Anxiety Disorder Resources
There are a number of resources—online and offline—to help you get in contact with a mental health professional or other forms of support.

Anxiety Disorder Resources
If you think you or a loved one may have generalized anxiety disorder or panic disorder, talk to your doctor. Get more information about these conditions by visiting:

Generalized Anxiety Disorder and Panic Disorder Resources
Understanding Anxiety
• http://www.adaa.org/understanding-anxiety
• http://www.apa.org/topics/anxiety/index.aspx

Generalized Anxiety Disorder (GAD)
• http://www.adaa.org/generalized-anxiety-disorder-gad

Panic Disorder and Agoraphobia
• http://www.apa.org/topics/anxiety/panic-disorder.aspx

Anxiety Treatment Resources
If you or a loved one require additional help with managing anxiety, some resources include:

Treatment Settings

Self-help Publications
• http://www.adaa.org/finding-help/self-help-publications

Support Groups
• http://www.adaa.org/supportgroups

Other Resources for Support and Learning
• http://www.apa.org/helpcenter/index.aspx
• http://locator.apa.org/

Proper Use Resources
Psychological dependence is a risk with all medications called benzodiazepines, including XANAX. This risk may increase if someone:
• takes a dose greater than 4 mg/day for an extended period of time
• has a history of alcohol or drug abuse

Proper use may be an issue for some people taking XANAX. Some people have experienced considerable difficulty when tapering off of or stopping XANAX use, especially those taking higher dosages over a longer period. Anyone prone to addiction should be watched carefully when taking XANAX.

The following resources offer information about the proper and improper use of benzodiazepines:

Medication As Treatment
• http://www.adaa.org/finding-help/treatment/medication

Safety Concerns and Risk Factors
• http://www.helpguide.org/articles/anxiety/anxiety-medication.htm#safety

Drug Dependence and Withdrawal
• http://www.helpguide.org/articles/anxiety/anxiety-medication.htm#dependence

If you or a loved one think you see the warning signs of benzodiazepine abuse, call the Substance Abuse and Mental Health Services Administration’s (SAMHSA) National Helpline at 1-800-662-HELP (4357).

The websites mentioned are neither owned nor controlled by Pfizer. Pfizer does not endorse and is not responsible for the content or services of these sites.

XANAX tablets are available in 0.25, 0.5, 1, and 2 mg.

IMPORTANT SAFETY INFORMATION AND INDICATION

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
XANAX is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma, and death.

Please see additional Important Safety Information and Indication on next page and accompanying Full Prescribing Information, including BOXED WARNING and Medication Guide.
IMPORTANT SAFETY INFORMATION AND INDICATION (continued)

Do not take XANAX if you are allergic to alprazolam, other benzodiazepines, or any of the ingredients in XANAX.

Do not take XANAX if you are currently taking antifungal treatments including ketoconazole or itraconazole.

XANAX is a federal controlled substance (C-IV) because it can be abused or lead to dependence. Keep XANAX in a safe place to prevent misuse and abuse.

XANAX can make you sleepy or dizzy, and can slow your thinking and motor skills.

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how XANAX affects you.
- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking XANAX without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, XANAX may make your sleepiness or dizziness much worse.

Before you take XANAX, tell your healthcare provider about all of your medical conditions, including if you:

- Have or have had depression, mood problems, or suicidal thoughts or behavior.
- Have liver or kidney problems.
- Have lung disease or breathing problems.
- Are pregnant or plan to become pregnant. XANAX may harm your unborn baby. You and your healthcare provider should decide if you should take XANAX while you are pregnant.
- Are breastfeeding or plan to breastfeed. You should not breastfeed while taking XANAX.

Before taking XANAX, tell your healthcare provider about all prescriptions, over-the-counter medicines and supplements you take. Taking XANAX with certain other medicines can cause side effects or affect how well XANAX or the other medicines work.

Do not increase the dose of XANAX, even if you think it isn't working, without consulting your doctor. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.

Do not stop taking this medication abruptly or decrease the dose without consulting your doctor, since withdrawal symptoms can occur. Withdrawal symptoms can be serious and include seizures.

XANAX may cause an increase in activity and talking (hypomania and mania) in people who have depression.

