**of nefazodone hydrochloride tablets or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Nefazodone hydrochloride tablets are not approved for use in pediatric patients (see WARNINGS, Clinical Worsening and Suicide Risk; PRECAUTIONS, Information for Patients; and PRECAUTIONS, Pediatric Use).**

Before prescribing nefazodone hydrochloride tablets, the physician should be thoroughly familiar with the details of this prescribing information.

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

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

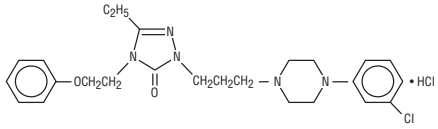
**Patients should be advised to be alert for signs and symptoms of liver dysfunction (jaundice, anorexia, gastrointestinal complaints, malaise, etc.) and to report them to their doctor immediately if they occur.**

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

## DESCRIPTION

Nefazodone hydrochloride tablets USP are an antidepressant for oral administration with a chemical structure unrelated to selective serotonin reuptake inhibitors, tricyclics, tetracyclics, or monoamine oxidase inhibitors (MAOI).

Nefazodone hydrochloride is a synthetically derived phenylpiperazine antidepressant. The chemical name for nefazodone hydrochloride is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one monohydrochloride. The structural formula is:



$C_{25}H_{32}ClN_5O_2 \cdot HCl$ M.W. 506.5

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

Nefazodone hydrochloride tablets USP are supplied as capsule-shaped tablets containing 50 mg, 100 mg, 150 mg, 200 mg, or 250 mg of nefazodone hydrochloride and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and povidone. Additionally, the 50 mg tablets include ferric oxide red as a colorant, the 150 mg tablets include ferric oxide red and yellow as colorants, and the 200 mg tablets include ferric oxide yellow as a colorant.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

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

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

Nefazodone occupies central 5-$HT_2$ receptors at nanomolar concentrations, and acts as an antagonist at this receptor. Nefazodone was shown to antagonize alpha$_1$-adrenergic receptors, a property which may be associated with postural hypotension. *In vitro* binding studies showed that nefazodone had no significant affinity for the following receptors: alpha$_2$ and beta adrenergic, 5-$HT_{1A}$, cholinergic, dopaminergic, or benzodiazepine.

### Pharmacokinetics

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

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

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

**AUC Multiples and $T_{1/2}$ for Three Metabolites of Nefazodone (100 mg BID)**

| Metabolite | AUC Multiple | $T_{1/2}$ |
|---|---|---|
| HO-NEF | 0.4 | 1.5 to 4 h |
| mCPP | 0.07 | 4 to 8 h |
| Triazole-dione | 4.0 | 18 h |

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

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

*Distribution*

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

*Protein Binding*

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

*Effect of Food*

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

*Renal Disease*

In studies involving 29 renally impaired patients, renal impairment (creatinine clearances ranging from 7 to 60 mL/min/1.73 m$^2$) 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 to 45 years) and older patients (> 65 years), $C_{max}$ 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 nefazodone was evaluated at doses within the therapeutic range in five well-controlled, short-term (6 to 8 weeks) clinical investigations. These trials enrolled outpatients meeting DSM-III or DSM-IIIR criteria for major depression. Among these trials, two demonstrated the effectiveness of nefazodone, and two provided additional support for that conclusion.

One trial was a 6 week dose-titration study comparing nefazodone 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 nefazodone (up to 600 mg/day; mean modal dose was 375 mg/day), imipramine (up to 300 mg/day), and placebo, all on a BID schedule. Both studies demonstrated nefazodone, at doses titrated between 300 mg to 600 mg/day (therapeutic dose range), to be superior to placebo on at least three of the following four measures: 17 Item Hamilton Depression Rating Scale or HDRS (total score), Hamilton Depressed Mood item, Clinical Global Impressions (CGI) Severity score, and CGI Improvement score. Significant differences were also found for certain factors of the HDRS (e.g., anxiety factor, sleep disturbance factor, and retardation factor). In the two supportive studies, nefazodone was titrated up to 500 or 600 mg/day (mean modal doses of 462 mg/day and 363 mg/day). In the fifth study, the differentiation in response rates between nefazodone and placebo was not statistically significant. Three additional trials were conducted using subtherapeutic doses of nefazodone.

