

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**FINAL PRINTED LABELING**

**CAUTION: Federal law prohibits dispensing without prescription.**

# SERZONE<sup>®</sup>

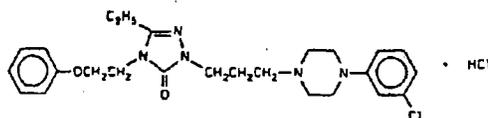
## (nefazodone hydrochloride)

### Tablets

#### 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  $C_{25}H_{32}ClN_5O_2 \cdot HCl$ , 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 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  $C_{max}$  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;  $C_{max}$  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  $C_{max}$  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 T1/2 for Three Metabolites of Nefazodone (100 mg BID)		
Metabolite	AUC Multiple	T1/2
HO-NEF	0.4	1.5-4 hrs
mCPP	0.07	4-8 hrs
Triazole-dione	4.0	18 hrs

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 radiolabelled 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*. While nefazodone did not alter the *in vitro* protein binding of chlorpromazine, desipramine, diazepam, diphenylhydantoin, lidocaine, prazosin, propranolol, verapamil, or warfarin, it is unknown whether or not displacement of either nefazodone or other 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 and older patients, 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 should be initiated at half the usual dose in elderly patients, especially women (see **DOSAGE AND ADMINISTRATION** Section), but the therapeutic dose range is similar in younger and older patients.

### **Clinical Trials Supporting the Effectiveness Claim**

The efficacy of SERZONE (nefazodone hydrochloride) as a treatment for depression was established in two placebo-controlled, short-term trials in outpatients meeting DSM-III or DSM-III-R criteria for major depression. One 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 about 400 mg/day], on a BID schedule) and placebo. The other 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. Overall, these studies demonstrated SERZONE, at doses titrated up to 600 mg/day, 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, 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). Two other 6-8 week placebo- and imipramine-controlled studies in depressed outpatients provided additional support for the superiority of nefazodone (titrated up to 500 or 600 mg/day; mean modal doses of 462 mg/day and 363 mg/day) over placebo.

There were no efficacy studies focusing specifically on the elderly or on men and women separately. 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.

## 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 whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depressive disorder (see **CLINICAL PHARMACOLOGY** Section).

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 5 of the following 9 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 antidepressant effectiveness of SERZONE in hospitalized depressed patients has not been adequately studied.

The effectiveness of SERZONE in long-term use, that is, for more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SERZONE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

## CONTRAINDICATIONS

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

SERZONE is contraindicated in patients with known hypersensitivity to nefazodone or other phenylpiperazine antidepressants.

## WARNINGS

### 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, 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 a 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 a MAOI.

### Interaction with Triazolobenzodiazepines

Interaction studies of nefazodone with two triazolobenzodiazepines, i.e., triazolam and alprazolam, metabolized by cytochrome P<sub>450</sub>III<sub>A</sub><sub>4</sub>, 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. For many patients, e.g., the elderly, it is recommended that triazolam not be used in combination with nefazodone. No dosage adjustment is required for SERZONE.

#### *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.

### Potential Terfenadine, Astemizole and Cisapride Interactions

Terfenadine, astemizole, and cisapride are all metabolized by the cytochrome P<sub>450</sub>III<sub>A</sub><sub>4</sub> isozyme, and it has been demonstrated that ketoconazole, erythromycin, and other inhibitors of III<sub>A</sub><sub>4</sub> can block the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, and cisapride 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 III<sub>A</sub><sub>4</sub>. Consequently, it is recommended that nefazodone not be used in combination with either terfenadine, astemizole, or cisapride (see CONTRAINDICATIONS and PRECAUTIONS Sections).

## PRECAUTIONS

### General

#### *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 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 (nefazodone hydrochloride) 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** Section). 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** Section).

#### *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** Section). 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 ( $p \leq 0.05$ ). 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**

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

#### *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** Section, **Nursing Mothers** Subsection).

#### *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 either HALCION®<sup>1</sup> or XANAX®<sup>1</sup>, and concomitant use with SELDANE®<sup>2</sup>, HISMANOL®<sup>3</sup> or PROPULSID®<sup>3</sup> is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS** Sections).

#### *Alcohol*

Patients should be advised to avoid alcohol while taking SERZONE.

#### *Allergic Reactions*

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

### 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** Section, **Pharmacokinetics** Subsection), administration of SERZONE 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.

#### *CNS Active Drugs*

Monoamine Oxidase Inhibitors - See **WARNINGS** Section

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 **WARNINGS** Section

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.

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 (nefazodone hydrochloride) 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.

#### *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 P<sub>450</sub>IID<sub>6</sub> extensive metabolizers, C<sub>max</sub>, C<sub>min</sub>, and AUC of digoxin were increased by 29%, 27%, and 15%, respectively. Digoxin had no effect 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 5.5 days to healthy male volunteers (n=18), including 3 poor and 15 extensive P<sub>450</sub>IID<sub>6</sub> metabolizers, resulted in 30% and 14% reductions in C<sub>max</sub> and AUC of propranolol, respectively, and a 14% reduction in C<sub>max</sub> for the metabolite, 4-hydroxypropranolol. The kinetics of nefazodone, hydroxynefazodone, and triazole-dione were not affected by coadministration of propranolol. However, C<sub>max</sub>, C<sub>min</sub>, 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.

