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

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

Concentrations in breast milk—At concentrations in plasma of 3.5–20 μg/mL, nefazodone was detectable in breast milk. Nefazodone and hydroxynefazodone are bound to human 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 to an average of 125% at baseline. The AUCs of warfarin in these subjects were unaffected by nefazodone. Nefazodone did not alter the in vitro protein binding of chlorpromazine, desipramine, diazepam, diphenhydramine, lidocaine, prazosin, propranolol, or verapamil. It is unknown whether displacement of warfarin from plasma proteins may occur 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%. Nefazodone in studies involving 29 renally impaired patients, renal impairment (creatinine clearance values ranging from 70 to 80 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), Cmax and AUC for nefazodone and hydroxynefazodone were up to twice as high in the older patients. Weigh of body differences were very small (25%). A similar result was seen for gender, with a higher Cmax and AUC in women after single doses but no difference after multiple doses.

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

Clinical Efficacy Trial Results

Studies in Outpatients with Depression

During its premarketing development, the efficacy of SERZONE was evaluated at doses within the therapeutic range in five well-controlled, short-term (6–8 weeks) clinical investigations. These trials enrolled outpatients meeting DSM-III or DSM-III-R criteria for major depression. Among these trials, two demonstrated antidepressant effectiveness (mean HDRS total score reduction of at least 50% over 6 weeks); the other two did not meet the predefined standard of significance. A third additional clinical investigation 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 BID) and placebo, on a BID schedule. In one study, SERZONE was superior to placebo. In this study, the mean modal dose of SERZONE was 400 mg/day, and 95% of patients titrated to the therapeutic dose range, to be superior to placebo on at least three of the following four measures: 17-item Hamilton Depression Rating Scale (HDRS) total score, Global Rating of Severity (GRS) item, Clinical Global Impressions (CGI) Severity score, and CGI Improvement score. Significant differences were also found for certain factors of the GRS (e.g., anxiety factor, sleep disturbance factor, and removal of the subject from prior antidepressant therapy), and in the two-item subscales of GRS. In the third study, SERZONE was titrated up to 500 or 600 mg/day (mean modal doses of 482 mg/day and 363 mg/day). In the fifth study, the differentiation in response rates between SERZONE and placebo was not statistically significant. Three additional trials were conducted using therapeutic doses of SERZONE.

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

In 1995, the marketing authorization for nefazodone in Europe was based on studies involving 1184 patients. 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.

These 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 antidepressant treatment period. The first study was an open treatment with patients continuing on their previously effective antidepressant regimen. In this open trial, SERZONE treatment 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 rate of relapse of depression for the total cohort of patients. 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, comparisons among the findings of different studies evaluating the same drug are problematic. Since different antidepressant drugs are inherently different, it is unreasonable to expect that 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 different clinical investigations, it is virtually impossible to arrive at a direct comparison in drug effect from one 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 closely to the DSM-III or DSM-III-R category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually lasts at least 2 weeks and is associated with at least five of the following symptoms which have been present during the major portion of nearly every day: appetite or weight loss, anhedonia or alogia, 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...
**BOXED WARNING**

- **Hepatotoxicity**: (See BOXED WARNING.)
- **Postural Hypotension**: A pooled analysis of the vital signs monitored during placebo-controlled premarketing studies revealed that 5.1% of nefazodone patients compared to 2.5% of placebo patients (p=0.01) met criteria for a 20 mmHg decrease in diastolic blood pressure at some time during treatment (systolic blood pressure ≤90 mmHg and a change from baseline of 220 mmHg). While there was no difference in the proportion of nefazodone and placebo patients having adverse events characterized as "syncope" (nelfazodone 0.0%, placebo, 0.3%), the rate for adverse events characterized as "postural hypotension" were as follows: nefazodone (2.6%), tricyclic antidepressants (10.9%), SSRIs (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. Nefazodone (nefazodone hydrochloride) should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose to hypotension (defibrillation, hypovolemia, and treatment with antihypertensive medication).

