CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-152/S-028

APPROVAL LETTER

NDA 20-152/S-028

Bristol-Myers Squibb Company
Attention: Ronald Marcus, M.D.
Group Director, Regulatory Science
Five Research Parkway
Wallingford, CT 06492

Dear Dr. Marcus:

We acknowledge receipt of your supplemental new drug application dated November 26, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serzone (nefazodone hydrochloride) 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg Tablets.

Supplemental application S-028, submitted under "Changes Being Effected", provides for revisions to Serzone labeling to incorporate the postmarketing data related to Serzone and hepatic failure.

We have completed the review of this supplemental application, S-028, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted November 26, 2001/Label Code1017710B3), which incorporates all of the revisions listed below. Accordingly, this supplemental application is approved effective on the date of this letter.

Specifically, this supplement provides for the following revisions to product labeling.

[Revisions to product labeling.]

SERZONE®
(nefazodone hydrochloride)
TABLETS

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

[The addition of a bolded and enclosed black box at the beginning of prescriber labeling.]

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.

[Revisions to the **CONTRAINDICATIONS** section.]

CONTRAINDICATIONS

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, its ingredients, or other phenylpiperazine antidepressants

[Subsection addition in bolded text to the **WARNINGS** section]

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 SERZONE treatment. 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.

[Subsection addition to the **PRECAUTIONS-General** section.]

PRECAUTIONS-General
Hepatotoxicity (see **Boxed Warning**)

[Subsection addition to **PRECAUTIONS – Information for Patients** section.]

PRECAUTIONS – Information for Patients:
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.

[Addition of a reference to the WARNINGS section in the ADVERSE REACTIONS-Postintroduction Clinical Experience section.]

ADVERSE REACTIONS-Postintroduction Clinical Experience (2nd paragraph)
Anaphylactic reactions; angioedema; convulsions (including grand mal seizures); galactorrhea; gynecomastia (male); liver necrosis and liver failure, in some cases leading to liver transplantation and/or death (see WARNINGS); ...

Labeling changes of the kind which you have proposed under the above supplemental application are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplement, have been made.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
12/4/01 09:52:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-152/S-028

FINAL PRINTED LABELING

ORIGINAL

APPROVED

DEC 4 2001

1017710B3

SERZONE®
(nefazodone hydrochloride) Tablets

128 FP0

1234567A1

Bristol-Myers Squibb

Rx only

SERZONE®
(nefazodone hydrochloride) Tablets

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.

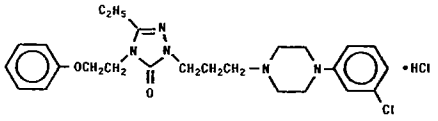
Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.

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 ≥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 $C_{25}H_{32}ClN_5O_2 \cdot HCl$, 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 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_2 receptors at nanomolar concentrations, and acts as an antagonist at this receptor. Nefazodone was shown to antagonize alpha$_1$-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$_2$ and beta adrenergic, 5-HT_{1A}, 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 $T_{1/2}$ for Three Metabolites of Nefazodone (100 mg BID)

Metabolite	AUC Multiple	$T_{1/2}$
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 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*. 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, diphenylhydantoin, 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/1.73m²) 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_{max} 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_{max} 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**), 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-IIR 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 t
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300 mg/day), and placebo, all on a BID sc
doses titrated between 300 mg to 600 mg
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Scale or HDRS (total score), Hamilton Depre
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certain factors of the HDRS (e.g., anxiety
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Overall, approximately two thirds of patie
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basis of sex. There were too few elderly pati
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Since its initial marketing as an antidepress
of SERZONE have been conducted. These stu
evaluated fully at the time initial marketing a

Studies in "Inpatients"

Two studies were conducted to evaluate SE
patients. These were 6-week, dose-titration
and placebo, on a BID schedule. In one study
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melancholic; at baseline, patients were di
Severity scale, as follows: 4=moderately i
(32%). In the other study, the differentiation i
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neous improvement among the patients ran

Studies of "Relapse Prevention in Patients Re

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one study, SERZONE was superior to placebo
to continuation on SERZONE or placebo for
demonstrated a significantly lower relapse
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Comparisons of Clinical Trial Results

Highly variable results have been seen in
drugs. Furthermore, in those circumstances
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effectiveness of different antidepressant dr
conditions of testing (e.g., patient samples,
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distinguish a difference in drug effect fr
confounding factors just enumerated.

