary capillary wedge pressure and systemic vascular resistance and increased cardiac output/index. Similar favorable hemodynamic effects were seen with oral quinapril in baseline-controlled trials, and such effects appeared to be maintained during chronic oral quinapril therapy. Quinapril reduced renal hepatic vascular resistance and increased renal and hepatic blood flow with glomerular filtration rate remaining unchanged.

A significant dose response relationship for improvement in maximal exercise tolerance has been observed with ACCUPRIL therapy. Beneficial effects on the severity of heart failure as measured by New York Heart Association (NYHA) classification and Quality of Life and on symptoms of dyspnea, fatigue, and edema were evident after 6 months in a double blind, placebo controlled study. Favorable effects were maintained for up to two years of open label therapy. The effects of quinapril on long-term mortality in heart failure have not been evaluated.

## INDICATIONS AND USAGE

### **Hypertension**

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

### **Heart Failure**

ACCUPRIL is indicated in the management of heart failure as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

**Angioedema in black patients:** Black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. It should also be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

## CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

## WARNINGS

### Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Accupril) may be subject to a variety of adverse reactions, some of them serious.

**Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL.

In two similarly sized U.S. postmarketing trials that, combined, enrolled over 3,000 black patients and over 19,000 non-blacks, angioedema was reported in 0.30% and 0.55% of blacks (in study 1 and 2 respectively) and 0.39% and 0.17% of non-blacks.

Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

**Patients with a history of angioedema:** Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

**Anaphylactoid reactions during desensitization:** Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

**Anaphylactoid reactions during membrane exposure:** Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

**Hepatic Failure:** Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

**Hypotension:** Excessive hypotension is rare in patients with uncomplicated hypertension treated with ACCUPRIL alone. Patients with heart failure given ACCUPRIL commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. Caution should be observed when initiating therapy in patients with heart failure (see DOSAGE AND ADMINISTRATION). In controlled studies, syncope was observed in 0.4% of patients (N=3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include patients with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or cautiously increase salt intake (except in patients with heart failure) before initiating therapy with ACCUPRIL in patients at risk for excessive hypotension who are able to tolerate such adjustments.

In patients at risk of excessive hypotension, therapy with ACCUPRIL should be started under close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of ACCUPRIL and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of ACCUPRIL, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops a dose reduction or discontinuation of ACCUPRIL or concomitant diuretic may be necessary.

**Neutropenia/Agranulocytosis:** Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with

other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

**Fetal/Neonatal Morbidity and Mortality:** ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

## PRECAUTIONS

### General

**Impaired renal function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

**Evaluation of patients with hypertension or heart failure should always include assessment of renal function** (see DOSAGE AND ADMINISTRATION).

**Hyperkalemia and potassium-sparing diuretics:** In clinical trials, hyperkalemia (serum potassium  $\geq 5.8$  mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

**Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent non-productive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

**Surgery/anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

#### **Information for Patients**

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Angioedema:** Angioedema, including laryngeal edema can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

**Symptomatic hypotension:** Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual

syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

**Hyperkalemia:** Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

**Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

#### **Drug Interactions**

**Concomitant diuretic therapy:** As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

**Agents increasing serum potassium:** Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

**Tetracycline and other drugs that interact with magnesium:** Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

**Lithium:** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

**Other agents:** Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.

- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on an mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on an mg/m<sup>2</sup> basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m<sup>2</sup> respectively).

#### **Pregnancy**

**Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

#### **Nursing Mothers**

Because ACCUPRIL is secreted in human milk, caution should be exercised when this drug is administered to a nursing woman.

#### **Pediatric Use**

The safety and effectiveness of ACCUPRIL in pediatric patients have not been established.

#### **Geriatric Use**

Clinical studies of ACCUPRIL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients exhibited increased area under the plasma concentration time curve and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself.

**ADVERSE REACTIONS**

**Hypertension**

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 4.7% of patients with hypertension.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials		
	Accupril (N=1563) Incidence (Discontinuance)	Placebo (N=579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea and/or Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

**Heart Failure**

Accupril has been evaluated for safety in 1222 ACCUPRIL treated patients. Of these, 632 patients participated in controlled clinical trials. In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 6.8% of patients with congestive heart failure.

Adverse experiences probably or possibly related or of unknown relationship to therapy occurring in 1% or more of the 585 patients in placebo-controlled congestive heart failure trials who were treated with ACCUPRIL are shown below.

	Accupril (N=585) Incidence (Discontinuance)	Placebo (N=295) Incidence (Discontinuance)
Dizziness	7.7 (0.7)	5.1 (1.0)
Coughing	4.3 (0.3)	1.4
Fatigue	2.6 (0.2)	1.4
Nausea and/or Vomiting	2.4 (0.2)	0.7
Chest Pain	2.4	1.0
Hypotension	2.9 (0.5)	1.0
Dyspnea	1.9 (0.2)	2.0
Diarrhea	1.7	1.0
Headache	1.7	1.0 (0.3)
Myalgia	1.5	2.0
Rash	1.4 (0.2)	1.0
Back Pain	1.2	0.3

See PRECAUTIONS, Cough.

**Hypertension and/or Heart Failure**

Clinical adverse experiences probably, possibly, or definitely related, or of uncertain relationship to therapy occurring in 0.5% to 1.0% (except as noted) of the patients with CHF or hypertension treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N=4847) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

**General:** back pain, malaise, viral infections

**Cardiovascular:** palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances, cardiogenic shock*

**Hematology:** *hemolytic anemia*

**Gastrointestinal:** flatulence, dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

**Nervous/Psychiatric:** somnolence, vertigo, syncope, nervousness, depression, insomnia, paresthesia

**Integumentary:** alopecia, increased sweating, pemphigus, pruritus, *exfoliative dermatitis, photosensitivity reaction, dermatopolymyositis*

**Urogenital:** urinary tract infection, impotence, *acute renal failure, worsening renal failure*

**Respiratory:** *eosinophilic pneumonitis*

**Other:** amblyopia, edema, arthralgia, pharyngitis, *agranulocytosis, hepatitis, thrombocytopenia*

### **Fetal/Neonatal Morbidity and Mortality**

See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

#### **Angioedema**

Angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See **WARNINGS.**)

#### **Clinical Laboratory Test Findings**

**Hematology:** (See **WARNINGS**)

**Hyperkalemia:** (See **PRECAUTIONS**)

**Creatinine and Blood Urea Nitrogen:** Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of all patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy. In controlled studies of heart failure, increases in blood urea nitrogen and serum creatinine were observed in 11% and 8%, respectively, of patients treated with ACCUPRIL; most often these patients were receiving diuretics with or without digitalis.

### **OVERDOSAGE**

No data are available with respect to overdosage in humans. Doses of 1440 to 4280 mg/kg of quinapril cause significant lethality in mice and rats.

The most likely clinical manifestation would be symptoms attributable to severe hypotension.

Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose.

No data are available to suggest physiological maneuvers (eg, maneuvers to change pH of the urine) that might accelerate elimination of quinapril and its metabolites.

Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of quinapril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of quinapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat quinapril overdose by infusion of normal saline solution.

### **DOSAGE AND ADMINISTRATION**

#### **Hypertension**

**Monotherapy:** The recommended initial dosage of ACCUPRIL in patients not on diuretics is 10 or 20 mg once daily. Dosage should be adjusted according to blood pressure response measured at peak (2-6 hours after dosing) and trough (predosing). Generally, dosage adjustments should be made at intervals of at least 2 weeks. Most patients have required dosages of 20, 40, or 80 mg/day, given as a single

dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice daily administration may be warranted. In general, doses of 40-80 mg and divided doses give a somewhat greater effect at the end of the dosing interval.

**Concomitant Diuretics:** If blood pressure is not adequately controlled with ACCUPRIL monotherapy, a diuretic may be added. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ACCUPRIL. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2 to 3 days prior to beginning therapy with ACCUPRIL (see WARNINGS). Then, if blood pressure is not controlled with ACCUPRIL alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg ACCUPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized.

The dosage should subsequently be titrated (as described above) to the optimal response (see WARNINGS, PRECAUTIONS, and Drug Interactions).

**Renal Impairment:** Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. Recommended starting doses, based on clinical and pharmacokinetic data from patients with renal impairment, are as follows:

Creatinine Clearance	Maximum Recommended Initial Dose
>60 mL/min	10 mg
30-60 mL/min	5 mg
10-30 mL/min	2.5 mg
<10 mL/min	Insufficient data for dosage recommendation

Patients should subsequently have their dosage titrated (as described above) to the optimal response.

**Elderly (≥65 years):** The recommended initial dosage of ACCUPRIL in elderly patients is 10 mg given once daily followed by titration (as described above) to the optimal response.