**WARNINGS**

**Hepatotoxicity (See BOXED WARNING.)**

Cases of life-threatening hepatic failure have been reported in patients treated with SERZONE. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000–300,000 patient-years of use. This represents a rate of about 3-4 times the spontaneous rate of liver failure. The incidence of liver failure in clinical trials and postmarketing, 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 during a 10,000-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 the onset of clear prodromal symptoms prior to the onset of liver injury, 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. In addition, adverse event assessments 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 hepatic injury should be withdrawn from SERZONE immediately. Because of the potential for rapid deterioration of liver function, a hepatic transplant may be required. Patients who present with signs and symptoms of liver injury during therapy with SERZONE should be withdrawn from the drug. These patients should be presumed to be at increased risk for liver injury if SERZONE is reinstituted. 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 resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have occurred in patients who recently discontinued or switched to the use of monoamine oxidase inhibitors (MAIS) and MAOs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAO.

Although the effects of combined use of nefazodone and MAOIs have not been evaluated in humans, it is believed that the hepatic dysfunction and potential for a serious, life-threatening, drug-related syndrome associated with discontinuation of a monoamine oxidase inhibitor is an important consideration when MAOIs are used in patients concurrently treated with SERZONE.

**INTERACTIONS**

**Interaction with Triazolobenzodiazepines**

Interaction studies of nefazodone with two triazolobenzodiazepines, i.e., triazolam and alprazolam, metabolized by cytochrome CYP3A4, have revealed substantial and clinically important increases in plasma concentrations of these compounds when administered concomitantly with nefazodone.

**Terfenadine, Astemizole, Cisapride, and Pimozide Interactions**

Nefazodone tablets are contraindicated in patients who were withdrawn from SERZONE because of evidence of hepatic dysfunction. SERZONE tablets are also contraindicated in patients who have demonstrated hypersensitivity to nefazodone hydrochloride, its inactive ingredients, or other phenylpiperazinergic antidepressants.

The coadministration of triazolam and nefazodone causes a significant increase in the plasma levels of triazolam with no apparent increase in its elimination rate. Coadministration of nefazodone and triazolam should be avoided for most patients, including the elderly.

**WARNINGS**

**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 patient reportedly experienced a grand mal seizure while taking nefazodone. 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).

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

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

- **Hepatotoxicity**

Physicians should be informed that SERZONE has been associated with liver abnormalities ranging from mild elevations in liver function tests to fatal hepatic failure. In a total of 153 patients who received nefazodone in 6- to 8-week, double-blind, placebo-controlled trials, 10.5% of nefazodone-treated patients compared to 0.4% of placebo-treated patients (p=0.05). Because patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical trials, such patients should be treated with caution.

**Use in Patients with Concomitant Illness**

SERZONE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product’s premarketing testing. Evaluation of electrocardiograms from 1% of patients in clinical trials showed that the use of nefazodone did not indicate that nefazodone is associated with the development of clinically important ECG abnormalities. However, since 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<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.

**Time to Response/Continuation**

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.

**Intolerance 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.

**Primary Caregivers**

Physicians should be advised to notify their patients if they become pregnant or intend to become pregnant during therapy.

**Aurora**

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.

**Hepatotoxicity**

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

**Alcohol**

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

**Allergic Reactions**

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

**Visual Disturbances**

Physicians should be advised to notify their physician if they develop visual disturbances. (See ADVERSE REACTIONS.)
**Drug Interactions**

Because nefazodone is highly bound to plasma protein (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**), administration of SERZONE (nefazodone hydrochloride) to a patient taking another or multiple highly bound drugs (e.g., digoxin, phenytoin) may result in increased free plasma concentrations of the other. Sudden changes in plasma drug levels may result in adverse effects. Conversely, adverse effects could result from displacement of nefazodone by other highly bound drugs.

Warfarin administration for 7 days in healthy volunteers (n=18) who were phenotyped as CYP2D6 extensive metabolizers, C max, C min, and AUC of digoxin were increased by 23%, 54%, and 48%, respectively. No change in initial dose is necessary and dose adjustments should be made on the basis of clinical response.

