DESCRIPTION

XANAX XR Tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a] [1,4] benzodiazepine. The molecular formula is C17H15ClN4 which corresponds to a molecular weight of 308.76.

The structural formula is represented to the right:

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each XANAX XR extended-release tablet, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam. The inactive ingredients are lactose, magnesium stearate, colloidal silicon dioxide, and hypromellose. In addition, the 1 mg and 3 mg tablets contain D & C Yellow No. 10 and the brand of alprazolam extended-release tablets

Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3–26.9 hours) in healthy adults.

The mean absolute bioavailability of alprazolam from XANAX XR Tablets is approximately 90%, and the relative bioavailability compared to XANAX Tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of XANAX XR Tablets are similar to that for XANAX Tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of XANAX XR Tablets. A high-fat meal given up to 2 hours before dosing with XANAX XR Tablets increased the mean Cmax by about 25%. The effect of this meal on Tmax depended on the timing of the meal, with a reduction in Tmax, by about 1/3 for subjects eating immediately before dosing and an increase in Tmax by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life (t1/2) were not affected by eating.

There were significant differences in absorption rate for the XANAX XR Tablet, depending on the time of day administered, with the Cmax increased by 30% and the Tmax decreased by an hour following dosing at night, compared to morning dosing.

DISTRIBUTION

The apparent volume of distribution of alprazolam is similar for XANAX XR and XANAX Tablets. In vitro, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and α-hydroxyalprazolam) were similar for XANAX and XANAX XR Tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration after both XANAX XR and XANAX Tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Elimination

Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of XANAX XR Tablet ranges from 10.7–15.8 hours in healthy adults.

Special Populations

While pharmacokinetic studies have not been performed in special populations with XANAX XR Tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of XANAX
The rate of relapse, rebound, and withdrawal in patients with panic disorder who received XANAX XR.
Tables has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received XANAX Tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to XANAX Tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, 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 where the ability of patients to discontinue medication was measured, 71%–93% of patients treated with XANAX Tablets tapered completely off therapy compared to 89%–96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with XANAX Tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. Seizures were reported for three patients in panic disorder clinical trials with XANAX XR. In two cases, the patients had completed 6 weeks of treatment with XANAX XR 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued XANAX XR, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with XANAX XR 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of XANAX Tablets, the immediate release form of alprazolam. Seizures attributable to XANAX were seen after drug discontinuance 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. These 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 three 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

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAX Tablets. 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 Tablets have been reported in patients with panic disorder taking prescribed maintenance doses. 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.

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 (e.g., the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of XANAX XR should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

CNS Depression and Impaired Performance

Because of its CNS depressant effects, patients receiving XANAX XR 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 XR.

Risk of Fetal Harm

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam 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, alprazolam 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 these drugs 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 very potent inhibitors of CYP3A. 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. Cimetidine — Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other Drugs Possibly Affecting Alprazolam Metabolism

Other drugs possibly affecting alprazolam metab-
Information for Patients
To assure safe and effective use of XANAX XR, the physician should provide the patient with the following guidance.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machines, etc.
5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.
7. Some patients may find it very difficult to discontinue treatment with XANAX XR due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day, especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

Laboratory Tests
Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

Drug Interactions
Use with Other CNS Depressants
If XANAX XR Tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

Use of Imipramine 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)

Fluoxetine — 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: dil-tiazem, 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. Data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclopamine, amiodarone, nicardipine, and nifedipine.

Caution is recommended during the coadministration of any of these with alprazolam (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 clinical 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 (15 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 microsome 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
brand of alprazolam extended-release tablets

XANAX XR®

brand of alprazolam extended-release tablets

XANAX XR®

Adverse Event Occurring at an Incidence of 1% or More Among Patients Treated with XANAX XR

The prescribing physician should be aware that adverse event incidence cannot be used to predict the incidence of adverse events 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 event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following table shows the incidence of treatment-emergent adverse events that occurred during 6- to 8-week placebo-controlled trials in 1% or more of patients treated with XANAX XR where the incidence in patients treated with XANAX XR was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with XANAX XR (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see table).

**Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with XANAX XR**

<table>
<thead>
<tr>
<th>System Organ Class/Adverse Event</th>
<th>Percentage of Patients Reporting Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XANAX XR</strong>&lt;br&gt;(n=531)</td>
<td><strong>Placebo</strong>&lt;br&gt;(n=349)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>45.2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>23.0</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>15.4</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>10.9</td>
</tr>
<tr>
<td>Coordination abnormal</td>
<td>9.4</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>7.2</td>
</tr>
<tr>
<td>Ataxia</td>
<td>7.2</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>3.2</td>
</tr>
<tr>
<td>Balance impaired</td>
<td>3.2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2.4</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1.3</td>
</tr>
<tr>
<td>General disorders/administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13.9</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1.7</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>2.4</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>1.9</td>
</tr>
</tbody>
</table>

(continued)
(continued) Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with XANAX XR

<table>
<thead>
<tr>
<th>Class/Adverse Event</th>
<th>XANAX XR (n=422)</th>
<th>Placebo (n=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Tremor</td>
<td>28.2</td>
</tr>
<tr>
<td>Headache</td>
<td>26.5</td>
<td>12.6</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>7.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>7.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>24.2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>21.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Depression</td>
<td>10.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Derealization</td>
<td>8.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Depersonalization</td>
<td>5.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>12.1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Hyperventilation</td>
<td>8.5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Appetite decreased</td>
<td>9.5</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle twitching</td>
<td>7.4</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flashes</td>
<td>1.5</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Dyspnea</td>
<td>1.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with XANAX XR. All potentially important reported events are included except those already listed in the above table or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with XANAX XR, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Cardiac disorders: Frequent: palpitation; infrequent: sinus tachycardia