**Heart Failure**

ACCUPRIL is indicated as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis. The recommended starting dose is 5 mg twice daily. This dose may improve symptoms of heart failure, but increases in exercise duration have generally required higher doses. Therefore, if the initial dosage of ACCUPRIL is well tolerated, patients should then be titrated at weekly intervals until an effective dose, usually 20 to 40 mg daily given in two equally divided doses, is reached or undesirable hypotension, orthostatis, or azotemia (see WARNINGS) prohibit reaching this dose.

Following the initial dose of ACCUPRIL, the patient should be observed under medical supervision for at least two hours for the presence of hypotension or orthostatis and, if present, until blood pressure stabilizes. The appearance of hypotension, orthostatis, or azotemia early in dose titration should not

preclude further careful dose titration. Consideration should be given to reducing the dose of concomitant diuretics.

### **DOSE ADJUSTMENTS IN PATIENTS WITH HEART FAILURE AND RENAL IMPAIRMENT OR HYPONATREMIA**

Pharmacokinetic data indicate that quinapril elimination is dependent on level of renal function. In patients with heart failure and renal impairment, the recommended initial dose of ACCUPRIL is 5 mg in patients with a creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance of 10 to 30 mL/min. There is insufficient data for dosage recommendation in patients with a creatinine clearance less than 10 mL/min. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions).

If the initial dose is well tolerated, ACCUPRIL may be administered the following day as a twice daily regimen. In the absence of excessive hypotension or significant deterioration of renal function, the dose may be increased at weekly intervals based on clinical and hemodynamic response.

### **HOW SUPPLIED**

ACCUPRIL tablets are supplied as follows:

**5-mg tablets:** brown, film-coated, elliptical scored tablets, coded "PD 527" on one side and "5" on the other.

N0071-0527-23 bottles of 90 tablets

N0071-0527-40 10 x 10 unit dose blisters

**10-mg tablets:** brown, film-coated, triangular tablets, coded "PD 530" on one side and "10" on the other.

N0071-0530-23 bottles of 90 tablets

N0071-0530-40 10 x 10 unit dose blisters

**20-mg tablets:** brown, film-coated, round tablets, coded "PD 532" on one side and "20" on the other.

N0071-0532-23 bottles of 90 tablets

N0071-0532-40 10 x 10 unit dose blisters

**40-mg tablets:** brown, film-coated, elliptical tablets, coded "PD 535" on one side and "40" on the other.

N0071-0535-23 bottles of 90 tablets

Dispense in well-closed containers as defined in the USP.

**Storage: Store at controlled room temperature 15°-30°C (59°-86°F).**

**Protect from light.**

**Rx only**

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Revised March 2001

Accupril® (quinapril HCl)  
Pediatric Use

035

Manufactured by:  
**Parke Davis Pharmaceuticals, Ltd.**  
Vega Baja, PR 00694

Distributed by:  
**PARKE-DAVIS**  
Div of Warner-Lambert Co  
Morris Plains, NJ 07950 USA  
0527G079

# SERZONE® (nefazodone hydrochloride) Tablets

Rx only

## (Patient Information Included)

Before prescribing SERZONE, the physician should be thoroughly familiar with the details of this prescribing information.

### WARNING

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 - 300,000 patient-years of SERZONE treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. (See WARNINGS.)

Ordinarily, treatment with SERZONE should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that pre-existing liver disease increases the likelihood of developing liver failure, however, baseline abnormalities can complicate patient monitoring.

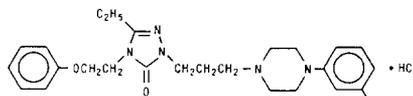
Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRECAUTIONS: Information for Patients). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels  $\geq$  3 times the upper limit of NORMAL, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

### DESCRIPTION

SERZONE® (nefazodone hydrochloride) is an antidepressant for oral administration with a chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics, tetracyclics, or monoamine oxidase inhibitors (MAOI).

Nefazodone hydrochloride is a synthetically derived phenylpiperazine antidepressant. The chemical name for nefazodone hydrochloride is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one monohydrochloride. The molecular formula is  $C_{22}H_{23}ClN_5O_2 \cdot HCl$ , which corresponds to a molecular weight of 506.5. The structural formula is:



Nefazodone hydrochloride is a nonhygroscopic, white crystalline solid. It is freely soluble in chloroform, soluble in propylene glycol, and slightly soluble in polyethylene glycol and water.

SERZONE is supplied as hexagonal tablets containing 50 mg, 100 mg, 150 mg, 200 mg, or 250 mg of nefazodone hydrochloride and the following inactive ingredients: microcrystalline cellulose, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and iron oxides (red and/or yellow) as colorants.

### CLINICAL PHARMACOLOGY

#### Pharmacodynamics

The mechanism of action of nefazodone, as with other antidepressants, is unknown.

Preclinical studies have shown that nefazodone inhibits neuronal uptake of serotonin and norepinephrine.

Nefazodone occupies central 5-HT<sub>2</sub> receptors at nanomolar concentrations, and acts as an antagonist at this receptor. Nefazodone was shown to antagonize alpha<sub>1</sub>-adrenergic receptors, a property which may be associated with postural hypotension. *In vitro* binding studies showed that nefazodone had no significant affinity for the following receptors: alpha<sub>2</sub> and beta adrenergic, 5-HT<sub>1A</sub>, cholinergic, dopaminergic, or benzodiazepine.

#### Pharmacokinetics

Nefazodone hydrochloride is rapidly and completely absorbed but is subject to extensive metabolism, so that its absolute bioavailability is low, about 20%, and variable. Peak plasma concentrations occur at about one hour and the half-life of nefazodone is 2-4 hours.

Both nefazodone and its pharmacologically similar metabolite, hydroxynefazodone, exhibit nonlinear kinetics for both dose and time, with AUC and C<sub>max</sub> increasing more than proportionally with dose increases and more than expected upon multiple dosing over time, compared to single dosing. For example, in a multiple-dose study involving BID dosing with 50, 100, and 200 mg, the AUC for nefazodone and hydroxynefazodone increased by about 4-fold with an increase in dose from 200 to 400 mg per day. C<sub>max</sub> increased by about 3-fold with the same dose increase. In a multiple-dose study involving BID dosing with 25, 50, 100, and 150 mg, the accumulation ratios for nefazodone and hydroxynefazodone AUC, after 5 days of BID dosing relative to the first dose, ranged from approximately 3 to 4 at the lower doses (50-100 mg/day) and from 5 to 7 at the higher doses (200-300 mg/day); there were also approximately 2- to 4-fold increases in C<sub>max</sub> after 5 days of BID dosing relative to the first dose, suggesting extensive and greater than predicted accumulation of nefazodone and its hydroxy metabolite with multiple dosing. Steady-state plasma nefazodone and metabolite concentrations are attained within 4 to 5 days of initiation of BID dosing or upon dose increase or decrease.

Nefazodone is extensively metabolized after oral administration by *n*-dealkylation and aliphatic and aromatic hydroxylation, and less than 1% of administered nefazodone is excreted unchanged in urine. Attempts to characterize three metabolites identified in plasma, hydroxynefazodone (HO-NEF), meta-chlorophenylpiperazine (mCPP), and a triazole-dione metabolite, have been carried out. The AUC (expressed as a multiple of the AUC for nefazodone dosed at 100 mg BID) and elimination half-lives for these three metabolites were as follows:

AUC Multiples and T <sub>1/2</sub> for Three Metabolites of Nefazodone (100 mg BID)		
Metabolite	AUC Multiple	T <sub>1/2</sub>
HO-NEF	0.4	1.5 - 4 h
mCPP	0.07	4 - 8 h
Triazole-dione	4.0	18 h

HO-NEF possesses a pharmacological profile qualitatively and quantitatively similar to that of nefazodone. mCPP has some similarities to nefazodone, but also has agonist activity at some serotonergic receptor subtypes. The pharmacological profile of the triazole-dione metabolite has not yet been well characterized. In addition to the above compounds, several other metabolites were present in plasma but have not been tested for pharmacological activity.

After oral administration of radiolabeled nefazodone, the mean half-life of total label ranged between 11 and 24 hours. Approximately 55% of the administered radioactivity was detected in urine and about 20-30% in feces.

**Distribution**—Nefazodone is widely distributed in body tissues, including the central nervous system (CNS). In humans the volume of distribution of nefazodone ranges from 0.22 to 0.87 L/kg.