There are no specific laboratory tests recommended.

Carcinogenesis

There is no evidence of carcinogenicity with nefazodone. The dietary administration of nefazodone to rats and mice at a dose approximately three times the maximum human oral dose on a mg/m2 basis, produced no increased incidence of tumors. However, increased early pup mortality was seen in rats at a dose approximately five times the maximum human oral dose on a mg/m2 basis. Therefore, dosage adjustment is not necessary for either drug when coadministered.

**ADVERSE REACTIONS:**

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, nor- fluoxetine. However, fluoxetine (20 mg QD) coadministered in the presence of nefazodone (23%) and its metabolites hydroxynefazodone (17%) and mCPP (9%). Subjects receiving nefazodone 250 mg b.i.d. and buspirone 5 mg b.i.d experienced lightheadedness, asthma, dizziness, and somnolence. In this study, no drug interactions with either drug alone. The two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg q.d) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Cimetidine—Administration of CYP2D6 substrates by SERZONE (nefazodone hydrochloride) because, in the same study, SERZONE had no significant effect on the plasma concentrations of pravastatin, which is not metabolized by CYP3A4 to a clinically significant extent.

There have been reports of rhabdomyolysis involving patients receiving the combination of SERZONE (nefazodone) and a substituted cyclosporine. The use of SERZONE in patients receiving cyclosporine should be monitored and dosage adjusted according respectively.

**Laboratory Tests**

There are no specific laboratory tests recommended.

Other CNS-Active Drugs—The use of nefazodone in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if concomitant administration of SERZONE and such drugs is required.

**Ciclosporine—**Cyclosporine plasma levels may be increased with nelfinavir, ritonavir, and saquinavir. Therefore, dosage adjustment is necessary in patients taking ciclosporine.

**Immunosuppressive Agents**

There have been reports of increased blood concentrations of ciclosporine and tacrolimus into toxic levels in patients taking cyclosporine, tacrolimus, or any other immunosuppressive agent. Nefazodone has been shown to inhibit CYP3A4 and, therefore, increase the concentrations of ciclosporine and tacrolimus. Administration of nefazodone concomitantly with ciclosporine or tacrolimus should be avoided.

**Postintroduction Clinical Experience:** Rhabdomyolysis has been observed in patients receiving HMG-CoA reductase inhibitors at doses that are clinically relevant. Concomitant use with nefazodone should be avoided, as increases in the concentration of ciclosporine may result in nephrotoxicity.

**Pregnancy**

There is no evidence of increased toxicity with nefazodone in rats and mice at a dose approximately three times the maximum human oral dose on a mg/m2 basis. Nefazodone is a drug of pregnancy category C.

**Mutagenesis**

Nefazodone has been shown to have no genotoxic effects based on the following assays: bacterial mutagenicity assays, a human lymphocyte assay, and a mouse micronucleus assay. However, nefazodone is a weak inhibitor of CYP3A4. Consequently, in a study using the mouse bone marrow micronucleus assay and the rat bone marrow micronucleus assay, no genotoxic effect was observed with nefazodone.

**Electroconvulsive Therapy (ECT)**

There are no clinical studies of the combined use of ECT and nefazodone.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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 increased incidence of tumors. However, increased early pup mortality was seen in rats at a dose approximately five times the maximum human oral dose on a mg/m2 basis. Therefore, dosage adjustment is not necessary for either drug when coadministered.

**Mutagenesis**

Nefazodone has been shown to have no genotoxic effects based on the following assays: bacterial mutagenicity assays, a human lymphocyte assay, and a mouse micronucleus assay. However, nefazodone is a weak inhibitor of CYP3A4. Consequently, in a study using the mouse bone marrow micronucleus assay and the rat bone marrow micronucleus assay, no genotoxic effect was observed with nefazodone.

**Impairment of Fertility**

A fertility study in rats showed a slight decrease in fertility at 300 mg/kg/day (approximately 3 times the maximum human daily dose on a mg/m2 basis) but not at 120 mg/kg/day (approximately 1.5 times the maximum human daily dose on a mg/m2 basis).

