After oral administration of radiolabeled nefazodone, the mean half-life of total labeled range between 11 and 24 hours. Approximately 55% of the administered radiolactivity 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 0.2 to 0.8 L/kg. At concentrations in the therapeutic range, approximately 60% of the drug 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 to an average of 1.25. In these studies, 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 lidocaine 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 nefa- zodone by approximately 20%.

Nefazodone in studies involving 296 randomly assigned patients, renal impairment (creatinine clearances ranging from 7 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 nefa- zodone 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. Weight of dose, however, differences were much smaller (9–15%). A similar result was seen for gender, with a higher Cmax and AUC in women after single doses but no difference after multiple doses.

Clinical Efficacy Trial Results

Studies in Outpatients with Depression

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

One trial was a 6-week dose-titration study comparing SERZONE in two dose ranges (up to 300 mg/day and up to 600 mg/day [mean modal dose for this group was about 400 mg/day], on a BID schedule) and placebo. The second trial was an 8-week dose-titration study comparing SERZONE (up to 600 mg/day, mean modal dose 275 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: the Hamilton Depression Rating Scale (Ham-D) and Hamilton Anxiety Rating Scale, the Clinical Global Impressions (CGI) Severity score, and CGI Improvement score. Significant differences were also found for certain factors of the HRS (e.g., anxiety factor, sleep disturbance factor, and ratings for everyday function). In the two 8-week trials, the CGI severity scores were especially important. Results from the first study are explained by the "high" rate of spontaneous improvement among the patients randomized to placebo. Results from the "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 (HOPS total score ≤10) after a 16-week open trial of the same active drug but who were suffering from a second episode of depression. One of these studies 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 in the total sample of patients treated for the second episode. 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 investigation, comparisons among drugs have been difficult. Studies evaluating the effects of antidepressant drugs on depression in nonclinical populations are inherently unreliable. Because conditions of testing (e.g., patient samples, investigators, doses of the treatments administered and compared, outcome measures, etc.) vary among such trials, it is virtually impossible to draw a clinical 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 closely to the DSM-III-R or DSM-IV-TR category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually occurs with or without associated vegetative symptoms. However, drug trials are generally inappropriate for evaluating antidepressant treatment of drug-induced 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 idea. 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).

Access to this document is restricted to patients who are currently receiving treatment with SERZONE. Upon discontinuation, these patients may be re-challenged to the drug if treatment is subsequently reinstated. Other patients may not be considered for re-treatment.

SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRE- CAUTIONS: Information for Patients). Patients who develop evidence of hepatic cellular 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 hepatic failure if levels are sustained for more than 2-4 weeks. 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 (MAOIs).

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-dihydropyridine-3-one hydrochloride. The molecular formula is C25H29ClN2O2.HCl and the molecular weight is 425.93. The primary structure of nefazodone is shown below:

\[
\text{C}_2\text{H}_5\text{Cl}\text{N}_2\text{O}_2\cdot\text{HCl}
\]

Nefazodone hydrochloride is a non-norergic, white crystalline solid. It is freely soluble in chloroform, relatively soluble in alcohol and methylene chloride, and sparingly soluble in water.

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-HT2 receptors at nanomolar concentrations, and acts as an antago-nist at this receptor. Nefazodone was shown to antagonize alpha-1 adrenergic receptors, a property which may be associated with postural hypotension.

Nefazodone is rapidly and completely absorbed but is subject to extensive metabolism, and can complicate patient monitoring. Nefazodone or its active metabolites may be excreted in breast milk and should be used with caution in nursing mothers.

Nefazodone is metabolized in vivo to at least 15 metabolites. Five of these metabolites (including hydroxynefazodone [HO-NEF], mCPP, 5-ethyl-2,4-dihydro-1H-3-[3-(3-chlorophenyl)-1-piperaizinylpropyl]-1-piperazinylpropyl-5-ethyl-2,4-dih- ydro-1H-3-phenoxynil-3H-1,2,4-triazole-3-one monohydrochloride) are pharmacologically active.

Attempts to characterize three metabolites identified in plasma, hydroxynefazodone (HO-NEF), meta- bolite A and mCPP, were not successful.