**Protein Binding**—At concentrations of 25-2500 ng/mL nefazodone is extensively (>99%) bound to human plasma proteins *in vitro*. The administration of 200 mg BID of nefazodone for 1 week did not increase the fraction of unbound warfarin in subjects whose prothrombin times had been prolonged by warfarin therapy to 120-150% of the laboratory control (see **PRECAUTIONS: Drug Interactions**). While nefazodone did not alter the *in vitro* protein binding of chlorpromazine, desipramine, diazepam, diphenhydantoin, lidocaine, prazosin, propranolol, or verapamil, it is unknown whether displacement of either nefazodone or these drugs occurs *in vivo*. There was a 5% decrease in the protein binding of haloperidol; this is probably of no clinical significance.

**Effect of Food**—Food delays the absorption of nefazodone and decreases the bioavailability of nefazodone by approximately 20%.

**Renal Disease**—In studies involving 29 renally impaired patients, renal impairment (creatinine clearances ranging from 7 to 60 mL/min/1.73m<sup>2</sup>) had no effect on steady-state nefazodone plasma concentrations.

**Liver Disease**—In a multiple-dose study of patients with liver cirrhosis, the AUC values for nefazodone and HO-NEF at steady state were approximately 25% greater than those observed in normal volunteers.

**Age/Gender Effects**—After single doses of 300 mg to younger (18-45 years) and older patients (>65 years), C<sub>max</sub> and AUC for nefazodone and hydroxynefazodone were up to twice as high in the older patients. With multiple doses, however, differences were much smaller, 10-20%. A similar result was seen for gender, with a higher C<sub>max</sub> and AUC in women after single doses but no difference after multiple doses.

Treatment with SERZONE (nefazodone hydrochloride) should be initiated at half the usual dose in elderly patients, especially women (see **DOSAGE AND ADMINISTRATION**), but the therapeutic dose range is similar in younger and older patients.

### Clinical Efficacy Trial Results

#### Studies in Outpatients with Depression

During its premarketing development, the efficacy of SERZONE was evaluated at doses within the therapeutic range in five well-controlled, short-term (6-8 weeks) clinical investigations. These trials enrolled outpatients meeting DSM-III or DSM-III-R criteria for major depression. Among these trials, two demonstrated the effectiveness of SERZONE, and two provided additional support for that conclusion.

One trial was a 6-week dose-titration study comparing SERZONE in two dose ranges (up to 300 mg/day and up to 600 mg/day [mean modal dose for this group was about 400 mg/day]), on a BID schedule) and placebo. The second trial was an 8-week dose-titration study comparing SERZONE (up to 600 mg/day; mean modal dose was 375 mg/day), imipramine (up to 300 mg/day), and placebo, all on a BID schedule. Both studies demonstrated SERZONE, at doses titrated between 300 mg to 600 mg/day (therapeutic dose range), to be superior to placebo on at least three of the following four measures: 17-item Hamilton Depression Rating Scale or HDRS (total score), Hamilton Depressed Mood item, Clinical Global Impressions (CGI) Severity score, and CGI Improvement score. Significant differences were also found for certain factors of the HDRS (e.g., anxiety factor, sleep disturbance factor, and retardation factor). In the two supportive studies, SERZONE was titrated up to 500 or 600 mg/day (mean modal doses of 482 mg/day and 363 mg/day). In the fifth study, the differentiation in response rates between SERZONE and placebo was not statistically significant. Three additional trials were conducted using subtherapeutic doses of SERZONE.

Overall, approximately two thirds of patients in these trials were women, and an analysis of the effects of gender on outcome did not suggest any differential responsiveness on the basis of sex. There were too few elderly patients in these trials to reveal possible age-related differences in response.

Since its initial marketing as an antidepressant drug product, additional clinical investigations of SERZONE have been conducted. These studies explored SERZONE's use under conditions not evaluated fully at the time initial marketing approval was granted.

#### Studies in "Inpatients"

Two studies were conducted to evaluate SERZONE's effectiveness in hospitalized depressed patients. These were 6-week, dose-titration trials comparing SERZONE (up to 600 mg/day) and placebo, on a BID schedule. In one study, SERZONE was superior to placebo. In this study, the mean modal dose of SERZONE was 503 mg/day, and 85% of these inpatients were melancholic; at baseline, patients were distributed at the higher end of the 7-point CGI Severity scale, as follows: 4-moderately ill (17%); 5-moderately ill (48%); 6-severely ill (32%). In the other study, the differentiation in response rates between SERZONE and placebo was not statistically significant. This result may be explained by the "high" rate of spontaneous improvement among the patients randomized to placebo.

#### Studies of "Relapse Prevention in Patients Recently Recovered (Clinically) from Depression"

Two studies were conducted to assess SERZONE's capacity to maintain a clinical remission in acutely depressed patients who were judged to have responded adequately (HDRS total score  $\leq$ 10) after a 16-week period of open treatment with SERZONE (titration up to 600 mg/day). In one study, SERZONE was superior to placebo. In this study, patients (n=131) were randomized to continuation on SERZONE or placebo for an additional 36 weeks (1 year total). This study demonstrated a significantly lower relapse rate (HDRS total score  $\geq$ 18) for patients taking SERZONE compared to those on placebo. The second study was of appropriate design and power, but the sample of patients admitted for evaluation did not suffer relapses at a high enough incidence to provide a meaningful test of SERZONE's efficacy for this use.

#### Comparisons of Clinical Trial Results

Highly variable results have been seen in the clinical development of all antidepressant drugs. Furthermore, in those circumstances when the drugs have not been studied in the same controlled clinical trial(s), comparisons among the findings of studies evaluating the effectiveness of different antidepressant drug products are inherently unreliable. Because conditions of testing (e.g., patient samples, investigators, doses of the treatments administered and compared, outcome measures, etc.) vary among trials, it is virtually impossible to distinguish a difference in drug effect from a difference due to one or more of the confounding factors just enumerated.

### INDICATIONS AND USAGE

SERZONE (nefazodone hydrochloride) is indicated for the treatment of depression.

The efficacy of SERZONE in the treatment of depression was established in 6-8 week controlled trials of outpatients and in a 6-week controlled trial of depressed inpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depressive disorder (see **CLINICAL PHARMACOLOGY**).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). It must include either depressed mood or loss of interest or pleasure and at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of SERZONE in reducing relapse in patients with major depression who were judged to have had a satisfactory clinical response to 16 weeks of open-label SERZONE treatment for an acute depressive episode has been demonstrated in a randomized placebo-controlled trial (see **CLINICAL PHARMACOLOGY**). Although remitted patients were followed for as long as 36 weeks in the study cited

(i.e., 52 weeks total), the physician who elects to use SERZONE for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

#### CONTRAINDICATIONS

Coadministration of terfenadine, astemizole, cisapride, pimozide, or carbamazepine with SERZONE (nefazodone hydrochloride) is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

SERZONE tablets are contraindicated in patients who were withdrawn from SERZONE because of evidence of liver injury (see **BOXED WARNING**). SERZONE tablets are also contraindicated in patients who have demonstrated hypersensitivity to nefazodone hydrochloride, its inactive ingredients, or other phenylpiperazine antidepressants.

The coadministration of triazolam and nefazodone causes a significant increase in the plasma level of triazolam (see **WARNINGS** and **PRECAUTIONS**), and a 75% reduction in the initial triazolam dosage is recommended if the two drugs are to be given together. Because not all commercially available dosage forms of triazolam permit a sufficient dosage reduction, the coadministration of triazolam and SERZONE should be avoided for most patients, including the elderly.

#### WARNINGS

##### Hepatotoxicity (See **BOXED WARNING**.)

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE.

The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000 – 300,000 patient-years of use. This represents a rate of about 3-4 times the estimated background rate of liver failure. This rate is an underestimate because of under reporting, and the true risk could be considerably greater than this. A large cohort study of antidepressant users found no cases of liver failure leading to death or transplant among SERZONE users in about 30,000 patient-years of exposure. The spontaneous report data and the cohort study results provide estimates of the upper and lower limits of the risk of liver failure in nefazodone-treated patients, but are not capable of providing a precise risk estimate.

The time to liver injury for the reported liver failure cases resulting in death or transplant generally ranged from 2 weeks to 6 months on SERZONE therapy. Although some reports described dark urine and nonspecific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms), other reports did not describe the onset of clear prodromal symptoms prior to the onset of jaundice.

The physician may consider the value of liver function testing. Periodic serum transaminase testing has not been proven to prevent serious injury but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur. Ongoing clinical assessment of patients should govern physician interventions, including diagnostic evaluations and treatment.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see **PRECAUTIONS: Information for Patients**). Patients who develop evidence of hepatocellular injury such as increased serum AST or serum ALT levels  $\geq 3$  times the upper limit of **NORMAL**, while on SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reintroduced. Accordingly, such patients should not be considered for re-treatment.

##### Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving antidepressants with pharmacological properties similar to nefazodone in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor (SSRI), these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI.

Although the effects of combined use of nefazodone and MAOI have not been evaluated in humans or animals, because nefazodone is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that nefazodone not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 1 week should be allowed after stopping nefazodone before starting an MAOI.