**Teratogenic Effects—Pregnancy Category C**

Reproductive studies have been performed in pregnant rabbits and rats at doses up to 200 and 300 mg/kg/day, respectively, (approximately 6 and 18 times 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 daily dose, and rats received nefazodone (23%) and its metabolites hydroxynefazodone (17%) and mCPP (9%). Subjects receiving nefazodone 250 mg b.i.d and buspirone 5 mg b.i.d experienced lightheadedness, asthma, dizziness, and somnolence. In this study, no drug interactions with either drug alone. The two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg q.d) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

**Pimozide—**Nefazodone is a weak inhibitor of CYP2D6. However, it is a potent inhibitor of the P-glycoprotein pump in membranes derived from human placenta (see **CONTRAINDICATIONS and WARNINGS**).

**Cyclosporine—**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 nefazodone and its metabolites are increased in poor metabolizers, and nefazodone should be used with caution in these patients. Therefore, dosage adjustment is necessary in patients taking ciclosporine.

Pharmacokinetics of Nefazodone in “Poor Metabolizers” and Potential Interaction with Drugs that Inhibit and/or Are Metabolized by Cytochrome P450 Isoenzymes.

Nefazodone is a substrate for CYP3A4 and is also a weak inhibitor of CYP2D6. Furthermore, nefazodone is a weak inhibitor of P-glycoprotein, an important drug transport protein that is responsible for the efflux of drugs from the central nervous system into the bloodstream.

**CYP2D6 Isozyme—**Nefazodone is a weak inhibitor of CYP2D6. However, it is an extremely weak inhibitor of CYP2D6. Thus, it is not likely that nefazodone will decrease the metabolic clearance of drugs metabolized by this isozyme.
Labor and Delivery

The effect of SERZONE on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether SERZONE or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERZONE is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in individuals below 18 years of age have not been established.

Geriatric Use

Of the approximately 7000 patients in clinical studies who received SERZONE for the treatment of depression, 18% were 65 years and older, while 5% were 75 years and older. Based on monitoring of adverse events, vital signs, electrocardiograms, and results of laboratory tests, no overall differences in safety between elderly and younger patients were observed in clinical studies. Efficacy in the elderly has not been demonstrated in placebo-controlled trials. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some other populations 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 comorbid 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 premarking 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 a drop at a rate approximately twice or greater for SERZONE compared to placebo) included nausea (3.5%), dizziness (1.9%), insomnia (2.1%), 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, postural hypotension, nausea, dizziness, constipation, asthenia, lightheadedness, blurred vision, confusion, and abnormal vision.

Adverse Events Occurring at an Incidence of 1% or More Among SERZONE-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among SERZONE-treated patients who participated in short-term (6- to 8-week) placebo-controlled trials in which patients were dosed with SERZONE to ranges of 300 to 600 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using standard COSTART-based Dictionary terminology. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Dose Dependency of Adverse Events in Placebo-Controlled Trials

The table that follows shows the percentage of events that were more frequent in the SERZONE dose range of 300 to 600 mg/day than in the SERZONE dose range of up to 300 mg/day. This table shows only those adverse events for which there was a statistically significant difference (p<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

<table>
<thead>
<tr>
<th>Body System</th>
<th>SERZONE 300–600 mg/day (n=209)</th>
<th>SERZONE ≤300 mg/day (n=211)</th>
<th>Placebo (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Nausea 23</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Nervous</td>
<td>Constipation 17</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Abnormal vision 10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Blurred vision 9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tinnitus 3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

1 Events for which there was a statistically significant difference (p<0.05) between the nefazodone dose groups.

VisualDisturbances

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-dependendency 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.)

VisualDisturbances

(See PRECAUTIONS, Postural Hypotension.)

WeightChanges

In a pooled analysis of placebo-controlled premarking 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 premarking 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<0.10). Decreases in hematocrit, presumably dilutional, have been reported with many other drugs that block alpha-adrenergic receptors. There was no apparent clinical significance of the observed changes in the few patients meeting these criteria.