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

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

*Studies in "Inpatients"*

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

*Studies of "Relapse Prevention in Patients Recently Recovered (Clinically) From Depression"*

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

*Comparisons of Clinical Trial Results*

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

## INDICATIONS AND USAGE

Nefazodone hydrochloride tablets are indicated for the treatment of depression. When deciding among the alternative treatments available for this condition, the prescriber should consider the risk of hepatic failure associated with nefazodone hydrochloride treatment (see **WARNINGS**). In many cases, this would lead to the conclusion that other drugs should be tried first.

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

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

The efficacy of nefazodone in reducing relapse in patients with major depression who were judged to have had a satisfactory clinical response to 16 weeks of open-label nefazodone treatment for an acute depressive episode has been demonstrated in a randomized placebo-controlled trial (see **CLINICAL PHARMACOLOGY**). Although remitted patients were followed for as long as 36 weeks in the study cited (i.e., 52 weeks total), the physician who elects to use nefazodone for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

## CONTRAINDICATIONS

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

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

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

## WARNINGS

### Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1**.

**Table 1**

| Age Range | Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated |
|---|---|
| | Increases Compared to Placebo |
| < 18 | 14 additional cases |
| 18 to 24 | 5 additional cases |
| | Decreases Compared to Placebo |
| 25 to 64 | 1 fewer case |
| ≥ 65 | 6 fewer cases |

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

The following symptoms, anxiety, agitation, panic at aggressiveness, impulsivity, akathisia (psychomotor re have been reported in adult and pediatric patients being depressive disorder as well as for other indications, Although a causal link between the emergence of such s depression and/or the emergence of suicidal impulses has that such symptoms may represent precursors to emergi

Consideration should be given to changing the ther discontinuing the medication, in patients whose depre are experiencing emergent suicidality or symptoms tha depression or suicidality, especially if these symptoms a part of the patient's presenting symptoms.

**Families and caregivers of patients being treate depressive disorder or other indications, both psy be alerted about the need to monitor patients for the unusual changes in behavior, and the other symptor emergence of suicidality, and to report such sym providers. Such monitoring should include daily obse** Prescriptions for nefazodone hydrochloride tablets shou of tablets consistent with good patient management, in

*Screening Patients for Bipolar Disorder*

A major depressive episode may be the initial presentat believed (though not established in controlled trials) t antidepressant alone may increase the likelihood of pre patients at risk for bipolar disorder. Whether any of the such a conversion is unknown. However, prior to initia patients with depressive symptoms should be adequatel risk for bipolar disorder; such screening should include a family history of suicide, bipolar disorder, and depressi hydrochloride tablets are not approved for use in treating

*Angle-Closure Glaucoma*

The pupillary dilation that occurs following use of r nefazodone hydrochloride tablets may trigger an ang anatomically narrow angles who does not have a patent i

### Hepatotoxicity

(See **BOXED WARNING**.)

**Cases of life-threatening hepatic failure have been nefazodone hydrochloride tablets.**

**The reported rate in the United States is about 1 case transplant per 250,000 to 300,000 patient-years of ne a rate of about 3 to 4 times the estimated backgroun underestimate because of under reporting, and the tru than this. A large cohort study of antidepressant users to death or transplant among nefazodone users in abo The spontaneous report data and the cohort study resul lower limits of the risk of liver failure in nefazodone-tr providing a precise risk estimate.**

**The time to liver injury for the reported liver failure c generally ranged from 2 weeks to 6 months on nefazo described dark urine and nonspecific prodromal symp gastrointestinal symptoms), other reports did not de symptoms prior to the onset of jaundice.**

**The physician may consider the value of liver function testing has not been proven to prevent serious injury l detection of drug-induced hepatic injury along with imm enhances the likelihood for recovery.**

**Patients should be advised to be alert for signs and sy anorexia, gastrointestinal complaints, malaise, etc.) immediately if they occur. Ongoing clinical assessmen interventions, including diagnostic evaluations and tre**

**Nefazodone should be discontinued if clinical signs (see PRECAUTIONS, Information for Patients). P hepatocellular injury such as increased serum AST or limit of NORMAL, while on nefazodone should be with should be presumed to be at increased risk for liver Accordingly, such patients should not be considered fo**

**Potential for Interaction With Monoamine Oxidase Inhi In patients receiving antidepressants with pharmacolog in combination with a monoamine oxidase inhibitor serious, sometimes fatal, reactions. For a selective ser reactions have included hyperthermia, rigidity, myoclon rapid fluctuations of vital signs, and mental status ch progressing to delirium and coma. These reactions who have recently discontinued that drug and have be presented with features resembling neuroleptic malignan seizures, sometimes fatal, have been reported in associa antidepressants and MAOIs. These reactions have also recently discontinued these drugs and have been started**

**Although the effects of combined use of nefazodone a humans or animals, because nefazodone is an inhibitor reuptake, it is recommended that nefazodone not be u within 14 days of discontinuing treatment with an MAO after stopping nefazodone before starting an MAOI.**

**Interaction With Triazolobenzodiazepines**

Interaction studies of nefazodone with two triazolo alprazolam, metabolized by cytochrome P450 3A4, ha important increases in plasma concentrations of th concomitantly with nefazodone.