Clinical Pharmacokinetics

 Pharmacokinetics

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The coadministration of carbamazepine 200 mg BID with nefazodone 200 mg BID, at steady state for
Interaction with Carbamazepine
bitor of CYP3A4. Consequently, it is recommended that nefazodone not be used in combination
cases of serious cardiovascular adverse events, including death, due principally to ventricular
3A4 (CYP3A4) isozyme, and it has been demonstrated that ketoconazole, erythromycin, and
SERZONE (nefazodone hydrochloride).
When alprazolam (1 mg BID) and nefazodone (200 mg BID) were coadministered, steady-state peak
Alprazolam
enhances the likelihood for recovery.
Ongoing clinical assessment of patients should govern physician interven-
tions, including diagnostic evaluations and treatment.
SERZONE should be discontinued if clinical signs or symptoms suggest liver failure (see PRE-
CAUTIONS: Information for Patients). Patients who develop evidence of hepatic cellular injury such as
jaundice, dark urine, and pain in the upper right quadrant of the abdomen should be discontinued
Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia,
jaundice, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immedi-
ately. If severe hepatic dysfunction is established, patients should govern physician interven-
tions, including diagnostic evaluations and treatment.
Serotonin syndrome: Successful outcomes have been reported in patients who have recently discon-
Interaction with Monoamine Oxidase Inhibitors
patients receiving antidepressants with pharmacological properties similar to nefazodone in
combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious,
some reported to occur in patients receiving a selective serotonin reuptake inhibitor (SSRI), these
have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluc-
tuations 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 discon-
continued drug and that have been started on an MAOI. Some cases presented with features
resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal,
total. These cases have also been reported in patients who have recently discon-
trials and MAOIs. These reactions have also been reported in patients who have recently discon-
tined these drugs and have been started on an MAOI.
Although the effects of combined use of nefazodone and MAOIs have not been evaluated in humans,
additional precautions of the use of MAOIs is an issue of concern, the risk of
Interaction with Triazolobenzodiazepines
Interactions 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 1.7-5-fold.
Nefazodone has a significant effect on triazolam metabolism by triazolam.
Coadministration of nefazodone
potentially the effects of triazolam on psychomotor performance tests. If triazolam is coadminis-
tered with SERZONE, a 75% reduction in the initial triazolam dosage is recommended. Because not
levels < 2 times the upper limit of normal, while on
SERZONE should be withdrawn from the drug. These patients should be presumed to be at an increased risk for liver failure 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, such as
phenylpiperazine antidepressants. SERZONE tablets are contraindicated in patients who were withdrawn from SERZONE because of evidence of MAO activity. 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 electrocardio-
grams of 1153 patients who received nefazodone in 6- to 8-week, double-blind, placebo-controlled tri-
als did not indicate that nefazodone is associated with the development of clinically important ECG abnormalities. However, sinal bradycardia, defined as heart rate <50 bpm and a decrease of at least 20 bpm from baseline, was observed in 1.5% of nefazodone-treated patients compared to 0.4% of placebo-treated patients (p<0.05). Because patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical trials, such patients should be treated with caution.
In patients with cirrhosis of the liver, the AUC values of nefazodone and H2-NEF were increased by approximately 25%.
Information for Patients (See Patient Information.)
Physicians are advised to discuss the following issues with patients for whom they prescribe SERZONE:
Hepatotoxicity
Patients should be informed that SERZONE therapy has been associated with liver abnormalities rang-
ing from mild elevations of liver function tests to rare reports of severe hepatic injury leading to death
or transplantation, including fatal outcomes. About 16% of patients who received nefazodone in 6- to 8-week, double-blind, placebo-controlled tri-
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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 electrocardio-
rhythm and may occur in both the average patient and those with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotent-
In patients receiving 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).
Prapiam
While prapiam did not occur during premarketing experience with nefazodone, rare reports of prapiam have been received since market introduction. A causal relationship to nefazodone has not been estab-
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In patients with cirrhosis of the liver, the AUC values of nefazodone and H2-NEF were increased by approximately 25%.
Pharmacokinetics of Nefazodone in ‘Poor Metabolizers’ and Potential Interaction with Drugs that Inhibit or Are Metabolized by Cytochrome P450 Isozymes

Although nefazodone is extensively metabolized by multiple CYP isoenzymes, a subset (3% to 10%) of the population has reduced activity of the drug-metabolizing CYP2D6 isozyme (see CONTRAINDICATIONS and WARNINGS). Because nefazodone is a CYP2D6 substrate, the pharmacokinetics of nefazodone and its active metabolites may be altered in some patients. Therefore, dosage adjustment of either nefazodone or desipramine is necessary and dose adjustments should be made on the basis of clinical response. CYP2D6 Metabolism—In a study of healthy adult volunteers who had received SERZONE 200 mg BID for 7 days, although there was a 23% decrease in peak nefazodone plasma concentrations or time of peak, this change is of unknown clinical significance and did not suggest a pharmacokinetic interaction in warfarin dosages required when nefazodone is administered to patients stabilized on warfarin, such patients should be monitored as required by standard medical practices.