The most common side effects of XANAX include drowsiness and light-headedness.

INDICATION

XANAX (alprazolam) is indicated for the management of anxiety disorders and the short-term relief of symptoms of anxiety in adults. XANAX is also indicated for the treatment of panic disorder in adults with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia).

The health information contained herein is provided for educational purposes only and is not intended to replace discussions with a healthcare provider. All decisions regarding patient care must be made with a healthcare provider, considering the unique characteristics of the patient.

Please see accompanying Full Prescribing Information, including BOXED WARNING and Medication Guide.
INDICATIONS AND USAGE

XANAX Tablets were compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety associated with depressive symptomatology. XANAX was significantly better than placebo at each of the evaluation periods of these 4-week studies as judged by the following psychometric instruments: Physician’s Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient’s Global Impressions and Self-Rating Symptom Scale.

Panic Disorder

Support for the effectiveness of XANAX in the treatment of panic disorder came from three short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R criteria for panic disorder.

The average dose of XANAX was 5-6 mg/day in two of the studies, and the doses of XANAX were fixed at 2 and 6 mg/day in the third study. In all three studies, XANAX was superior to placebo on a variable defined as “the number of patients with zero panic attacks” (range, 37-83% met this criterion), as well as on a global improvement score. XANAX were fixed at 2 and 6 mg/day in the third study. In all three studies, XANAX was superior to placebo on a variable defined as “the number of patients with zero panic attacks” (range, 37-83% met this criterion), as well as on a global improvement score.

CLINICAL STUDIES

Anxiety Disorders

XANAX Tablets are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-IV] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of 6 months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: Motor Tension (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); Autonomic Hyperactivity (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold flushes); abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat'); Vigilance and Scanning

Anxiety associated with depression is responsive to XANAX.
Occasional voluntary reports of patients developing seizures while apparently tapering from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in one instance, a single dose of 1 mg after tapering at a rate of 1 mg every 3 days was administered. Withdrawal symptoms were specifically sought, and the following were identified: tinnitus; (13) chills or hot flushes. The importance of dose and the risks of XANAX as a treatment for panic disorder: the risk of dependence among panic disorder patients may be considered severe. In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with XANAX compared to placebo-treated patients. Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline. In a controlled clinical trial in which 63 patients were randomized to XANAX and placebo, withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysomnia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound or withdrawal. In two controlled trials of 6 to 8 weeks duration the ability of patients to discontinue treatment was measured. 71%-93% of patients treated with XANAX tapered completely off therapy compared to 89%-96% of placebo-treated patients. In a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures attributable to XANAX were seen after drug discontinuation or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of XANAX greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from XANAX. The risk of seizure seems to be greatest 24-72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

Status Epilepticus and its Treatment
The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAX. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. Interdose Symptoms
Early morning anxiety and emergence of anxiety symptoms between doses of XANAX have been reported in patients with panic disorder taking therapeutic or supratherapeutic doses of XANAX. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

Risk of Dose Reduction
Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets to take the daily dose). Therefore, the dosage of XANAX should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

CNS Depression and Impaired Performance
Because of its CNS depressant effects, patients receiving XANAX should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with XANAX.

Risk of Fatal Harm
Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If XANAX is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, XANAX is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of the drug in the first trimester is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Alprazolam Interaction with Drugs that Inhibit Metabolism via Cytochrome P450 3A
The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving concomitant treatment with drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from in vitro data and/or experience with similar drugs in the same pharmacologic class. The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

Potent CYP3A Inhibitors
Azole antifungal agents—Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)
Nefazodone—Coadministration of nefazodone increased alprazolam concentration two-fold. Fluvoxamine—Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance. Cimetine—Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 88%, decreased clearance by 42%, and increased half-life by 160%. HIV protease inhibitors – Interactions involving HIV protease inhibitors (eg, ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset the inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

Other drugs possibly affecting alprazolam metabolism
Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS
General
Suicide
As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or
Use with Digoxin
Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Use with Impiramine and Desipramine
The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of XANAX Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Drugs that inhibit alprazolam metabolism via cytochrome P450 3A
The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)
Fluvoxetine—Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene—Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives—Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these benzodiazepines (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A
Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

Drug/Laboratory Test Interactions
Although interactions between benzodiazepines and commonly employed laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic in vitro in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy
Teratogenic Effects: See WARNINGS section.
Nonteratogenic Effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of women who have been receiving benzodiazepines.