*Triazolam*

When a single oral 0.25 mg dose of triazolam was coadmi at steady state, triazolam half-life and AUC increased 4 f 1.7 fold. Nefazodone plasma concentrations were unaff ***of nefazodone potentiated the effects of triazolam o*** triazolam is coadministered with nefazodone, a 75% re is recommended. Because not all commercially availab sufficient dosage reduction, coadministration of triazolam most patients, including the elderly. In the exceptional ca with nefazodone may be considered appropriate, only should be used (see **CONTRAINDICATIONS** and **PRECAU**

*Alprazolam*

When alprazolam (1 mg BID) and nefazodone (200 mg B peak concentrations, AUC and half-life values for alp 2 fold. Nefazodone plasma concentrations were una is coadministered with nefazodone, a 50% reduction recommended. No dosage adjustment is required for nef

**Potential Terfenadine, Astemizole, Cisapride, and Pimo Terfenadine, astemizole, cisapride, and pimozide are all m (CYP3A4) isozyme, and it has been demonstrated that inhibitors of CYP3A4 can block the metabolism of these plasma concentrations of parent drug. Increased plasma co cisapride, and pimozide are associated with QT prolon cardiovascular adverse events, including death, due p the torsade de pointes type. Nefazodone has been shown Consequently, it is recommended that nefazodone not terfenadine, astemizole, cisapride, or pimozide** (see **CONTI**

**Interaction With Carbamazepine**

The coadministration of carbamazepine 200 mg BID steady state for both drugs, resulted in almost 95% re hydroxynefazodone, likely resulting in insufficient plasm concentrations for achieving an antidepressant effe is recommended that nefazodone not be used i (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

## PRECAUTIONS

### General

*Hepatotoxicity*

(See **BOXED WARNING**.)

*Postural Hypotension*

A pooled analysis of the vital signs monitored during pl revealed that 5.1% of nefazodone patients compared to 2 criteria for a potentially important decrease in blood pr (systolic blood pressure ≤ 90 mmHg *and* a change f there was no difference in the proportion of nefazodone events characterized as 'syncope' (nefazodone, 0.2%; p events characterized as 'postural hypotension' were as antidepressants (10.9%), SSRI (1.1%), and placebo

**NEFAZODONE HYDROCHLORIDE TABLETS USP**

**(Patient Information Included)**

7178
1024
7113
1025 Rev. M 5/2014
1026 322K063620514

℞ only

an eye examination to see if you are at risk and receive preventative treatment if you are.

- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Manufactured In Israel By:
**TEVA PHARMACEUTICAL IND. LTD.**
Jerusalem, 91010, Israel
Manufactured For:
**TEVA PHARMACEUTICALS USA**
Sellersville, PA 18960

Rev. F 5/2014

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 nefazodone without talking with your doctor first.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Your doctor has prescribed nefazodone for you and you alone. Do not give nefazodone 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 nefazodone. If you would like more information, talk with your doctor or pharmacist. You can ask for information about nefazodone that is written for healthcare professionals.

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Sellersville, PA 18960

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This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

Buspirone – In a study of steady-state pharmacokinetics in healthy volunteers, coadmini
of buspirone (2.5 or 5 mg BID) with nefazodone (250 mg BID) resulted in marked incre
plasma buspirone concentrations (increases up to 20 fold in $C_{max}$ and up to 50 fold i
and statistically significant decreases (about 50%) in plasma concentrations of the bu
metabolite 1-pyrimidinylpiperazine. With 5 mg BID doses of buspirone, slight incre
AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (17
mCPP (9%). Subjects receiving nefazodone 250 mg BID and buspirone 5 mg BID expe
lightheadedness, asthenia, dizziness, and somnolence, adverse events also observed wit
drug alone. If the two drugs are to be used in combination, a low dose of buspiron
2.5 mg QD) is recommended. Subsequent dose adjustment of either drug should be ba
clinical assessment.