INDICATIONS AND USAGE

SERZONE (nefazodone hydrochloride) is indi

The efficacy of SERZONE in the treatmer
controlled trials of outpatients and in a 6-we
diagnoses corresponded most closely to the
disorder (see **CLINICAL PHARMACOLOGY**).

A major depressive episode implies a pr
dysphoric mood that usually interferes with
weeks). It must include either depressed mo
of the following nine symptoms: depressed m
change in weight and/or appetite, insomnia o
tion, increased fatigue, feelings of guilt o
concentration, a suicide attempt or suicidal id

The efficacy of SERZONE in reducing relap
judged to have had a satisfactory clinical res
ment for an acute depressive episode has be
trolled trial (see **CLINICAL PHARMACOLOG**
as long as 36 weeks in the study cited (i.e.,
SERZONE for extended periods should period
drug for the individual patient.

CONTRAINDICATIONS

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WARNINGS

Hepatotoxicity (See **BOXED WARNING.**)

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Potential for Interaction with Monoamine
In patients receiving antidepressants w

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 462 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=markedly 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 ≤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 ≥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-IIIR 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 SERZONE treatment. 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 ≥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.

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 ($p \leq 0.01$) met criteria for a potentially important decrease in blood pressure at some time during treatment (systolic blood pressure ≤90 mmHg *and* a change from baseline of ≥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**). 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 (nefazodone hydrochloride) 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 ≤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 nefazodo increased by approximately 25%.

Information for Patients

Physicians are advised to discuss the following issues with patients fo SERZONE:

Hepatotoxicity

Patients should be informed that SERZONE therapy has been associ malities ranging from asymptomatic reversible serum transaminase liver failure resulting in transplant and/or death. At present, there is nc likely to develop liver failure. Ordinarily, patients with active liver d treated with SERZONE. Patients should be advised to be alert for sig (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and t doctor immediately if they occur.

Time to Response/Continuation

As with all antidepressants, several weeks on treatment may be req antidepressant effect. Once improvement is noted, it is important fc drug treatment as directed by their physician.

Interference With Cognitive and Motor Performance

Since any psychoactive drug may impair judgment, thinking, or moto be cautioned about operating hazardous machinery, including auto reasonably certain that SERZONE therapy does not adversely affect th such activities.

Pregnancy

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

Nursing

Patients should be advised to notify their physician if they are breas **PRECAUTIONS: Nursing Mothers**).

Concomitant Medication

Patients should be advised to inform their physicians if they are taki prescription or over-the-counter drugs, since there is a potential for caution is indicated if SERZONE is to be used in combination with XAI with HALCION®01 should be avoided for most patients including the e use with SELDANE®02, HISMANAL®03, PROPULSID®03, ORAP®04, or TI dicated (see **CONTRAINDICATIONS** and **WARNINGS**).

Alcohol

Patients should be advised to avoid alcohol while taking SERZONE (ne

Allergic Reactions

Patients should be advised to notify their physician if they develop a allergic phenomenon.

Visual Disturbances

There have been reports of visual disturbances associated with including blurred vision, scotoma, and visual trails. Patients should l physician if they develop visual disturbances. (See **ADVERSE REAC**

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 **CLI Pharmacokinetics**), administration of SERZONE to a patient taking a protein bound may cause increased free concentrations of the other dr adverse events. Conversely, adverse effects could result from displa other highly bound drugs.

Warfarin—There were no effects on the prothrombin or bleeding ti cokinetics of R-warfarin when nefazodone (200 mg BID) was ad subjects who had been pretreated for 2 weeks with warfarin. Altho of nefazodone did decrease the subjects' exposure to S-warfarin b on the prothrombin and bleeding times indicates this modest chan cant. Although these results suggest no adjustments in warfarin d nefazodone is administered to patients stabilized on warfarin, such tored as required by standard medical practices.

CNS-Active Drugs

Monoamine Oxidase Inhibitors—See **WARNINGS**.

Haloperidol—When a single oral 5-mg dose of haloperidol v nefazodone (200 mg BID) at steady state, haloperidol apparent cle with no significant increase in peak haloperidol plasma concentrat change is of unknown clinical significance. Pharmacodynamic ef generally not altered significantly. There were no changes in the ters for nefazodone. Dosage adjustment of haloperidol m coadministered with nefazodone.

Lorazepam—When lorazepam (2 mg BID) and nefazodone (200 tered to steady state, there was no change in any pharmacokinetic compared to each drug administered alone. Therefore, dosage ad for either drug when coadministered.