Labor and Delivery
XANAX has no established use in labor or delivery.

Nursing Mothers
Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use XANAX.

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

Geriatric Use
The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective
dose of XANAX should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Side effects to XANAX Tablets, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, eg, drowsiness or light-headedness.

The data cited in the two tables below are estimates of untoward clinical event incidence among patients who participated under the following conditions: relatively short duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of XANAX (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of XANAX in patients with panic disorder, with or without agoraphobia.

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (eg, increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Anxiety Disorders

<table>
<thead>
<tr>
<th>ANXIETY DISORDERS</th>
<th>Treatment-Emergent Symptom Incidence</th>
<th>Incidence of Intervention Because of Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients Reporting:</td>
<td>XANAX</td>
<td>PLACEBO</td>
</tr>
<tr>
<td>% of Patients</td>
<td>565</td>
<td>505</td>
</tr>
</tbody>
</table>

Central Nervous System

Drowsiness 41.0 21.6 15.1
Light-headedness 20.8 19.3 1.2
Depression 13.9 18.1 2.4
Headache 12.9 19.6 1.1
Confusion 9.9 10.0 0.9
Insomnia 8.9 18.4 1.3
Nervousness 4.1 10.3 1.1
Syncope 3.1 4.0 1.1
Dizziness 1.8 0.8 2.5
Akathisia 1.6 1.2 1.8
Tiredness/Sleepiness * * 1.8

Gastrointestinal

Dry Mouth 14.7 13.3 0.7
Constipation 10.4 11.4 0.9
Diarrhea 10.1 10.3 1.2
Nausea/Vomiting 9.6 12.8 1.7
Increased Salivation 4.2 2.4 *

Cardiovascular

Tachycardia/Palpitations 7.7 15.6 0.4
Hypotension 4.7 2.2 *

Sensory

Blurred Vision 6.2 6.2 0.4

Musculoskeletal

Rigidity 4.2 5.3 *
Tremor 4.0 8.8 0.4

Cutaneous

Dermatitis/Allergy 3.8 3.1 0.6

Other

Nasal Congestion 7.3 9.3 *
Weight Gain 2.7 2.7 *
Weight Loss 2.3 3.0 *

* None reported

1 Events reported by 1% or more of XANAX patients are included.

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of XANAX: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

PANIC DISORDER

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Panic Disorder

<table>
<thead>
<tr>
<th>XANAX</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients Reporting:</td>
<td>1388</td>
</tr>
</tbody>
</table>

Central Nervous System

Drowsiness 76.8 42.7
Fatigue and Tiredness 48.6 42.3
Impaired Coordination 40.1 17.9
Irritability 33.1 30.1
Memory Impairment 33.1 22.1
Light-headedness/Dizziness 29.8 36.9
Insomnia 29.4 41.8
Headache 29.2 35.6
Cognitive Disorder 28.8 10.5
Dysarthria 23.3 6.3
Anxiety 16.6 24.9
Abnormal Involuntary Movement 14.8 21.0
Decreased Libido 14.4 8.0
Depression 13.8 14.0
Confusional State 10.4 8.2
Muscular Twitching 7.9 11.8
Increased Libido 7.7 4.1
Change in Libido (Not Specified) 7.1 5.6
Weakness 7.1 8.4
Muscle Tone Disorders 6.3 7.5
Syncope 3.8 4.8
Akathisia 3.0 4.3
Agitation 2.9 2.6
Disinhibition 2.7 1.5
Paresthesia 2.4 3.2
Talkativeness 2.2 1.0
Vasomotor Disturbances 2.0 2.6
Derealization 1.9 1.2
Dream Abnormalities 1.8 1.5
Fear 1.4 1.0
Feeling Warm 1.3 0.5

Gastrointestinal

Decreased Salivation 32.8 34.2
Constipation 26.2 15.4
Nausea/Vomiting 22.0 31.8
Diarrhea 20.6 22.8
Abdominal Distress 18.3 21.5
Increased Salivation 5.6 4.4