##### Interaction with Triazolobenzodiazepines

Interaction studies of nefazodone with two triazolobenzodiazepines, i.e., triazolam and alprazolam, metabolized by cytochrome P450 3A4, have revealed substantial and clinically important increases in plasma concentrations of these compounds when administered concomitantly with nefazodone.

##### Triazolam

When a single oral 0.25-mg dose of triazolam was coadministered with nefazodone (200 mg BID) at steady state, triazolam half-life and AUC increased 4-fold and peak concentrations increased 1.7-fold. Nefazodone plasma concentrations were unaffected by triazolam. **Coadministration of nefazodone potentiated the effects of triazolam on psychomotor performance tests.** If triazolam is coadministered with SERZONE, a 75% reduction in the initial triazolam dosage is recommended. Because not all commercially available dosage forms of triazolam permit sufficient dosage reduction, coadministration of triazolam with SERZONE should be avoided for most patients, including the elderly. In the exceptional case where coadministration of triazolam with SERZONE may be considered appropriate, only the lowest possible dose of triazolam should be used (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

##### Alprazolam

When alprazolam (1 mg BID) and nefazodone (200 mg BID) were coadministered, steady-state peak concentrations, AUC and half-life values for alprazolam increased by approximately 2-fold. Nefazodone plasma concentrations were unaffected by alprazolam. If alprazolam is coadministered with SERZONE, a 50% reduction in the initial alprazolam dosage is recommended. No dosage adjustment is required for SERZONE (nefazodone hydrochloride).

##### Potential Terfenadine, Astemizole, Cisapride, and Pimozide Interactions

Terfenadine, astemizole, cisapride, and pimozide are all metabolized by the cytochrome P450 3A4 (CYP3A4) isozyme, and it has been demonstrated that ketoconazole, erythromycin, and other inhibitors of CYP3A4 can block the metabolism of these drugs, which can result in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, cisapride, and pimozide are associated with QT prolongation and with rare cases of serious cardiovascular adverse events, including death, due principally to ventricular tachycardia of the torsades de pointes type. Nefazodone has been shown *in vitro* to be an inhibitor of CYP3A4. Consequently, it is recommended that nefazodone not be used in combination with either terfenadine, astemizole, cisapride, or pimozide (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

##### Interaction with Carbamazepine

The coadministration of carbamazepine 200 mg BID with nefazodone 200 mg BID, at steady state for both drugs, resulted in almost 95% reductions in AUCs for nefazodone and hydroxynefazodone, likely resulting in insufficient plasma nefazodone and hydroxynefazodone concentrations for achieving an

antidepressant effect for SERZONE. Consequently, it is recommended that SERZONE not be used in combination with carbamazepine (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

#### PRECAUTIONS

##### General

##### Hepatotoxicity (See **BOXED WARNING**.)

##### Postural Hypotension

A pooled analysis of the vital signs monitored during placebo-controlled premarketing studies revealed that 5.1% of nefazodone patients compared to 2.5% of placebo patients ( $p < 0.01$ ) met criteria for a potentially important decrease in blood pressure at some time during treatment (systolic blood pressure  $\leq 90$  mmHg and a change from baseline of  $\geq 20$  mmHg). While there was no difference in the proportion of nefazodone and placebo patients having adverse events characterized as 'syncope' (nefazodone, 0.2%; placebo, 0.3%), the rates for adverse events characterized as 'postural hypotension' were as follows: nefazodone (2.8%), tricyclic antidepressants (10.9%), SSRI (1.1%), and placebo (0.8%). Thus, the prescriber should be aware that there is some risk of postural hypotension in association with nefazodone use. SERZONE (nefazodone hydrochloride) should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

##### Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in 0.3% of nefazodone-treated unipolar patients, compared to 0.3% of tricyclic- and 0.4% of placebo-treated patients. In patients classified as bipolar the rate of manic episodes was 1.6% for nefazodone, 5.1% for the combined tricyclic-treated groups, and 0% for placebo-treated patients. Activation of mania/hypomania is a known risk in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, SERZONE should be used cautiously in patients with a history of mania.

##### Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for SERZONE should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

##### Seizures

During premarketing testing, a recurrence of a petit mal seizure was observed in a patient receiving nefazodone who had a history of such seizures. In addition, one nonstudy participant reportedly experienced a convulsion (type not documented) following a multiple-drug overdose (see **OVERDOSAGE**). Rare occurrences of convulsions (including grand mal seizures) following nefazodone administration have been reported since market introduction. A causal relationship to nefazodone has not been established (see **ADVERSE REACTIONS**).

##### Priapism

While priapism did not occur during premarketing experience with nefazodone, rare reports of priapism have been received since market introduction. A causal relationship to nefazodone has not been established (see **ADVERSE REACTIONS**). If patients present with prolonged or inappropriate erections, they should discontinue therapy immediately and consult their physicians. If the condition persists for more than 24 hours, a urologist should be consulted to determine appropriate management.

##### Use in Patients with Concomitant Illness

SERZONE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. Evaluation of electrocardiograms of 1153 patients who received nefazodone in 6- to 8-week, double-blind, placebo-controlled trials did not indicate that nefazodone is associated with the development of clinically important ECG abnormalities. However, sinus bradycardia, defined as heart rate  $\leq 50$  bpm and a decrease of at least 15 bpm from baseline, was observed in 1.5% of nefazodone-treated patients compared to 0.4% of placebo-treated patients ( $p < 0.05$ ). Because patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical trials, such patients should be treated with caution.

In patients with cirrhosis of the liver, the AUC values of nefazodone and HO-NEF were increased by approximately 25%.

##### Information for Patients (See **Patient Information**.)

Physicians are advised to discuss the following issues with patients for whom they prescribe SERZONE:

##### Hepatotoxicity

Patients should be informed that SERZONE therapy has been associated with liver abnormalities ranging from asymptomatic reversible serum transaminase increases to cases of liver failure resulting in transplant and/or death. At present, there is no way to predict who is likely to develop liver failure. Ordinarily, patients with active liver disease should not be treated with SERZONE. Patients should be advised to be alert for signs of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

##### Time to Response/Continuation

As with all antidepressants, several weeks on treatment may be required to obtain the full antidepressant effect. Once improvement is noted, it is important for patients to continue drug treatment as directed by their physician.

##### Interference With Cognitive and Motor Performance

Since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SERZONE therapy does not adversely affect their ability to engage in such activities.

##### Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

##### Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant (see **PRECAUTIONS: Nursing Mothers**).

##### Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Significant caution is indicated if SERZONE is to be used in combination with XANAX<sup>®</sup>, concomitant use with HALCION<sup>®</sup> should be avoided for most patients including the elderly, and concomitant use with SELDANE<sup>®</sup>, HISMANAL<sup>®</sup>, PROPULSID<sup>®</sup>, ORAP<sup>®</sup>, or TEGRETOL<sup>®</sup> is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS**).

##### Alcohol

Patients should be advised to avoid alcohol while taking SERZONE (nefazodone hydrochloride).

##### Allergic Reactions

Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

##### Visual Disturbances

There have been reports of visual disturbances associated with the use of nefazodone, including blurred vision, scotoma, and visual trails. Patients should be advised to notify their physician if they develop visual disturbances. (See **ADVERSE REACTIONS**.)

## Laboratory Tests

There are no specific laboratory tests recommended.

## Drug Interactions

### Drugs Highly Bound to Plasma Protein

Because nefazodone is highly bound to plasma protein (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**), administration of SERZONE (nefazodone hydrochloride) to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of nefazodone by other highly bound drugs.

**Warfarin**—There were no effects on the prothrombin or bleeding times or upon the pharmacokinetics of R-warfarin when nefazodone (200 mg BID) was administered for 1 week to subjects who had been pretreated for 2 weeks with warfarin. Although the coadministration of nefazodone did decrease the subjects' exposure to S-warfarin by 12%, the lack of effects on the prothrombin and bleeding times indicates this modest change is not clinically significant. Although these results suggest no adjustments in warfarin dosage are required when nefazodone is administered to patients stabilized on warfarin, such patients should be monitored as required by standard medical practices.

### CNS-Active Drugs

**Monoamine Oxidase Inhibitors**—See **WARNINGS**.

**Haloperidol**—When a single oral 5-mg dose of haloperidol was coadministered with nefazodone (200 mg BID) at steady state, haloperidol apparent clearance decreased by 35% with no significant increase in peak haloperidol plasma concentrations or time of peak. This change is of unknown clinical significance. Pharmacodynamic effects of haloperidol were generally not altered significantly. There were no changes in the pharmacokinetic parameters for nefazodone. Dosage adjustment of haloperidol may be necessary when coadministered with nefazodone.