Triazolam/Alprazolam—See **CONTRAINDICATIONS** and **WARNING**

Alcohol—Although nefazodone did not potentiate the cognitive a alcohol in experiments with normal subjects, the concomitant use depressed patients is not advised.

Buspirone—In a study of steady-state pharmacokinetics in healt tration of buspirone (2.5 or 5 mg BID) with nefazodone (250 m increases in plasma buspirone concentrations (increases up to 20 fold in AUC) and statistically significant decreases (about 50%) ir the buspirone metabolite 1-pyrimidinylpiperazine. With 5-mg BID increases in AUC were observed for nefazodone (23%) and its zodone (17%) and mCPP (9%).

Pimozide—See **CONTRAINDICATIONS, WARNINGS**, and **PRECAU**

Nefazodone in 'Poor Metabolizers' and Potential Interaction with D Metabolized by Cytochrome P450 Isozymes.

Fluoxetine—When fluoxetine (20 mg QD) and nefazodone (200 r at steady state there were no changes in the pharmacokinetic p its metabolite, norfluoxetine. Similarly, there were no changes in meters of nefazodone or HO-NEF; however, the mean AUC metabolites mCPP and triazole-dione increased by 3- to 6-fold When a 200-mg dose of nefazodone was administered to subjec fluoxetine for 1 week, there was an increased incidence of transi headache, lightheadedness, nausea, or paresthesia, possibly levels. Patients who are switched from fluoxetine to nefazo washout period may experience similar transient adverse eve happening can be minimized by allowing a washout period b therapy and by reducing the initial dose of nefazodone. Becau fluoxetine and its metabolites, this washout period may range depending on the dose of fluoxetine and other individual patier

Phenytoin—Pretreatment for 7 days with 200 mg BID of nefazodo macokinetics of a single 300-mg oral dose of phenytoin. Hov pharmacokinetics of phenytoin, the failure to observe a significa pharmacokinetics of phenytoin does not preclude the possibility of action with nefazodone when phenytoin is dosed chronically. How dosage of phenytoin is considered necessary and any subsequ dosage should be guided by usual clinical practices.

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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:

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®1, concomitant use with HALCION®1 should be avoided for most patients including the elderly, and concomitant use with SELDANE®2, HISMANAL®3, PROPULSID®3, ORAP®4, or TEGRETOL®5 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 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.

Buspirone—In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg BID) with nefazodone (250 mg BID) resulted in marked increases in plasma buspirone 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 buspirone metabolite 1-pyrimidinylpiperazine. With 5-mg BID doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (17%) and mCPP (9%).

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.

Phenytoin—Pretreatment for 7 days with 200 mg BID of nefazodone had no effect on the pharmacokinetics of a single 300-mg oral dose of phenytoin. However, due to the nonlinear pharmacokinetics of phenytoin, the failure to observe a significant effect on the single-dose pharmacokinetics of phenytoin does not preclude the possibility of a clinically significant interaction with nefazodone when phenytoin is dosed chronically. However, no change in the initial dosage of phenytoin is considered necessary and any subsequent adjustment of phenytoin 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-hydroxy desipramine. 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 (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.

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_1 measurements taken when theophylline and nefazodone were coadministered did not differ from baseline (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 5.5 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 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, buspirone, 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 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 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/m² 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/m² basis) but not at 100 mg/kg/day (approximately 1.5 times the maximum human daily dose on a mg/m² 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/m² 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/m² 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 (nefazodone hydrochloride) 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 **DOSAGE 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 (≥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≤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 (nefazodone hydrochloride) 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[1], SERZONE 300 to 600 mg/day Dose Range

		Percent of Patients	
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
Metabolic	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

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Body System	Pre
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[1] Events reported by at least 1% quent than the placebo group a 1% (<1% indicates an incidenc incidence was equal to or less th ed the following: abdominal pai neck pain, palpitation, migraine disorder, weight gain, edema, hypesthesia, CNS stimulation, dy menorrhea[4], dysuria.

[2] Vasodilatation—flushing, feeling

[3] Abnormal vision—scotoma, visua

[4] Incidence adjusted for gender.

Dose Dependency of Adverse Events

The table that follows enumerates a (nefazodone hydrochloride) dose ra range of up to 300 mg/day. This tab a statistically significant difference (p as well as a difference between the

Dose Dependency of Ac

Body System	Preferred Term
Gastrointestinal	Nausea
	Constipation
Nervous	Somnolence
	Dizziness
	Confusion
Special Senses	Abnormal vision
	Blurred vision
	Tinnitus

[1] Events for which there was a statis nefazodone dose groups.