ECGChanges

Of the ECG parameters monitored during placebo-controlled premarking 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.

OtherEventsObservedDuringthePremarkingEvaluationofSERZONE

During its premarking assessment, the adverse event rates of SERZONE were estimated from 3496 patients in placebo-controlled 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 list, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events for which a drug cause was very remote, and those events which were not serious and occurred in fewer than two patients.

It is important to emphasize that, although the events reported occurred during treatment with SERZONE ( nefazodone hydrochloride), they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a whole—Infrequent: allergic reaction, malaise, photosensitivity reaction, face edema, hang-over effect, abdomen enlarged, hermia, pelvic pain, and haitosis. Rare: cellulitis.

Cardiovascular system—Infrequent: tachycardia, hypertension, syncope, ventricular extrasystoles, and angina pectoris. Rare: AV block, congestive heart failure, hemorrhage, pailor, and vasoviscose vein.

Dermatological system—Infrequent: dry skin, acne, alopecia, urticaria, maculopapular rash, vesiculoulus rash, and eczema.

Gastrointestinal system—Frequent: gastrointestinal. Infrequent: enuriscation, periodontal abscess, abnormal liver function tests, ginvitis, 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, leuokpoina, and lymphadenopathy.

Metabolic and nutritional system—Infrequent: weight loss, guilt, dehydration, lactic dehydrogenase increased, SGOT increased, and SGPT increased. Rare: hypercholesterolemia and hypoglycemia.

Musculoskeletal system—Infrequent: arthritis, tenosynovitis, muscle stiffness, and burstitis. Rare: tendinous contracture.

Nervous system—Infrequent: vertigo, twitching, depersonalization, hallucinations, suicide attempt, aphaty, euphoria, hostility, suicidal thoughts, abnormal gait, thinking abnormal, attention decreased, derealization, neuralgia, paranoid reaction, dysaria, increased libido, and myoclonus. Rare: hyperkinisins, increased salivation, cerebrovascular accident, hyperesthesias, hypothitonia, and myoclonic malignant syndrome.

Respiratory system—Frequent: dyspnnea and bronchitis. Infrequent: asthma, pneumonia, laryngitis, voice alteration, epistaxis, hiccup. Rare: hyperventilation and yawning.

Special senses—Frequent: eye pain. Infrequent: dry eye, ear pain, abnormality of accommodation, diplopia, conjunctivitis, mydriasis, keratoconjunctivitis, hyperacrasia, and photophobia. Rare: deafness, glaucoma, [name of drug]; glaucoma; light blindness, and taste loss.

Urogenital system—Frequent: impotence. Infrequent: cystitis, urinary urgency, metroningia, amenorrhea, polyuria, vaginal hemorrhage, breast enlargement, menorrhagia, urinary incontinence, abnormal ejaculation, hematuria, norcturia, and kidney calculus. Rare: uterine fibroids enlarged, uterine hemorrhage, anorgasia, and oliguria.

*Adjusted for gender.

PostIntroduction Clinical Experience

Postmarketing experience with SERZONE has shown a adverse event profile similar to that seen during the premarketing evaluation of nefazodone. Voluntary reports of adverse events temporarily 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); galactorrhoea; gynecomastia (male); hypoglycaemia; liver necrosis and liver failure, in some cases leading to liver transplantation and/or death (see WARNINGS); pruritis (see PRECAUTIONS); prolactin increased; rhabdomyolysis involving patients receiving the combination of SERZONE and lovastatin or simvastatin (see PRECAUTIONS); serotonin syndrome; and Stevens-Johnson syndrome and thrombocytopenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

SERZONE is not a controlled substance.

Physical and Psychological Dependence

In animal studies, nefazodone did not act as a reinforcer for intravenous self-administration in monkeys trained to self-administer cocaine, suggesting no abuse liability. In a controlled study of abuse liability in human subjects, nefazodone showed no potential for abuse.