Cardio-Respiratory

Nasal Congestion 17.4 16.5
Tachycardia 15.4 26.8
Chest Pain 10.6 18.1
Hyperventilation 9.7 14.5
Upper Respiratory Infection 4.3 3.7

Sensory

Blurred Vision 21.0 21.4
Tinnitus 6.6 10.4

Musculoskeletal

Muscular Cramps 2.4 2.4
Muscle Stiffness 2.2 3.3

Cutaneous

Sweating 15.1 23.5
 rash 10.8 8.1

Other

Increased Appetite 32.7 22.8
Decreased Appetite 27.8 24.1
Weight Gain 27.2 17.9
Weight Loss 22.6 16.5
Micturition Difficulties 12.2 8.6
Menstrual Disorders 10.4 8.7
Sexual Dysfunction 7.4 8.7
Edema 4.9 5.6
Incontinence 1.5 0.6
Infection 1.3 1.7

* Events reported by 1% or more of XANAX patients are included.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients (see PRECAUTIONS, General).
In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received XANAX, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with XANAX and at a greater rate than the placebo treated group were as follows:

**DISCONTINUATION-EMERGENT SYMPTOM INCIDENCE**

<table>
<thead>
<tr>
<th>Body System/Event</th>
<th>Percentage of 641 XANAX-Treated Panic Disorder Patients Reporting Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>29.5 Gastrointestinal</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>19.3 Nausea/Vomiting</td>
</tr>
<tr>
<td>Abnormal involuntary movement</td>
<td>Decreased salivation</td>
</tr>
<tr>
<td>Headache</td>
<td>17.0 Metabolic-Nutritional</td>
</tr>
<tr>
<td>Muscular twitching</td>
<td>6.9 Weight loss</td>
</tr>
<tr>
<td>Impaired coordination</td>
<td>6.6 Decreased appetite</td>
</tr>
<tr>
<td>Muscle tone disorders</td>
<td>5.9</td>
</tr>
<tr>
<td>Weakness</td>
<td>5.8 Dermatological</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>19.2</td>
</tr>
<tr>
<td>Fatigue and Tiredness</td>
<td>18.4 Cardiovascular</td>
</tr>
<tr>
<td>Irritability</td>
<td>10.5 Tachycardia</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>10.0</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>5.5 Special Senses</td>
</tr>
<tr>
<td>Depression</td>
<td>5.1 Blurred vision</td>
</tr>
<tr>
<td>Confusional state</td>
<td>5.0</td>
</tr>
</tbody>
</table>

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with XANAX in patients with panic disorder. There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of XANAX in patients with posttraumatic stress disorder.

To discontinue treatment in patients taking XANAX, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

**Post Introduction Reports:** Various adverse drug reactions have been reported in association with the use of XANAX since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of XANAX cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens- Johnson syndrome, photosensitivity reaction, angioedema, peripheral edema, hyperplactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).
Panic Disorder

The successful treatment of many panic disorder patients has required the use of XANAX at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of XANAX in panic disorder, doses in the range of 1 to 10 mg daily were used. The mean dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received XANAX in dosages of greater than 7 mg/day, including approximately 100 patients who received maximum dosages of greater than 9 mg/day. Ocasional patients required as much as 10 mg a day to achieve a successful response.

Dose Titration

Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of XANAX. To lessen the possibility of interdose symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a three or four times per day schedule.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Maintenance

For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of XANAX greater than 4 mg/day for 3 months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE.)

The necessary duration of treatment for panic disorder patients responding to XANAX is unknown. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

Dose Reduction

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

Dosing in Special Populations

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given two or three times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.