Pimozide – See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS,** *Pharmacokin
Nefazodone in 'Poor Metabolizers' and Potential Interaction With Drugs That Inhibit an
Metabolized by Cytochrome P450 Isozymes.*

Fluoxetine – When fluoxetine (20 mg QD) and nefazodone (200 mg BID) were admi
at steady state there were no changes in the pharmacokinetic parameters for fluoxetin
metabolite, norfluoxetine. Similarly, there were no changes in the pharmacokinetic par
of nefazodone or HO-NEF; however, the mean AUC levels of the nefazodone metabolites
and triazole-dione increased by 3 to 6 fold and 1.3 fold, respectively. When a 200 mg
nefazodone was administered to subjects who had been receiving fluoxetine for 1 wee
was an increased incidence of transient adverse events such as headache, lighthead
nausea, or paresthesia, possibly due to the elevated mCPP levels. Patients who are s
from fluoxetine to nefazodone without an adequate washout period may experience
transient adverse events. The possibility of this happening can be minimized by allo
washout period before initiating nefazodone therapy and by reducing the initial dose of nefa
Because of the long half-life of fluoxetine and its metabolites, this washout period may ran
one to several weeks depending on the dose of fluoxetine and other individual patient varia

Phenytoin – Pretreatment for 7 days with 200 mg BID of nefazodone had no effect
pharmacokinetics of a single 300 mg oral dose of phenytoin. However, due to the n
pharmacokinetics of phenytoin, the failure to observe a significant effect on the sing
pharmacokinetics of phenytoin does not preclude the possibility of a clinically sig
interaction with nefazodone when phenytoin is dosed chronically. However, no change
initial dosage of phenytoin is considered necessary and any subsequent adjustment of ph
dosage should be guided by usual clinical practices.

Desipramine – When nefazodone (150 mg BID) and desipramine (75 mg QD) were admi
together there were no changes in the pharmacokinetics of desipramine or its met
2-hydroxy desipramine. There were also no changes in the pharmacokinetics of nefa
or its triazole-dione metabolite, but the AUC and $C_{max}$ of mCPP increased by 44% an
respectively, while the AUC of HO-NEF decreased by 19%. No changes in doses o
nefazodone or desipramine are necessary when the two drugs are given concor
Subsequent dose adjustments should be made on the basis of clinical response.

Lithium – In 13 healthy subjects the coadministration of nefazodone (200 mg BID) with
(500 mg BID) for 5 days (steady-state conditions) was found to be well tolerated. W
two drugs were coadministered, there were no changes in the steady-state pharmacokin
either lithium, nefazodone, or its metabolite HO-NEF; however, there were small decrease
steady-state plasma concentrations of two nefazodone metabolites, mCPP and triazole
which are considered not to be of clinical significance. Therefore, no dosage adjustment o
lithium or nefazodone is required when they are coadministered.

Carbamazepine – The coadministration of nefazodone (200 mg BID) for 5 days to 12
subjects on carbamazepine who had achieved steady state (200 mg BID) was found to
tolerated. Steady-state conditions for carbamazepine, nefazodone, and several of their met
were achieved by day 5 of coadministration. With coadministration of the two drug
were significant increases in the steady-state $C_{max}$ and AUC of carbamazepine (2
23%, respectively), while the steady-state $C_{max}$ and the AUC of the carbamazepine me
10,11 epoxycarbamazepine, decreased by 21% and 20%, respectively. The coadministratio
two drugs significantly reduced the steady-state $C_{max}$ and AUC of nefazodone by 86% an
respectively. Similar reductions in the $C_{max}$ and AUC of HO-NEF were also observed (8
94%), while the reductions in $C_{max}$ and AUC of mCPP and triazole-dione were more mode
and 44% for the former and 28% and 57% for the latter). Due to the potential for coadministr
carbamazepine to result in insufficient plasma nefazodone and hydroxynefazodone concen
for achieving an antidepressant effect for nefazodone, it is recommended that nefazodone
used in combination with carbamazepine (see **CONTRAINDICATIONS** and **WARNINGS**).

General Anesthetics – Little is known about the potential for interaction between nefazod
general anesthetics; therefore, prior to elective surgery, nefazodone hydrochloride sh
discontinued for as long as clinically feasible.

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

*Cimetidine*
When nefazodone (200 mg BID) and cimetidine (300 mg QID) were coadministered
week, no change in the steady-state pharmacokinetics of either nefazodone or cimetid
observed compared to each dosed alone. Therefore, dosage adjustment is not neces
either drug when coadministered.