#### *Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Potential Interaction with Drugs That Inhibit and/or are Metabolized by Cytochrome P<sub>450</sub> Isozyme*

**III<sub>4</sub> Isozyme** - Nefazodone has been shown *in vitro* to be an inhibitor of cytochrome P<sub>450</sub>III<sub>4</sub>. This is consistent with the interaction observed between nefazodone and the benzodiazepines triazolam and alprazolam, drugs metabolized by this isozyme. Consequently, caution is indicated in the combined use of nefazodone with any drugs known to be metabolized by the III<sub>4</sub> isozyme. In particular, the combined use of nefazodone with terfenadine, astemizole, or cisapride is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS** Sections).

**IID<sub>6</sub> Isozyme** - A subset (3% to 10%) of the population has reduced activity of the drug-metabolizing enzyme cytochrome P<sub>450</sub>IID<sub>6</sub>. Such individuals are referred to commonly as "poor metabolizers" of drugs such as debrisoquin, 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 P<sub>450</sub>IID<sub>6</sub>. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme.

**IA<sub>2</sub> Isozyme** - Nefazodone and its metabolites have been shown *in vitro* not to inhibit cytochrome P<sub>450</sub>IA<sub>2</sub>. Thus, metabolic interactions between nefazodone and drugs metabolized by this isozyme are unlikely.

### *Electro-Convulsive 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 3 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**

Over 500 elderly ( $\geq 65$  years) individuals participated in clinical studies with nefazodone. No unusual adverse age-related phenomena were identified in this cohort of elderly patients treated with nefazodone. Due to the increased systemic exposure to nefazodone seen in single-dose studies in elderly patients (see **CLINICAL PHARMACOLOGY** Section, **Pharmacokinetics** Subsection), treatment should be initiated at half the usual dose, but titration upward should take place over the same range as in younger patients (see **DOSAGE AND ADMINISTRATION** Section). 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	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%
	Neck Rigidity	1%	0
Cardiovascular	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%
	Nausea & Vomiting	2%	1%
	Peripheral edema	3%	2%
Metabolic	Thirst	1%	<1%
	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%
	Psychomotor retardation	2%	1%
	Tremor	2%	1%
	Hypertonia	1%	0

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	SERZONE (n = 393)	Placebo (n = 394)
	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%
	Visual field defect	2%	0
Urogenital	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 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> Vásdilatation - flushing, feeling warm.

<sup>3</sup> Abnormal vision - scótoma, 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 (nefazodone hydrochloride) 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	SERZONE 300-600 mg/day (n=209)	SERZONE ≤ 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%
	Confusion	8%	2%	1%
Special Senses	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.

*Vital Sign Changes*

(See **PRECAUTIONS** Section, *Postural Hypotension* Subsection)

*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 ( $0.05 < p \leq 0.10$ ). 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, 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, hangover 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:* hypercholesteremia 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.<sup>a</sup> *Infrequent:* cystitis, urinary urgency, metrorrhagia<sup>a</sup>, amenorrhea<sup>a</sup>, polyuria, vaginal hemorrhage<sup>a</sup>, breast enlargement<sup>a</sup>, menorrhagia<sup>a</sup>, urinary incontinence, abnormal ejaculation<sup>a</sup>, hematuria, nocturia, and kidney calculus. *Rare:* uterine fibroids enlarged<sup>a</sup>, uterine hemorrhage<sup>a</sup>, anorgasmia, and oliguria.

<sup>a</sup> 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 that have been received since market introduction that are not listed above and for which a causal relationship has not been established include rare occurrences of convulsions (including grand mal seizures) and priapism (see **PRECAUTIONS** Section).

### **DRUG ABUSE AND DEPENDENCE**

#### **Controlled Substance Class**

SERZONE (nefazodone hydrochloride) 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**

There is very limited experience with nefazodone overdose. 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 the patients died.

### **Overdose Management**

Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see **ADVERSE REACTIONS** Section).

There is no specific antidote for SERZONE (nefazodone hydrochloride). Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation. Any patient suspected of having taken an overdose should have the stomach emptied by gastric lavage.

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

## **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, on a BID schedule. 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 six months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown. Although there are no efficacy data that specifically address maintenance antidepressant treatment with SERZONE, the safety of nefazodone 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<sup>®</sup> (nefazodone hydrochloride) 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 200 mg and 250 mg tablets are unscored.

<i>NDC CODE</i>	<i>DESCRIPTION</i>
NDC0087-0032-31	100 mg white tablet, bottle of 60
NDC0087-0032-44	100 mg white tablet, blister pack of 100
NDC0087-0039-31	150 mg peach tablet, bottle of 60
NDC0087-0039-01	150 mg peach tablet, blister pack of 100
NDC0087-0033-31	200 mg light yellow tablet, bottle of 60
NDC0087-0033-44	200 mg light yellow tablet, blister pack of 100
NDC0087-0041-31	250 mg white tablet, bottle of 60

U.S. Patent No. 4,338,317

Store at room temperature, below 40° C (104° F) and dispense in a tight container.

**REFERENCES**

1. HALCION<sup>®</sup> and XANAX<sup>®</sup> are registered trademarks of the Upjohn Company.
2. SELDANE<sup>®</sup> is a registered trademark of Merrell Pharmaceuticals, Incorporated, a subsidiary of Hoechst Marion Roussel.
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