HOW SUPPLIED

XANAX Tablets are available as follows:

0.25 mg (white, oval, scored, imprinted “XANAX 0.25”)
- Bottles of 100
- Bottles of 500
- Bottles of 1000
NDC 0009-0029-01
NDC 0009-0029-02
NDC 0009-0029-14

0.5 mg (peach, oval, scored, imprinted “XANAX 0.5”)  
- Bottles of 100
- Bottles of 500
- Bottles of 1000
NDC 0009-0055-01
NDC 0009-0055-03
NDC 0009-0055-15

1 mg (blue, oval, scored, imprinted “XANAX 1.0”)  
- Bottles of 100
- Bottles of 500
- Bottles of 1000
NDC 0009-0090-01
NDC 0009-0090-04
NDC 0009-0090-13

2 mg (white, oblong, multi-scored, imprinted “XANAX ” on one side and “2” on the reverse side)  
- Bottles of 100
- Bottles of 500
NDC 0009-0094-01
NDC 0009-0094-03

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

ANIMAL STUDIES

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.
What is the most important information I should know about XANAX?

- XANAX is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.

- XANAX can make you sleepy or dizzy, and can slow your thinking and motor skills.
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how XANAX affects you.
  - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking XANAX without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, XANAX may make your sleepiness or dizziness much worse.

- Do not take more Xanax than prescribed.

What is XANAX?

- XANAX is a prescription medicine used:
  - to treat anxiety disorders
  - for the short-term relief of the symptoms of anxiety
  - to treat panic disorder with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia)

- XANAX is a federal controlled substance (C-IV) because it can be abused or lead to dependence. Keep XANAX in a safe place to prevent misuse and abuse. Selling or giving away XANAX may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.

- It is not known if XANAX is safe and effective in children.

- Elderly patients are especially susceptible to dose related adverse effects when taking XANAX.

- It is not known if XANAX is safe and effective when used to treat anxiety disorder for longer than 4 months.

- It is not known if XANAX is safe and effective when used to treat panic disorder for longer than 10 weeks.

Do not take XANAX if:

- you are allergic to alprazolam, other benzodiazepines, or any of the ingredients in XANAX. See the end of this Medication Guide for a complete list of ingredients in XANAX.

- you are taking antifungal medicines including ketoconazole and itraconazole

Before you take XANAX, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have liver or kidney problems
- have lung disease or breathing problems
- are pregnant or plan to become pregnant. XANAX may harm your unborn baby. You and your healthcare provider should decide if you should take XANAX while you are pregnant.
- are breastfeeding or plan to breastfeed. XANAX passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take XANAX. You should not breastfeed while taking XANAX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking XANAX with certain other medicines can cause side effects or affect how well XANAX or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take XANAX?

- See “What is the most important information I should know about XANAX?”
- Take XANAX exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much XANAX to take and when to take it.
- If you take too much XANAX, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking XANAX?

- XANAX can cause you to be drowsy. Do not drive a car or operate heavy machinery until you know how XANAX affects you.
- You should not drink alcohol while taking XANAX. Drinking alcohol can increase your chances of having serious side effects.
What are the possible side effects of XANAX?

XANAX may cause serious side effects, including:

- **See “What is the most important information I should know about XANAX?”**
- **Abuse and dependence.** Taking XANAX can cause physical and psychological dependence. Physical and psychological dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking XANAX suddenly. Withdrawal symptoms can be serious and include seizures. Mild withdrawal symptoms include a depressed mood and trouble sleeping. Talk to your healthcare provider about slowly stopping XANAX to avoid withdrawal symptoms.
- **Seizures.** Stopping XANAX can cause seizures and seizures that will not stop (status epilepticus).
- **Mania.** XANAX may cause an increase in activity and talking (hypomania and mania) in people who have depression.

The most common side effects of XANAX include drowsiness and light-headedness. These are not all the possible side effects of XANAX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XANAX?

- Store XANAX between 68°F to 77°F 20°C to 25°C
- **Keep XANAX and all medicines out of the reach of children.**

General information about the safe and effective use of XANAX.

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- **Do not use XANAX for a condition for which it was not prescribed.**
- **Do not give XANAX to other people, even if they have the same symptoms that you have. It may harm them.**
- **You can ask your pharmacist or healthcare provider for information about XANAX that is written for health professionals.**

What are the ingredients in XANAX?

**Active ingredient:** alprazolam

**Inactive ingredients:** Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

XANAX® is a registered trademark of Pharmacia & Upjohn Company LLC. For more information, go to www.pfizer.com or call 1-800-438-1985.

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

This product’s label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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