Fluoxetine—When fluoxetine (20 mg QD) and nefazodone (200 mg BID) were administered at 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.

Trazodone/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.

Sertraline—Sertraline is not known to affect the metabolism of nefazodone, and nefazodone is not known to affect the metabolism of sertraline. The concomitant use of nefazodone and sertraline should be monitored and dosage adjusted accordingly, respectively.

Electroconvulsive Therapy (ECT) and Electroshock Therapy—In a small case series of depressed patients who received nefazodone in combination with ECT or electroshock therapy, nefazodone was well tolerated. Phenytoin—Pretreatment for 7 days with 200 mg BID of nefazodone had no effect on the pharmacokinetics of phenytoin when phenytoin was given at steady state (200 mg BID) as 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 29%, respectively). In clinical practice, however, the 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 pharmacokinetic interaction of carbamazepine to result in insufficient plasma nefazodone and hydroxynefazodone concentrations for achieving an antidepressant effect for SERZONE, it is recommended that SERZONE be not used in combination with carbamazepine (see CONTRAINDICATIONS and WARNINGS).

General Anesthetics—Little is known about the potential for interaction between nefazodone and general anesthetics; therefore, prior to elective surgery, SERZONE should be discontinued for as long as clinically feasible.

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

Other Drugs Highly Bound to Plasma Protein

Because nefazodone is highly bound to plasma protein (see CLINICAL PHARMACOLOGY: Pharmacokinetics), administration of SERZONE (nefazodone hydrochloride) to a patient taking another drug characterized by high protein binding, could result in displacement of that other drug from the same site of plasma binding, with resultant decrease in the plasma level of that other drug. Consequently, if a patient on SERZONE requires concomitant treatment with a drug highly bound to plasma protein, the drug or SERZONE should be discontinued for several half-lives of the other drug, or an alternative therapy should be selected. Should nefazodone administration be resumed, caution should be exercised in monitoring the patient for evidence of an adverse effect from the other drug.

Warfarin—There were no effects on the prothrombin or bleeding times or upon the pharmacokinetics of either drug when warfarin was coadministered for 1 week to healthy adult volunteers (n = 18). In the same study, no significant differences were found in warfarin dosages required when nefazodone is administered to patients stabilized on warfarin, such patients should be monitored as required by standard medical practices.

Further studies are being conducted to determine the appropriate dose and dose adjustment, if any, for nefazodone when coadministered with warfarin. These studies include:

1. Measurement of prothrombin time and International Normalized Ratio in a larger group of volunteers.
2. Measurement of the anti-Xa levels of unfractionated heparin and low molecular weight heparin in stable patients on these agents.
3. In the previously mentioned study, a comparison of the many anticoagulants in patients taking ACE inhibitors, aspirin, or warfarin.

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.

Drug Interactions

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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 under 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 a drop rate approximately twice or greater for SERZONE compared to placebo) included nausea (3.5%), dizziness (1.9%), insomnia (1.5%), 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 (8%), rash (6%), 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-weeks) 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 nondonor factors to the side-effect incidence rate in the population studied.

Treatment-Emergent Adverse Experience Incidence in 6- to 8-Week Placebo-Controlled Clinical Trials1, SERZONE 300 to 600 mg/day Dose Range

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>SERZONE (n=393)</th>
<th>Placebo (n=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body System</td>
<td>Preferring Term</td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Headache</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Flu syndrome</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
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<tr>
<td></td>
<td>Fever</td>
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<td>Neck rigidity</td>
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<tr>
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<td>Pruritus</td>
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<td>Rash</td>
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<tr>
<td>Gastrointestinal</td>
<td>Dry mouth</td>
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<tr>
<td></td>
<td>Nausea</td>
<td>22</td>
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<tr>
<td></td>
<td>Constipation</td>
<td>14</td>
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<tr>
<td></td>
<td>Dyspepsia</td>
<td>9</td>
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<tr>
<td></td>
<td>Diarrhea</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Increased appetite</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nausea &amp; vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Peripheral edema</td>
<td>3</td>
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<tr>
<td></td>
<td>Thirst</td>
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<td>Musculoskeletal</td>
<td>Arthralgia</td>
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<tr>
<td>Nervous</td>
<td>Somnolence</td>
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<tr>
<td></td>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Lightheadedness</td>
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<tr>
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<td>Confusion</td>
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</tr>
<tr>
<td></td>
<td>Memory impairment</td>
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<td></td>
<td>Parasthesia</td>
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<td></td>
<td>Vasodilatation2</td>
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<tr>
<td></td>
<td>Abnormal dreams</td>
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<td>Concentration decreased</td>
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<td>Incoordination</td>
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<td>Behavioral</td>
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<tr>
<td></td>
<td>Confusion</td>
<td>21</td>
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<tr>
<td></td>
<td>Hallucination</td>
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<td></td>
<td>Taste perversion</td>
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<td>Visual field defect</td>
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<td></td>
<td>Urinary tract infection</td>
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<td>Urinary retention</td>
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<td></td>
<td>Sexual dysfunction</td>
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<tr>
<td></td>
<td>Breast pain5</td>
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</tr>
</tbody>
</table>