Nefazodone has not been systematically studied in humans for its potential for tolerance, physical dependence, or withdrawal. While the premarketing clinical experience with nefazodone did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of SERZONE (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Human Experience

In premarketing clinical studies, there were seven reports of nefazodone overdose alone or in combination with other pharmacological agents. The amount of nefazodone ingested ranged from 1000 mg to 11,200 mg. Commonly reported symptoms from overdose of nefazodone included nausea, vomiting, and somnolence. One nonstudy participant took 2000–3000 mg of nefazodone with methocarbamol and alcohol; this person reportedly experienced a convulsion (type not documented). None of these patients died.

In postmarketing experience, overdose with SERZONE alone and in combination with alcohol and/or other substances has been reported. Commonly reported symptoms were similar to those reported from overdose in premarketing experience. While there have been rare reports of fatalities in patients taking overdoses of nefazodone, predominantly in combination with alcohol and/or other substances, the safety of nefazodone has not established a causal relationship to the adverse events or outcomes described.

Overdose Management

Treatment should consist of those general measures employed in the management of overdose with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the wide distribution of nefazodone in body tissues, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

No specific antidotes for nefazodone are known.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians’ Desk Reference (PDR).

DOSAGE AND ADMINISTRATION

Initial Treatment

The recommended starting dose for SERZONE ( nefazodone hydrochloride) is 200 mg/day, administered in two divided doses (BID). In the controlled clinical trials establishing the antidepressant efficacy of SERZONE, the effective dose range was generally 300 to 600 mg/day. Consequently, most patients, depending on tolerability and the need for further clinical effect, should have their dose increased. Dose increases should occur in increments of 100 mg/day to 200 mg/day, again on a BID schedule, at intervals of no less than 1 week. As with all antidepressants, several weeks on treatment may be required to obtain a full antidepressant response.

Dosage for Elderly or Debilitated Patients

The recommended initial dose for elderly or debilitated patients is 100 mg/day, administered in two divided doses (BID). These patients often have reduced nefazodone clearance and/or increased sensitivity to the side effects of CNS-active drugs. It may also be appropriate to modify the rate of subsequent dose titration. As steady-state plasma levels do not change with age, the final target dose based on a careful assessment of the patient’s clinical response may be similar in healthy younger and older patients.

Maintenance/Continuation/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the depressed patient should be treated with SERZONE. It is generally agreed, however, that pharmacological treatment for acute episodes of depression should continue for up to 6 months or longer. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain euthymia is unknown. Systematic evaluation of the efficacy of SERZONE has shown that efficacy is maintained for periods of up to 36 weeks following 16 weeks of open-label acute treatment (treated for 52 weeks total) at dosages that averaged 435 mg/day. For most patients, their maintenance dose was that at which they were euthymic. However, 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.

HOW SUPPLIED

SERZONE® tablets are hexagonal tablets imprinted with BMS and the strength (i.e., 100 mg) on one side and the identification code number on the other. The 100 mg and 150 mg tablets are bisect scored. In addition, the 200 mg tablets have a green band and the 250 mg tablets have a magenta band.

NDC Code Description

<table>
<thead>
<tr>
<th>NDC Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0087-0031-47</td>
<td>50 mg light pink tablet, bottle of 60</td>
</tr>
<tr>
<td>0087-0032-31</td>
<td>100 mg white tablet, bottle of 60</td>
</tr>
<tr>
<td>0087-0039-31</td>
<td>150 mg peach tablet, bottle of 60</td>
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<tr>
<td>0087-0033-31</td>
<td>200 mg light yellow tablet, bottle of 60</td>
</tr>
<tr>
<td>0087-0041-31</td>
<td>250 mg white tablet, bottle of 60</td>
</tr>
</tbody>
</table>

Bristol-Myers Squibb Company
PATIENT INFORMATION

SERZONE®
(nefazodone hydrochloride) Tablets

Read this information completely before using SERZONE. Read the information each time you get more medicine. There may be new information. This leaflet provides a summary about SERZONE and does not include everything there is to know about your medicine. This information is not meant to take the place of talking with your doctor.