Visual Disturbances

In controlled clinical trials, blurred vi compared to 3% of placebo-treated pa scotomata and visual trails, occurred i of placebo-treated (see Treatment-Eme dency was observed for these events trails at doses below 300 mg/day. Ho below 300 mg/day have been reporte **PRECAUTIONS: Information for Patie**

Vital Sign Changes

(See **PRECAUTIONS:** *Postural Hypotensi*

Weight Changes

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Laboratory Changes

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ECG Changes

Of the ECG parameters monitored dur nefazodone, a pooled analysis revealed a s and placebo for sinus bradycardia, i.e., 1.5 important decrease in heart rate (≤50 bpn placebo patients (p<0.05). There was no ot the few patients meeting these criteria.

Other Events Observed During the Pre

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In the tabulations that follow, reported COSTART-based Dictionary terminology. Th proportion of the 3496 patients exposed to event of the type cited on at least one occa are included except those already listed Incidence table, those events listed in other experiences subsumed under COSTART te specific so as to be uninformative, those ev those events which were not serious and oc

It is important to emphasize that, although SERZONE, they were not necessarily caused

(table continued from previous column)

Body System	Preferred Term	Percent of Patients SERZONE (n=393)	Placebo (n=394)
Nervous	Paresthesia	4	2
	Vasodilatation[2]	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
	Libido decreased	1	<1
Respiratory	Pharyngitis	6	5
	Cough increased	3	1
Special Senses	Blurred vision	9	3
	Abnormal vision[3]	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[4]	2	1
	Breast pain[4]	1	<1

[1] 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[4], dysuria.

[2] Vasodilatation—flushing, feeling warm.

[3] Abnormal vision—scotoma, visual trails.

[4] 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[1]

Body System	Preferred Term	Percent of Patients 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

[1] 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 postmarketing 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 ≥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 (≤37% male or ≤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 (≤50 bpm and a decrease of ≥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 (nefazodone hydrochloride) 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[a]. *Infrequent:* cystitis, urinary urgency, metrorrhagia[a], amenorrhea[a], polyuria, vaginal hemorrhage[a], breast enlargement[a], menorrhagia[a], urinary incontinence, abnormal ejaculation[a], hematuria, nocturia, and kidney calculus. *Rare:* uterine fibroids enlarged[a], uterine hemorrhage[a], anorgasmia, and oliguria.

[a]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; Stevens-Johnson syndrome; and thrombocytopenia.

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

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 overdosage 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 overdosage, 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.

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Treatment should consist of those general measures employed in the management of overdosage 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 overdosage, 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® (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 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.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Revised October 2001

101771083

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-152/S-028

ADMINISTRATIVE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

Review Date: December 2, 2001
NDA: 20-152
Sponsor: Bristol-Myers Squibb (BMS)
DRUG: Serzone (nefazodone hydrochloride) 50 mg, 100 mg. 150 mg, 200 mg, and 250 mg Tablets
Supplements: SLR-028 dated 11-26-01

Notes of interest:

- The last approved labeling (Label Code 1092982A8) was submitted with SLR-026 which was approved in an Agency letter dated 3-21-01.
- This project initiated when BMS inserted the terms "liver necrosis" and "liver failure" in the **ADVERSE REACTIONS-Postintroduction Clinical Experience** section in CBE supplement SLR-016 dated 11-20-98. The Division (including the safety team) as well as OPDRA and the Office Level (Dr. Temple) [for some of the meetings], convened internally to discuss the association of Serzone and hepatic failure in internal meetings dated 1-13-99, 4-15-99, 5-13-99, 5-27-99, 7-1-99, 7-13-99, 7-20-99, 8-16-99, 8-18-99, 9-3-99, 2-1-00, 8-27-00, 4-25-01, 6-29-01, 7-23-01, 10-3-01, 10-25-01, and 11-13-01. The Agency and BMS discussed these issues in meetings dated 7-16-99, 8-20-99, 9-17-99, 2-3-00, 4-26-01, 9-6-01, and 10-30-01. Prior to making any changes in prescriber labeling, BMS conducted a large epidemiological study since their assertion was that the rate of hepatic failure was no different than the other drugs approved for the treatment of major depressive disorder (MDD). The post-marketing data, in conjunction with the data from the epidemiologic study, strongly suggest that Nefazadone can cause acute liver failure resulting in death or transplant. The data from BMS's epidemiologic study did not demonstrate that other drugs approved for the treatment of MDD had the same incidence rate since the study was not powered to detect this difference. Therefore, the Agency issued a letter requesting extensive changes to the labeling, including the addition of a boxed warning, a PPI, and a "Dear Healthcare Practitioner" letter in a letter dated 7-27-01. The prescriber labeling revisions were agreed upon between BMS and the Agency on 10-31-01.