**Lorazepam**—When lorazepam (2 mg BID) and nefazodone (200 mg BID) were coadministered to steady state, there was no change in any pharmacokinetic parameter for either drug compared to each drug administered alone. Therefore, dosage adjustment is not necessary for either drug when coadministered.

**Triazolam/Alprazolam**—See **CONTRAINDICATIONS** and **WARNINGS**.

**Alcohol**—Although nefazodone did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of SERZONE and alcohol in depressed patients is not advised.

**Bupropion**—In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of bupropion (2.5 or 5 mg BID) with nefazodone (250 mg BID) resulted in marked increases in plasma bupropion concentrations (increases up to 20-fold in  $C_{max}$  and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of the bupropion metabolite 1-pyrimidinylpiperazine. With 5 mg BID doses of bupropion, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (17%) and mCPP (9%). Subjects receiving nefazodone 250 mg b.i.d. and bupropion 5 mg b.i.d. experienced lightheadedness, asthenia, dizziness, and somnolence, adverse events also observed with either drug alone. If the two drugs are to be used in combination, a low dose of bupropion (eg, 2.5 mg q.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

**Pimozide**—See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS: Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Potential Interaction with Drugs that Inhibit and/or Are Metabolized by Cytochrome P450 Isozymes**.

**Fluoxetine**—When fluoxetine (20 mg QD) and nefazodone (200 mg BID) were administered at steady state there were no changes in the pharmacokinetic parameters for fluoxetine or its metabolite, norfluoxetine. Similarly, there were no changes in the pharmacokinetic parameters of nefazodone or HO-NEF; however, the mean AUC levels of the nefazodone metabolites mCPP and triazole-dione increased by 3- to 6-fold and 1.3-fold, respectively. When a 200-mg dose of nefazodone was administered to subjects who had been receiving fluoxetine for 1 week, there was an increased incidence of transient adverse events such as headache, lightheadedness, nausea, or paresthesia, possibly due to the elevated mCPP levels. Patients who are switched from fluoxetine to nefazodone without an adequate washout period may experience similar transient adverse events. The possibility of this happening can be minimized by allowing a washout period before initiating nefazodone therapy and by reducing the initial dose of nefazodone. Because of the long half-life of fluoxetine and its metabolites, this washout period may range from one to several weeks depending on the dose of fluoxetine and other individual patient variables.

**Phenytin**—Pretreatment for 7 days with 200 mg BID of nefazodone had no effect on the pharmacokinetics of a single 300-mg oral dose of phenytin. However, due to the nonlinear pharmacokinetics of phenytin, the failure to observe a significant effect on the single-dose pharmacokinetics of phenytin does not preclude the possibility of a clinically significant interaction with nefazodone when phenytin is dosed chronically. However, no change in the initial dosage of phenytin is considered necessary and any subsequent adjustment of phenytin dosage should be guided by usual clinical practices.

**Desipramine**—When nefazodone (150 mg BID) and desipramine (75 mg QD) were administered together there were no changes in the pharmacokinetics of desipramine or its metabolite, 2-hydroxydesipramine. There were also no changes in the pharmacokinetics of nefazodone or its triazole-dione metabolite, but the AUC and  $C_{max}$  of mCPP increased by 44% and 48%, respectively, while the AUC of HO-NEF decreased by 19%. No changes in doses of either nefazodone or desipramine are necessary when the two drugs are given concomitantly. Subsequent dose adjustments should be made on the basis of clinical response.

**Lithium**—In 13 healthy subjects the coadministration of nefazodone (200 mg BID) with lithium (500 mg BID) for 5 days (steady-state conditions) was found to be well tolerated. When the two drugs were coadministered, there were no changes in the steady-state pharmacokinetics of either lithium, nefazodone, or its metabolite HO-NEF; however, there were small decreases in the steady-state plasma concentrations of two nefazodone metabolites, mCPP and triazole-dione, which are considered not to be of clinical significance. Therefore, no dosage adjustment of either lithium or nefazodone is required when they are coadministered.

**Carbamazepine**—The coadministration of nefazodone (200 mg BID) for 5 days to 12 healthy subjects on carbamazepine who had achieved steady state (200 mg BID) was found to be well tolerated. Steady-state conditions for carbamazepine, nefazodone, and several of their metabolites were achieved by day 5 of coadministration. With coadministration of the two drugs there were significant increases in the steady-state  $C_{max}$  and AUC of carbamazepine (23% and 23%, respectively), while the steady-state  $C_{max}$  and the AUC of the carbamazepine metabolite, 10,11-epoxycarbamazepine, decreased by 21% and 20%, respectively. The coadministration of the two drugs significantly reduced the steady-state  $C_{max}$  and AUC of nefazodone by 86% and 93%, respectively. Similar reductions in the  $C_{max}$  and AUC of HO-NEF were also observed (85% and 94%), while the reductions in  $C_{max}$  and AUC of mCPP and triazole-dione were more modest (13% and 44% for the former and 28% and 57% for the latter). Due to the potential for coadministration of carbamazepine to result in insufficient plasma nefazodone and hydroxynefazodone concentrations for achieving an antidepressant effect for SERZONE, it is recommended that SERZONE not be used in combination with carbamazepine (see **CONTRAINDICATIONS** and **WARNINGS**).

**General Anesthetics**—Little is known about the potential for interaction between nefazodone and general anesthetics; therefore, prior to elective surgery, SERZONE should be discontinued for as long as clinically feasible.

**Other CNS-Active Drugs**—The use of nefazodone in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if concomitant administration of SERZONE and such drugs is required.

## Cimetidine

When nefazodone (200 mg BID) and cimetidine (300 mg QID) were coadministered for one week, no change in the steady-state pharmacokinetics of either nefazodone or cimetidine was observed compared to each dosed alone. Therefore, dosage adjustment is not necessary for either drug when coadministered.

## Theophylline

When nefazodone (200 mg BID) was given to patients being treated with theophylline (600-1200 mg/day) for chronic obstructive pulmonary disease, there was no change in the steady-state pharmacokinetics of either nefazodone or theophylline. FEV<sub>1</sub> measurements taken when theophylline and nefazodone were coadministered did not differ from baseline dosage (i.e., when theophylline was administered alone). Therefore, dosage adjustment is not necessary for either drug when coadministered.

## Cardiovascular-Active Drugs

**Digoxin**—When nefazodone (200 mg BID) and digoxin (0.2 mg QD) were coadministered for 9 days to healthy male volunteers (n=18) who were phenotyped as CYP2D6 extensive metabolizers,  $C_{max}$ ,  $C_{min}$ , and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Digoxin had no effects on the pharmacokinetics of nefazodone and its active metabolites. Because of the narrow therapeutic index of digoxin, caution should be exercised when nefazodone and digoxin are coadministered; plasma level monitoring for digoxin is recommended.

**Propranolol**—The coadministration of nefazodone (200 mg BID) and propranolol (40 mg BID) for 5 days to healthy male volunteers (n=18), including 3 poor and 15 extensive CYP2D6 metabolizers, resulted in 30% and 14% reductions in  $C_{max}$  and AUC of propranolol, respectively, and a 14% reduction in  $C_{max}$  for the metabolite, 4-hydroxypropranolol. The kinetics of nefazodone, hydroxynefazodone, and triazole-dione were not affected by coadministration of propranolol. However,  $C_{max}$ ,  $C_{min}$ , and AUC of m-chlorophenylpiperazine were increased by 23%, 54%, and 28%, respectively. No change in initial dose of either drug is necessary and dose adjustments should be made on the basis of clinical response.

**HMG-CoA Reductase Inhibitors**—When single 40-mg doses of simvastatin or atorvastatin, both substrates of CYP3A4, were given to healthy adult volunteers who had received SERZONE 200 mg BID for 6 days, approximately 20-fold increases in plasma concentrations of simvastatin and simvastatin acid and 3- to 4-fold increases in plasma concentrations of atorvastatin and atorvastatin lactone were seen. These effects appear to be due to the inhibition of CYP3A4 by SERZONE (nefazodone hydrochloride) because, in the same study, SERZONE had no significant effect on the plasma concentrations of pravastatin, which is not metabolized by CYP3A4 to a clinically significant extent.

There have been rare reports of rhabdomyolysis involving patients receiving the combination of SERZONE and either simvastatin or lovastatin, also a substrate of CYP3A4 (see **ADVERSE REACTIONS: Postintroduction Clinical Experience**). Rhabdomyolysis has been observed in patients receiving HMG-CoA reductase inhibitors administered alone (at recommended dosages) and in particular, for certain drugs in this class, when given in combination with inhibitors of the CYP3A4 isozyme.