Ear and Labyrinth disorders: Frequent: Vertigo; infrequent: tinnitus, ear pain

Eye disorders: Frequent: blurred vision; infrequent: mydriasis, photophobia

Gastrointestinal disorders: Frequent: diarrhea, vomiting, dyspepsia, abdominal pain; infrequent: dysphagia, salivary hypersecretion

General disorders and administration site conditions: Frequent: malaise, weakness, chest pains; infrequent: fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthma, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors

Musculoskeletal and connective tissue disorders: Frequent: back pain, muscle cramps, muscle twitching

Nervous system disorders: Frequent: headache, dizziness, tremor; infrequent: amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor

Psychiatric system disorders: Frequent: irritability, insomnia, nervousness, derealization, libido increased, restlessness, agitation, depersonalization, nightmares; infrequent: abnormal dreams, apathy, aggression, anger, bradysperhenia, euphoric mood, logorhea, mood swings, dysphoria, hallucination, homicidal ideation,mania, hypomania, impulse control, psychomotor retardation, suicidal ideation

Renal and urinary disorders: Frequent: difficulty in micturition; infrequent: urinary frequency, urinary incontinence

Respiratory, thoracic, and mediastinal disorders: Frequent: nasal congestion, hyperventilation; infrequent: choking sensation, epistaxis, rhinorrhea

Skin and subcutaneous tissue disorders: Frequent: sweating increased; infrequent: clamminess, rash, urticaria

Vascular disorders: Frequent: hypotension

The categories of adverse events reported in the clinical development program for XANAX Tablets in the treatment of panic disorder differ somewhat from those reported for XANAX XR Tablets because the clinical trials with XANAX Tablets and XANAX XR Tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with XANAX XR Tablets were generally the same as those reported in the clinical trials with XANAX XR Tablets. 

Discontinuation-Emergent Adverse Events: Occurring at an Incidence of 5% or More Among Patients Treated with XANAX XR

The following table shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with XANAX XR where the incidence in patients treated with XANAX XR was two times greater than the incidence in placebo-treated patients.

Discontinuation-Emergent Symptoms: Incidence in Short-Term, Placebo-Controlled Trials with XANAX XR
There have been also reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS). To discontinue treatment in patients taking XANAX XR Tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX XR Tablets 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 Tablets 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 Tablets cannot be readily determined. Reported events include: liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, hyperprolactinemia, gynecomastia, and galactorrhea.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence
Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodi- azepines, including alprazolam. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal pain, vomiting, diarrhea,Colitis, cramps, vomiting, sweating, tremors, and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long-term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of alprazolam sufficient to suppress symp- toms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substi- tuted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time. In recurring panic disorder symptoms similar to those observed before treatment may recur either early or late, and they will persist. While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with alprazolam at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (see WARNINGS). Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontin- ued from any CNS depressant agent, including alpra- zolam. It is recommended that all patients on alprazo- lam who require a dosage reduction be gradually tapered under close supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodi- azepines, including alprazolam. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experi- enced considerable difficulty in tapering and con- tinuing from alprazolam, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving alprazolam. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

Controlled Substance Class
Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and XANAX XR Tablets have been assigned to Schedule IV.

OVERDOSAGE

Clinical Experience
Overdose reports with XANAX Tablets are limited. Manifestations of alprazolam overdose include somno- lence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported in associ- ation with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol. Alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdose.

General Treatment of Overdose
As in all cases of drug overdose, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respi- ratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert including CONTRAINDICATIONS, WARN- INGS, and PRECAUTIONS should be consulted prior to use.

DOSAGE AND ADMINISTRATION

XANAX XR Tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.
The dosage may be titrated as outlined above. If the therapeutic response after switching is inadequate, the dose may be increased cautiously to avoid adverse effects.

Dosing in Special Populations

In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of XANAX XR is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see Dose Titration). The elderly may be especially sensitive to the effects of benzodiazepines.

Dose Titration

Treatment with XANAX XR may be initiated with a dose of 0.5 mg to 1 mg once 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/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of XANAX XR.

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

In controlled trials conducted to establish the efficacy of XANAX XR Tablets in panic disorder, doses in the range of 1 to 10 mg/day were used. Most patients showed efficacy in the dose range of 3 to 6 mg/day. Occasional patients required as much as 10 mg/day to achieve a successful response.

The necessary duration of treatment for panic disorder patients responding to XANAX XR is unknown. However, periodic reassessment is advised. 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 three days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

Switch from XANAX (immediate-release) Tablets to XANAX XR (extended-release) Tablets

Patients who are currently being treated with divided doses of XANAX (immediate-release) Tablets, the elderly may be especially sensitive to the effects of benzodiazepines.

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Switch from XANAX (immediate-release) Tablets to XANAX XR (extended-release) Tablets

Patients who are currently being treated with divided doses of XANAX (immediate-release) Tablets, for example 3 to 4 times a day, may be switched to XANAX XR Tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

HOW SUPPLIED

XANAX XR (extended-release) Tablets are available as follows:

- 0.5 mg (white, pentagonal-shaped tablets debossed with an “X” on one side and “0.5” on the other side) Bottles of 60 NDC 0009-0066-07
- 1 mg (yellow, square-shaped tablets debossed with a “X” on one side and “1” on the other side) Bottles of 60 NDC 0009-0059-07
- 2 mg (blue, round-shaped tablets debossed with a “X” on one side and “2” on the other side) Bottles of 60 NDC 0009-0068-07
- 3 mg (green, triangular-shaped tablets debossed with an “X” on one side and “3” on the other side) Bottles of 60 NDC 0009-0067-07

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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.

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, Michigan 49001, USA

January 2003 819 612 000
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