*Theophylline*
When nefazodone (200 mg BID) was given to patients being treated with theo
(600 to 1200 mg/day) for chronic obstructive pulmonary disease, there was no chang
steady-state pharmacokinetics of either nefazodone or theophylline. $FEV_1$ measurement
when theophylline and nefazodone were coadministered did not differ from baseline dosa
when theophylline was administered alone). Therefore, dosage adjustment is not neces
either drug when coadministered.

*Cardiovascular-Active Drugs*
Digoxin – When nefazodone (200 mg BID) and digoxin (0.2 mg QD) were coadmi
for 9 days to healthy male volunteers (n = 18) who were phenotyped as CYP2D6 ex
metabolizers, $C_{max}$, $C_{min}$, and AUC of digoxin were increased by 29%, 27%, an
respectively. Digoxin had no effects on the pharmacokinetics of nefazodone and its
metabolites. Because of the narrow therapeutic index of digoxin, caution should be ex
when nefazodone and digoxin are coadministered; plasma level monitoring for dig
recommended.

Propranolol – The coadministration of nefazodone (200 mg BID) and prop
(40 mg BID) for 5.5 days to healthy male volunteers (n = 18), including 3 poor and 15 ex
CYP2D6 metabolizers, resulted in 30% and 14% reductions in $C_{max}$ and AUC of prop
respectively, and a 14% reduction in $C_{max}$ for the metabolite, 4-hydroxypropranolol. The
of nefazodone, hydroxynefazodone, and triazole-dione were not affected by coadministr
propranolol. However, $C_{max}$, $C_{min}$, and AUC of m-chlorophenylpiperazine were increa
23%, 54%, and 28%, respectively. No change in initial dose of either drug is necessary a
adjustments should be made on the basis of clinical response.

HMG-CoA Reductase Inhibitors – When single 40 mg doses of simvastatin or atorvastat
substrates of CYP3A4, were given to healthy adult volunteers who had received nefa
hydrochloride, 200 mg BID for 6 days, approximately 20 fold increases in plasma concen
of simvastatin and simvastatin acid and 3 to 4 fold increases in plasma concentrat
atorvastatin and atorvastatin lactone were seen. These effects appear to be due to the ir
of CYP3A4 by nefazodone because, in the same study, nefazodone had no significant e
the plasma concentrations of pravastatin, which is not metabolized by CYP3A4 to a
significant extent.

There have been rare reports of rhabdomyolysis involving patients receiving the com
of nefazodone and either simvastatin or lovastatin, also a substrate of CYP3A4 (see **AD
REACTIONS**, **Postintroduction Clinical Experience**). Rhabdomyolysis has been observed in
receiving HMG-CoA reductase inhibitors administered alone (at recommended dosage
in particular, for certain drugs in this class, when given in combination with inhibitors
CYP3A4 isozyme.

Caution should be used if nefazodone is administered in combination with HMG-CoA re
inhibitors that are metabolized by CYP3A4, such as simvastatin, atorvastatin, and lovasta
dosage adjustments of these HMG-CoA reductase inhibitors are recommended. Since m
interactions are unlikely between nefazodone and HMG-CoA reductase inhibitors that u
little or no metabolism by the CYP3A4 isozyme, such as pravastatin or fluvastatin,
adjustments should not be necessary.

*Immunosuppressive Agents*
There have been reports of increased blood concentrations of cyclosporine and tac
into toxic ranges when patients received these drugs concomitantly with nefazodon
cyclosporine and tacrolimus are substrates of CYP3A4, and nefazodone is known to
this enzyme. If either cyclosporine or tacrolimus is administered with nefazodone
concentrations of the immunosuppressive agent should be monitored and dosage a
accordingly.

*Pharmacokinetics of Nefazodone in 'Poor Metabolizers' and Potential Interaction With Dru
Inhibit and/or Are Metabolized by Cytochrome P450 Isozymes*
CYP3A4 Isozyme – Nefazodone has been shown *in vitro* to be an inhibitor of CYP3A
is consistent with the interactions observed between nefazodone and triazolam, alpr
buspirone, atorvastatin, and simvastatin, drugs metabolized by this isozyme. Conse
caution is indicated in the combined use of nefazodone with any drugs known to be met
by CYP3A4. In particular, the combined use of nefazodone with triazolam should be avo
most patients, including the elderly. The combined use of nefazodone with terfenadine, ast
cisapride, or pimozide is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS**).

CYP2D6 Isozyme – A subset (3% to 10%) of the population has reduced activity
drug-metabolizing enzyme CYP2D6. Such individuals are referred to commonly as
metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepr

an eye examination to see if you are at risk and receive preventative treatment if you are.

- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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