Caution should be used if SERZONE is administered in combination with HMG-CoA reductase inhibitors that are metabolized by CYP3A4, such as simvastatin, atorvastatin, and lovastatin, and dosage adjustments of these HMG-CoA reductase inhibitors are recommended. Since metabolic interactions are unlikely between SERZONE and HMG-CoA reductase inhibitors that undergo little or no metabolism by the CYP3A4 isozyme, such as pravastatin or fluvastatin, dosage adjustments should not be necessary.

## Immunosuppressive Agents

There have been reports of increased blood concentrations of cyclosporine and tacrolimus into toxic ranges when patients received these drugs concomitantly with SERZONE. Both cyclosporine and tacrolimus are substrates of CYP3A4, and nefazodone is known to inhibit this enzyme. If either cyclosporine or tacrolimus is administered with SERZONE, blood concentrations of the immunosuppressive agent should be monitored and dosage adjusted accordingly.

**Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Potential Interaction with Drugs that Inhibit and/or Are Metabolized by Cytochrome P450 Isozymes**

**CYP3A4 Isozyme**—Nefazodone has been shown *in vitro* to be an inhibitor of CYP3A4. This is consistent with the interactions observed between nefazodone and triazolam, alprazolam, bupropion, atorvastatin, and simvastatin, drugs metabolized by this isozyme. Consequently, caution is indicated in the combined use of nefazodone with any drugs known to be metabolized by CYP3A4. In particular, the combined use of nefazodone with triazolam should be avoided for most patients, including the elderly. The combined use of nefazodone with terfenadine, astemizole, cisapride, or pimozide is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS**).

**CYP2D6 Isozyme**—A subset (3% to 10%) of the population has reduced activity of the drug-metabolizing enzyme CYP2D6. Such individuals are referred to commonly as "poor metabolizers" of drugs such as desibrucosin, dextromethorphan, and the tricyclic antidepressants. The pharmacokinetics of nefazodone and its major metabolites are not altered in these "poor metabolizers." Plasma concentrations of one minor metabolite (mCPP) are increased in this population; the adjustment of SERZONE dosage is not required when administered to "poor metabolizers." Nefazodone and its metabolites have been shown *in vitro* to be extremely weak inhibitors of CYP2D6. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme.

**CYP1A2 Isozyme**—Nefazodone and its metabolites have been shown *in vitro* not to inhibit CYP1A2. Thus, metabolic interactions between nefazodone and drugs metabolized by this isozyme are unlikely.

## Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and nefazodone.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

### Carcinogenesis

There is no evidence of carcinogenicity with nefazodone. The dietary administration of nefazodone to rats and mice for 2 years at daily doses of up to 200 mg/kg and 800 mg/kg, respectively, which are approximately 3 and 6 times, respectively, the maximum human daily dose on a mg/m<sup>2</sup> basis, produced no increase in tumors.

### Mutagenesis

Nefazodone has been shown to have no genotoxic effects based on the following assays: bacterial mutation assays, a DNA repair assay in cultured rat hepatocytes, a mammalian mutation assay in Chinese hamster ovary cells, an *in vivo* cytogenetics assay in rat bone marrow cells, and a rat dominant lethal study.

### Impairment of Fertility

A fertility study in rats showed a slight decrease in fertility at 200 mg/kg/day (approximately three times the maximum human daily dose on a mg/m<sup>2</sup> basis) but not at 100 mg/kg/day (approximately 1.5 times the maximum human daily dose on a mg/m<sup>2</sup> basis).

### Pregnancy

#### Teratogenic Effects—Pregnancy Category C

Reproduction studies have been performed in pregnant rabbits and rats at daily doses up to 200 and 300 mg/kg, respectively (approximately 6 and 5 times, respectively, the maximum human daily dose on a mg/m<sup>2</sup> basis). No malformations were observed in the offspring as a result of nefazodone treatment. However, increased early pup mortality was seen in rats at a dose approximately five times the maximum human dose, and decreased pup weights were seen at this and lower doses, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. The no-effect dose for rat pup mortality was 1.3 times the human dose on a mg/m<sup>2</sup> basis. There are no adequate and well-controlled studies in pregnant women. Nefazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Labor and Delivery

The effect of SERZONE on labor and delivery in humans is unknown.

### Nursing Mothers

It is not known whether SERZONE or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERZONE is administered to a nursing woman.

### Pediatric Use

Safety and effectiveness in individuals below 18 years of age have not been established.

### Geriatric Use

Of the approximately 7000 patients in clinical studies who received SERZONE for the treatment of depression, 18% were 65 years and older, while 5% were 75 years and older. Based on monitoring of adverse events, vital signs, electrocardiograms, and results of laboratory tests, no overall differences in safety between elderly and younger patients were observed in clinical studies. Efficacy in the elderly has not been demonstrated in placebo-controlled trials. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Due to the increased systemic exposure to nefazodone seen in single-dose studies in elderly patients (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**), treatment should be initiated at half the usual dose, but titration upward should take place over the same range as in younger patients (see **DOSE AND ADMINISTRATION**). The usual precautions should be observed in elderly patients who have concomitant medical illnesses or who are receiving concomitant drugs.

### ADVERSE REACTIONS

#### Associated with Discontinuation of Treatment

Approximately 16% of the 3496 patients who received SERZONE (nefazodone hydrochloride) in worldwide premarketing clinical trials discontinued treatment due to an adverse experience. The more common ( $\geq 1\%$ ) events in clinical trials associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for SERZONE compared to placebo) included: nausea (3.5%), dizziness (1.9%), insomnia (1.5%), asthenia (1.3%), and agitation (1.2%).

#### Incidence in Controlled Trials

##### Commonly Observed Adverse Events in Controlled Clinical Trials

The most commonly observed adverse events associated with the use of SERZONE (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., significantly higher incidence for SERZONE compared to placebo,  $p \leq 0.05$ ), derived from the table below, were: somnolence, dry mouth, nausea, dizziness, constipation, asthenia, lightheadedness, blurred vision, confusion, and abnormal vision.

##### Adverse Events Occurring at an Incidence of 1% or More Among SERZONE-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among SERZONE-treated patients who participated in short-term (6- to 8-week) placebo-controlled trials in which patients were dosed with SERZONE to ranges of 300 to 600 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Placebo-Controlled Clinical Trials<sup>1</sup>, SERZONE 300 to 600 mg/day Dose Range

Body System	Preferred Term	Percent of Patients	
		SERZONE (n=393)	Placebo (n=394)
Body as a Whole	Headache	36	33
	Asthenia	11	5
	Infection	8	6
	Flu syndrome	3	2
	Chills	2	1
	Fever	2	1
Cardiovascular	Neck rigidity	1	0
	Postural hypotension	4	1
	Hypotension	2	1
Dermatological	Pruritus	2	1
	Rash	2	1
Gastrointestinal	Dry mouth	25	13
	Nausea	22	12
	Constipation	14	8
	Dyspepsia	9	7
	Diarrhea	8	7
	Increased appetite	5	3
Metabolic	Nausea & vomiting	2	1
	Peripheral edema	3	2
	Thirst	1	<1
Musculoskeletal	Arthralgia	1	<1
Nervous	Somnolence	25	14
	Dizziness	17	5
	Insomnia	11	9
	Lightheadedness	10	3
	Confusion	7	2
	Memory impairment	4	2
	Paresthesia	4	2
	Vasodilatation <sup>2</sup>	4	2
	Abnormal dreams	3	2
	Concentration decreased	3	1
	Ataxia	2	0
	Incoordination	2	1

Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Placebo-Controlled Clinical Trials<sup>1</sup>, SERZONE 300 to 600 mg/day Dose Range (continued)

Body System	Preferred Term	Percent of Patients	
		SERZONE (n=393)	Placebo (n=394)
<i>Continued</i>			
	Psychomotor retardation	2	1
	Tremor	2	1
	Hypertonia	1	0
	Libido decreased	1	<1
Respiratory	Pharyngitis	6	5
	Cough increased	3	1
Special Senses	Blurred vision	9	3
	Abnormal vision <sup>3</sup>	7	1
	Tinnitus	2	1
	Taste perversion	2	1
Urogenital	Visual field defect	2	0
	Urinary frequency	2	1
	Urinary tract infection	2	1
	Urinary retention	2	1
	Vaginitis <sup>4</sup>	2	1
	Breast pain <sup>4</sup>	1	<1

<sup>1</sup> Events reported by at least 1% of patients treated with SERZONE and more frequent than the placebo group are included; incidence is rounded to the nearest 1% (<1% indicates an incidence less than 0.5%). Events for which the SERZONE (nefazodone hydrochloride) incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, accidental injury, chest pain, neck pain, palpitation, migraine, sweating, flatulence, vomiting, anorexia, tooth disorder, weight gain, edema, myalgia, cramp, agitation, anxiety, depression, hypesthesia, CNS stimulation, dysphoria, emotional lability, sinusitis, rhinitis, dysmenorrhea<sup>4</sup>, dysuria.