Before taking this medication, be sure to check the tablets imprinted with “BMS” and “50” on one face of the tablet; tablets imprinted with “BMS” and “100” on one face of the tablet; tablets imprinted with “BMS” and “150” on one face of the tablet; tablets imprinted with “BMS” and “200” on one face of the tablet; and tablets imprinted with “BMS” and “250” on one face of the tablet.

What is the most important information that I should know about SERZONE?

Rarely, people who take SERZONE can develop serious liver problems. If you get any of the following symptoms while taking SERZONE, call your doctor right away because you may be developing a liver problem:

- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Nausea
- Abdominal (lower stomach) pain

People who currently have liver problems should not take SERZONE.

What is SERZONE?

SERZONE (pronounced sir-ZONE) is a medicine used to treat depression. SERZONE is thought to treat depression by correcting an imbalance in the amounts of certain natural chemicals, such as serotonin and norepinephrine, which are in your brain.

Who should not take SERZONE?

Do not take SERZONE if you

- are allergic to SERZONE or the related medicine Desyrel® (trazodone);
- are taking Seldane® (terfenadine), an antihistamine; Hismanal® (astemizole), an antihistamine; Propulsid® (cisapride), used for heartburn; Halcion® (triazolam), used for insomnia; Orap® (pimozide), used to treat Tourette's syndrome; or Tegretol® (carbamazepine), used to control seizures;
- currently have liver problems;
- are taking or have taken within the last 14 days one of the medicines for depression known as monoamine oxidase inhibitors (MAOIs), such as Nardil® or Parnate®;
- are pregnant or breast-feeding.

Be sure to tell your doctor if you

- have ever had liver problems;
- are taking any other medicine, vitamin supplement, or herbal remedy, including those sold without a prescription (over-the-counter);
- have heart problems or have had a heart attack or stroke;
- have had manic episodes (extreme agitation or excitability);
- have ever attempted suicide;
- have had convulsions (seizures);
- are pregnant or breast-feeding.

How should I take SERZONE?

- Take SERZONE at the same time every day exactly as prescribed by your doctor. You may take SERZONE with or without food.
- It may take a while for you to feel that SERZONE is working. You may not feel the full effect for several weeks. Once you feel better, it is important to keep taking SERZONE as directed by your doctor.
- If you miss a dose of SERZONE, skip that dose and continue with your regular schedule. Never take 2 doses at the same time.
- If you think that you have taken more SERZONE than prescribed, contact your doctor, local poison control center, or emergency room right away.

What should I avoid while taking SERZONE?

- Do not drive or operate possibly dangerous machinery (such as an automobile, power mower, or power tool) or participate in any hazardous activity that requires full mental alertness until you know how SERZONE affects you.
- Before taking SERZONE, tell your doctor about any medicines you are taking, including vitamin supplements, herbal remedies, and any non-prescription (over-the-counter) medicines. Some of these medicines may affect how SERZONE works and should not be used in combination without talking to your doctor.
- Do not drink alcoholic beverages while taking SERZONE.
- Tell your doctor if you are pregnant, planning to become pregnant, or become pregnant while taking SERZONE. It is not known whether SERZONE can harm your unborn baby.
- Talk with your doctor before taking SERZONE if you are breast-feeding. It is not known whether SERZONE can pass through your breast milk to the baby.

What are the possible side effects of SERZONE?

The most common side effects of SERZONE (nefazodone hydrochloride) are sleepiness, dry mouth, nausea, dizziness, constipation, weakness, lightheadedness, problems with vision, and confusion.

Call your doctor right away if you have any of the following side effects:

- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Severe nausea
- Abdominal (lower stomach) pain
- Rash or hives
- Seizure (convulsion)
- Fainting
- Erection that lasts too long

Tell your doctor right away about any side effects that you have or discomfort that you experience. Do not change your dose or stop taking SERZONE without talking with your doctor first.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Your doctor has prescribed SERZONE for you and you alone. Do not give SERZONE to other people, even if they have the same condition. It may harm them.

This leaflet provides a summary of the most important information about SERZONE. If you would like more information, talk with your doctor or pharmacist. You can ask for information about SERZONE that is written for healthcare professionals. You can also get more information by visiting www.serzone.com.

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