1 Events reported by at least 1% of patients treated with SERZONE and more frequently than the placebo group are included. Incidence is rounded to the nearest 1% (<1% indicates an incidence less than 0.5%). Events for which the SERZONE (nefazodone hydrochloride) incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, back pain, accidental injury, chest pain, neck pain, palpitation, migraine, sweating, flatulence, vomiting, anorexia, tooth disorder, weight gain, edema, myalgia, cramp, agitation, anxiety, depression, hypotension, CNS stimulation, dysphoria, emotional lability, suicidality, irritability, dysmenorrhea, dysuria.

Dose Dependency of Adverse Events in Placebo-Controlled Trials

The table that follows enumerates adverse events that were more frequent in the SERZONE dose range of 300 to 600 mg/day than in the SERZONE dose range of up to 300 mg/day. This table shows only those adverse events for which there was a statistically significant difference (p<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 Trials1

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>SERZONE 300 to 600 mg/day (n=209)</th>
<th>SERZONE ≤300 mg/day (n=211)</th>
<th>Placebo (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body System</td>
<td>Preferring Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Nervous</td>
<td>Somnolence</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abnormal vision</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Tinnitus</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Events for which there was a statistically significant difference (p<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 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.)

Vaginal (See PRECAUTIONS, Pastoral 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 increase in hematocrit (≥35% male or ≥33% female) compared to 1.5% of placebo patients (0.05<p<0.01). 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.

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 Premeartking Evaluation of SERZONE

During its premarketing assessment, the highest doses of SERZONE were administered to 3406 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. Unfoward 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.
DRUG ABUSE AND DEPENDENCE

Substance Class

SRZONE 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 to the side effects of CNS-active drugs. It may also be appropriate to modify the rate of subse-

NUMBER SUPPLIED

SRZONE 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 bisected scored on both tablet faces. The 50 mg, 200 mg, and 250 mg tablets are unscored.

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

STORE at room temperature, below 40° C (104° F) and dispense in a tight container.
**PATIENT INFORMATION**

**SERZONE® (nefazodone hydrochloride) Tablets**

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

**Before taking this medication, be sure to check the tablets in the bottle to make sure they match one of the following descriptions:**
- 50 mg tablets are six-sided, light pink tablets imprinted with “BMS” and “50” on one face of the tablet;
- 100 mg tablets are six-sided, white tablets imprinted with “BMS” and “100” on one face of the tablet;
- 150 mg tablets are six-sided, peach-colored tablets imprinted with “BMS” and “150” on one face of the tablet;
- 200 mg tablets are six-sided, light yellow tablets imprinted with “BMS” and “200” on one face of the tablet; and
- 250 mg tablets are six-sided, white tablets imprinted with “BMS” and “250” on one face of the tablet.

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

Rarely, people who take SERZONE can develop serious liver problems. If you get any of the following symptoms while taking SERZONE, call your doctor right away because you may be developing a liver problem:
- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Nausea
- Abdominal (lower stomach) pain

People who currently have liver problems should not take SERZONE.

**What is SERZONE?**

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

**Who should not take SERZONE?**

Do not take SERZONE if you
- are allergic to SERZONE or the related medicine Desyrel® (trazodone);
- are taking Seldane® (terfenadine), an antihistamine; Hismanal® (astemizole), an antihistamine; Propulsid® (cisapride), used for heartburn; Halcion® (triazolam), used for insomnia; Orap® (pimozide), used to treat Tourette’s syndrome; or Tegretol® (carbamazepine), used to control seizures.
- currently have liver problems.
- are taking or have taken within the last 14 days one of the medicines for depression known as monoamine oxidase inhibitors (MAOIs), such as Nardil® or Parnate®.

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

**How should I take SERZONE?**

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

**What should I avoid while taking SERZONE?**

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

**What are the possible side effects of SERZONE?**

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

**Call your doctor right away if you have any of the following side effects:**
- Yellowing of the skin or whites of eyes (jaundice)
- Unusually dark urine
- Loss of appetite that lasts several days or longer
- Severe nausea
- Abdominal (lower stomach) pain
- Rash or hives
- Seizure (convulsion)
- Fainting
- Erection that lasts too long

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

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

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

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