<sup>2</sup> Vasodilatation—flushing, feeling warm.

<sup>3</sup> Abnormal vision—scotoma, visual trails.

<sup>4</sup> Incidence adjusted for gender.

#### Dose Dependency of Adverse Events

The table that follows enumerates adverse events that were more frequent in the SERZONE dose range of 300 to 600 mg/day than in the SERZONE dose range of up to 300 mg/day. This table shows only those adverse events for which there was a statistically significant difference ( $p \leq 0.05$ ) in incidence between the SERZONE dose ranges as well as a difference between the high dose range and placebo.

Dose Dependency of Adverse Events in Placebo-Controlled Trials<sup>1</sup>

Body System	Preferred Term	Percent of Patients		
		SERZONE 300-600 mg/day (n=209)	SERZONE $\leq 300$ mg/day (n=211)	Placebo (n=212)
Gastrointestinal	Nausea	23	14	12
	Constipation	17	10	9
Nervous	Somnolence	28	16	13
	Dizziness	22	11	4
Special Senses	Confusion	8	2	1
	Abnormal vision	10	0	2
	Blurred vision	9	3	2
	Tinnitus	3	0	1

<sup>1</sup> Events for which there was a statistically significant difference ( $p \leq 0.05$ ) between the nefazodone dose groups.

#### Visual Disturbances

In controlled clinical trials, blurred vision occurred in 9% of nefazodone-treated patients compared to 3% of placebo-treated patients. In these same trials abnormal vision, including scotomata and visual trails, occurred in 7% of nefazodone-treated patients compared to 1% of placebo-treated (see Treatment-Emergent Adverse Experience table, above). Dose-dependency was observed for these events in these trials, with none of the scotomata and visual trails at doses below 300 mg/day. However, scotomata and visual trails observed at doses below 300 mg/day have been reported in post-marketing experience with SERZONE. (See **PRECAUTIONS: Information for Patients**.)

#### Vital Sign Changes

(See **PRECAUTIONS, Postural Hypotension**.)

#### Weight Changes

In a pooled analysis of placebo-controlled premarketing studies, there were no differences between nefazodone and placebo groups in the proportions of patients meeting criteria for potentially important increases or decreases in body weight (a change of  $\geq 7\%$ ).

#### Laboratory Changes

Of the serum chemistry, serum hematology, and urinalysis parameters monitored during placebo-controlled premarketing studies with nefazodone, a pooled analysis revealed a statistical trend between nefazodone and placebo for hematocrit, i.e., 2.8% of nefazodone patients met criteria for a potentially important decrease in hematocrit ( $\leq 37\%$  male or  $\leq 32\%$  female) compared to 1.5% of placebo patients ( $0.05 < p < 0.10$ ). Decreases in hematocrit, presumably dilutional, have been reported with many other drugs that block  $\alpha_1$ -adrenergic receptors. There was no apparent clinical significance of the observed changes in the few patients meeting these criteria.

#### ECG Changes

Of the ECG parameters monitored during placebo-controlled premarketing studies with nefazodone, a pooled analysis revealed a statistically significant difference between nefazodone and placebo for sinus bradycardia, i.e., 1.5% of nefazodone patients met criteria for a potentially important decrease in heart rate ( $\leq 50$  bpm and a decrease of  $\geq 15$  bpm) compared to 0.4% of placebo patients ( $p < 0.05$ ). There was no obvious clinical significance of the observed changes in the few patients meeting these criteria.

#### Other Events Observed During the Premarketing Evaluation of SERZONE

During its premarketing assessment, multiple doses of SERZONE were administered to 3496 patients in clinical studies, including more than 250 patients treated for at least one year. The conditions and duration of exposure to SERZONE varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 3496 patients exposed to multiple doses of SERZONE who experienced an event of the type cited on at least one occasion while receiving SERZONE. All reported events are included except those already listed in the Treatment-Emergent Adverse Experience Incidence table, those events listed in other safety-related sections of this insert, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events for which a drug cause was very remote, and those events which were not serious and occurred in fewer than two patients.

It is important to emphasize that, although the events reported occurred during treatment with SERZONE (nefazodone hydrochloride), they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

**Body as a whole**—*Infrequent:* allergic reaction, malaise, photosensitivity reaction, face edema, hang-over effect, abdomen enlarged, hernia, pelvic pain, and halitosis. *Rare:* cellulitis.

**Cardiovascular system**—*Infrequent:* tachycardia, hypertension, syncope, ventricular extrasystoles, and angina pectoris. *Rare:* AV block, congestive heart failure, hemorrhage, pallor, and varicose vein.

**Dermatological system**—*Infrequent:* dry skin, acne, alopecia, urticaria, maculopapular rash, vesiculobullous rash, and eczema.

**Gastrointestinal system**—*Frequent:* gastroenteritis. *Infrequent:* eructation, periodontal abscess, abnormal liver function tests, gingivitis, colitis, gastritis, mouth ulceration, stomatitis, esophagitis, peptic ulcer, and rectal hemorrhage. *Rare:* glossitis, hepatitis, dysphagia, gastrointestinal hemorrhage, oral moniliasis, and ulcerative colitis.

**Hemic and lymphatic system**—*Infrequent:* ecchymosis, anemia, leukopenia, and lymphadenopathy.

**Metabolic and nutritional system**—*Infrequent:* weight loss, gout, dehydration, lactic dehydrogenase increased, SGOT increased, and SGPT increased. *Rare:* hypercholesterolemia and hypoglycemia.

**Musculoskeletal system**—*Infrequent:* arthritis, tenosynovitis, muscle stiffness, and bursitis. *Rare:* tendinous contracture.

**Nervous system**—*Infrequent:* vertigo, twitching, depersonalization, hallucinations, suicide attempt, apathy, euphoria, hostility, suicidal thoughts, abnormal gait, thinking abnormal, attention decreased, derealization, neuralgia, paranoid reaction, dysarthria, increased libido, suicide, and myoclonus. *Rare:* hyperkinesia, increased salivation, cerebrovascular accident, hyperesthesia, hypotonia, ptosis, and neuroleptic malignant syndrome.

**Respiratory system**—*Frequent:* dyspnea and bronchitis. *Infrequent:* asthma, pneumonia, laryngitis, voice alteration, epistaxis, hiccup. *Rare:* hyperventilation and yawn.

**Special senses**—*Frequent:* eye pain. *Infrequent:* dry eye, ear pain, abnormality of accommodation, diplopia, conjunctivitis, mydriasis, keratoconjunctivitis, hyperacusis, and photophobia. *Rare:* deafness, glaucoma, night blindness, and taste loss.

**Urogenital system**—*Frequent:* impotence. *Infrequent:* cystitis, urinary urgency, metrorrhagia, amenorrhea, polyuria, vaginal hemorrhage, breast enlargement, menorrhagia, urinary incontinence, abnormal ejaculation, hematuria, nocturia, and kidney calculus. *Rare:* uterine fibroids enlarged, uterine hemorrhage, anorgasmia, and oliguria.

\*Adjusted for gender.

#### Postintroduction Clinical Experience

Postmarketing experience with SERZONE has shown an adverse experience profile similar to that seen during the premarketing evaluation of nefazodone. Voluntary reports of adverse events temporally associated with SERZONE have been received since market introduction that are not listed above and for which a causal relationship has not been established. These include:

Anaphylactic reactions; angioedema; convulsions (including grand mal seizures); galactorrhea; gynecomastia (male); hyponatremia; liver necrosis and liver failure, in some cases leading to liver transplantation and/or death (see **WARNINGS**); priapism (see **PRECAUTIONS**); prolactin increased; rhabdomyolysis involving patients receiving the combination of SERZONE and lovastatin or simvastatin (see **PRECAUTIONS**); serotonin syndrome; and Stevens-Johnson syndrome; and thrombocytopenia.

#### DRUG ABUSE AND DEPENDENCE

##### Controlled Substance Class

SERZONE is not a controlled substance.

##### Physical and Psychological Dependence

In animal studies, nefazodone did not act as a reinforcer for intravenous self-administration in monkeys trained to self-administer cocaine, suggesting no abuse liability. In a controlled study of abuse liability in human subjects, nefazodone showed no potential for abuse.

Nefazodone has not been systematically studied in humans for its potential for tolerance, physical dependence, or withdrawal. While the premarketing clinical experience with nefazodone did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SERZONE (e.g., development of tolerance, dose escalation, drug-seeking behavior).