REVIEW

20-152/SLR-028
Dated: 11-26-01
CBE: Yes
Label Code:1017710B3
Reviewed by Medical Officer: Yes, acceptable.

The supplement provides for the following revisions to labeling:

SERZONE®
(nefazodone hydrochloride)
TABLETS

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

[The addition of a bolded and enclosed black box at the beginning of prescriber labeling with the following text.]

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.

[Revisions to the **CONTRAINDICATIONS** section.]

CONTRAINDICATIONS
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, its ingredients, or other phenylpiperazine antidepressants

[Subsection addition in bolded text to the **WARNINGS** section]

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 SERZONE treatment. 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.

[Subsection addition to the **PRECAUTIONS-General** section.]

PRECAUTIONS-General
Hepatotoxicity (see **Boxed Warning**)

[Subsection addition to **PRECAUTIONS – Information for Patients** section.]

PRECAUTIONS – Information for Patients:
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.

> [Addition of a reference to the **WARNINGS** section in the **ADVERSE REACTIONS-Postintroduction Clinical Experience** section.]

ADVERSE REACTIONS-Postintroduction Clinical Experience (2nd paragraph)
Anaphylactic reactions; angioedema; convulsions (including grand mal seizures); galactorrhea; gynecomastia (male); liver necrosis and liver failure, in some cases leading to liver transplantation and/or death (see **WARNINGS**); ...

The above revisions were based upon postmarketing reports of hepatic failure associated with Serzone use. This labeling was agreed upon by the Agency and BMS on 10-31-01. The Agency and BMS subsequently agreed upon labeling for a "Dear Healthcare Practitioner" letter as well as a PPI, and this will be submitted in a separate supplement within the next 1-2 weeks.

CONCLUSIONS

1. This supplement only provides for the labeling revisions listed above. The sponsor has incorporated the labeling text, verbatim, which was agreed upon on 10-31-01 into the FPL. See attachment denoting highlighted labeling revisions.
2. The medical officer and safety team concur with the revisions provided for in the application.
3. I recommend that an approval letter issue for SLR-028.

Paul David. R.Ph
Senior Regulatory Project Manager

Robbin Nighswander, R.Ph
Supervisory Regulatory Health Officer

ATTACHMENT A.

22 page(s) of draft labeling has been removed from this portion of the review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
12/3/01 11:08:35 AM
CSO

Jack Purvis
12/3/01 01:25:00 PM
CSO

Bristol-Myers Squibb
Pharmaceutical Research Institute
Richard L. Gelb Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

ORIGINAL

NDA SUPPLEMENT

NDA No. 20-152
SERZONE® (Nefazodone HCl) Tablets

SUBMISSION NO. 223 -
Special Supplement:
Changes Being Effected

November 26, 2001

NDA NO. 20-152 REF NO. SLR-028
NDA SUPPL FOR Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

NOV 27 2001

RECEIVED HFD-120

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Control Room 4008, HFD-120
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to our approved New Drug Application for SERZONE® (nefazodone hydrochloride) Tablets (NDA No. 20-152). In response to the outcome of the October 30, 2001 teleconference with the Division, we are submitting this "Special Supplement - Changes Being Effected" which revises the labeling for SERZONE Tablets. The implementation date for this supplement will be December 5, 2001.

Please see the enclosed "side by side" (**Attachment 1**) version of the labeling that indicates both the nature of the changes and the location where they are to be made. A clean copy (**Attachment 2**) of the label is also provided. We are also providing, for the convenience of the reviewer, an electronic version of the revised label (MSWord97) which is in the Archival copy of this submission.

Finally, we are providing in the Archival copy of this submission, 20 copies of final printed labeling that incorporates the changes provided for in this supplement. Ten copies of the final printed labeling are individually mounted on heavyweight paper.

If there are any questions or comments concerning this submission, please contact the undersigned at (203)-677-6763.

Very truly yours,

Ronald Marcus, M.D.

Ronald Marcus, M.D.
Group Director
Regulatory Science

/pk
Attachments