#### OVERDOSAGE

##### Human Experience

In premarketing clinical studies, there were seven reports of nefazodone overdose alone or in combination with other pharmacological agents. The amount of nefazodone ingested ranged from 1000 mg to 11,200 mg. Commonly reported symptoms from overdose of nefazodone included nausea, vomiting, and somnolence. One nonstudy participant took 2000–3000 mg of nefazodone with methocarbamol and alcohol; this person reportedly experienced a convulsion (type not documented). None of these patients died.

In postmarketing experience, overdose with SERZONE alone and in combination with alcohol and/or other substances has been reported. Commonly reported symptoms were similar to those reported from overdose in premarketing experience. While there have been rare reports of fatalities in patients taking overdoses of nefazodone, predominantly in combination with alcohol and/or other substances, no causal relationship to nefazodone has been established.

##### Overdosage Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the wide distribution of nefazodone in body tissues, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for nefazodone are known.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

#### DOSAGE AND ADMINISTRATION

##### Initial Treatment

The recommended starting dose for SERZONE (nefazodone hydrochloride) is 200 mg/day, administered in two divided doses (BID). In the controlled clinical trials establishing the antidepressant efficacy of SERZONE, the effective dose range was generally 300 to 600 mg/day. Consequently, most patients, depending on tolerability and the need for further clinical effect, should have their dose increased. Dose increases should occur in increments of 100 mg/day to 200 mg/day, again on a BID schedule, at intervals of no less than 1 week. As with all antidepressants, several weeks on treatment may be required to obtain a full antidepressant response.

##### Dosage for Elderly or Debilitated Patients

The recommended initial dose for elderly or debilitated patients is 100 mg/day, administered in two divided doses (BID). These patients often have reduced nefazodone clearance and/or increased sensitivity to the side effects of CNS-active drugs. It may also be appropriate to modify the rate of subsequent dose titration. As steady-state plasma levels do not change with age, the final target dose based on a careful assessment of the patient's clinical response may be similar in healthy younger and older patients.

##### Maintenance/Continuation/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with SERZONE. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to 6 months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown. Systematic evaluation of the efficacy of SERZONE has shown that efficacy is maintained for periods of up to 36 weeks following 16 weeks of open-label acute treatment (treated for 52 weeks total) at dosages that averaged 438 mg/day. For most patients, their maintenance dose was that associated with response during acute treatment. (See **CLINICAL PHARMACOLOGY**.) The safety of SERZONE in long-term use is supported by data from both double-blind and open-label trials involving more than 250 patients treated for at least one year.

##### 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 SERZONE. In addition, at least 7 days should be allowed after stopping SERZONE before starting an MAOI.

##### HOW SUPPLIED

SERZONE® tablets are hexagonal tablets imprinted with BMS and the strength (i.e., 100 mg) on one side and the identification code number on the other. The 100 mg and 150 mg tablets are bisect scored on both tablet faces. The 50 mg, 200 mg, and 250 mg tablets are unscored.

NDC CODE	DESCRIPTION
NDC 0087-0031-47	50 mg light pink tablet, bottle of 60
NDC 0087-0032-31	100 mg white tablet, bottle of 60
NDC 0087-0039-31	150 mg peach tablet, bottle of 60
NDC 0087-0033-31	200 mg light yellow tablet, bottle of 60
NDC 0087-0041-31	250 mg white tablet, bottle of 60

U.S. Patent Nos. 4,338,317 and 6,008,222

Store at room temperature, below 40° C (104° F) and dispense in a tight container.

##### REFERENCES

1. HALCION® and XANAX® are registered trademarks of Pharmacia & Upjohn.
2. SELDANE® is a registered trademark of Hoechst Marion Roussel, Inc. (now Aventis Pharmaceuticals).
3. HISMANAL® and PROPULSID® are registered trademarks of Janssen Pharmaceutica Products, L.P.
4. ORAP® is a registered trademark of Gate Pharmaceuticals, a division of Teva Pharmaceuticals USA.
5. TEGRETOL® is a registered trademark of Novartis Pharmaceuticals Corporation.

Rx only

## PATIENT INFORMATION

### SERZONE®

(nefazodone hydrochloride) Tablets

Read this information completely before using SERZONE. Read the information each time you get more medicine. There may be new information. This leaflet provides a summary about SERZONE and does not include everything there is to know about your medicine. This information is not meant to take the place of talking with your doctor.

Before taking this medication, be sure to check the tablets in the bottle to make sure they match one of the following descriptions:

- 50 mg tablets are six-sided, light pink tablets imprinted with "BMS" and "50" on one face of the tablet;
- 100 mg tablets are six-sided, white tablets imprinted with "BMS" and "100" on one face of the tablet;
- 150 mg tablets are six-sided, peach-colored tablets imprinted with "BMS" and "150" on one face of the tablet;
- 200 mg tablets are six-sided, light yellow tablets imprinted with "BMS" and "200" on one face of the tablet; and
- 250 mg tablets are six-sided, white tablets imprinted with "BMS" and "250" on one face of the tablet.

#### What is the most important information that I should know about SERZONE?

Rarely, people who take SERZONE can develop serious liver problems. If you get any of the following symptoms while taking SERZONE, call your doctor right away because you may be developing a liver problem:

- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Nausea
- Abdominal (lower stomach) pain

People who currently have liver problems should not take SERZONE.

#### What is SERZONE?

SERZONE (pronounced sir-ZONE) is a medicine used to treat depression. SERZONE is thought to treat depression by correcting an imbalance in the amounts of certain natural chemicals, such as serotonin and norepinephrine, which are in your brain.

#### Who should not take SERZONE?

Do *not* take SERZONE if you

- are allergic to SERZONE or the related medicine Desyrel® (trazodone).
- are taking Seldane® (terfenadine), an antihistamine; Hismanal® (astemizole), an antihistamine; Propulsid® (cisapride), used for heartburn; Halcion® (triazolam), used for insomnia; Orap® (pimozide), used to treat Tourette's syndrome; or Tegretol® (carbamazepine), used to control seizures.
- currently have liver problems.
- are taking or have taken within the last 14 days one of the medicines for depression known as monoamine oxidase inhibitors (MAOIs), such as Nardil® or Parnate®.

Be sure to tell your doctor if you

- have ever had liver problems;
- are taking *any* other medicine, vitamin supplement, or herbal remedy, including those sold without a prescription (over-the-counter);
- have heart problems or have had a heart attack or stroke;
- have had manic episodes (extreme agitation or excitability);
- have ever attempted suicide;
- have had convulsions (seizures);
- are pregnant or breast-feeding.

#### How should I take SERZONE?

- Take SERZONE at the same time every day exactly as prescribed by your doctor. You may take SERZONE with or without food.
- It may take a while for you to feel that SERZONE is working. You may not feel the full effect for several weeks. Once you feel better, it is important to keep taking SERZONE as directed by your doctor.
- If you miss a dose of SERZONE, skip that dose and continue with your regular schedule. Never take 2 doses at the same time.
- If you think that you have taken more SERZONE than prescribed, contact your doctor, local poison control center, or emergency room right away.

#### What should I avoid while taking SERZONE?

- Do not drive or operate possibly dangerous machinery (such as an automobile, power mower, or power tool) or participate in any hazardous activity that requires full mental alertness until you know how SERZONE affects you.
- Before taking SERZONE, tell your doctor about *any* medicines you are taking, including vitamin supplements, herbal remedies, and any non-prescription (over-the-counter) medicines. Some of these medicines may affect how SERZONE works and should not be used in combination without talking to your doctor.
- Do not drink alcoholic beverages while taking SERZONE.
- Tell your doctor if you are pregnant, planning to become pregnant, or become pregnant while taking SERZONE. It is not known whether SERZONE can harm your unborn baby.
- Talk with your doctor before taking SERZONE if you are breast-feeding. It is not known whether SERZONE can pass through your breast milk to the baby.

#### What are the possible side effects of SERZONE?

The most common side effects of SERZONE (nefazodone hydrochloride) are sleepiness, dry mouth, nausea, dizziness, constipation, weakness, lightheadedness, problems with vision, and confusion.

Call your doctor right away if you have any of the following side effects:

- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Severe nausea
- Abdominal (lower stomach) pain
- Rash or hives
- Seizure (convulsion)
- Fainting
- Erection that lasts too long

Tell your doctor right away about any side effects that you have or discomfort that you experience. Do not change your dose or stop taking SERZONE without talking with your doctor first.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Your doctor has prescribed SERZONE for you and you alone. Do not give SERZONE to other people, even if they have the same condition. It may harm them.

This leaflet provides a summary of the most important information about SERZONE. If you would like more information, talk with your doctor or pharmacist. You can ask for information about SERZONE that is written for healthcare professionals. You can also get more information by visiting [www.serzone.com](http://www.serzone.com).

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 Bristol-Myers Squibb Company  
Princeton, NJ 08543 U.S.A.

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