FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[*see *Warnings, Drug Interactions]*. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.**
- **. The use of benzodiazepines, including XANAX XR, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing XANAX XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction *[see Warnings and Precautions (5.2)]*.**

- **The continued use of benzodiazepines, including XANAX XR, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and, higher daily dose. Abrupt discontinuation or rapid dosage reduction of XANAX XR after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAX XR or reduce the dosage *[see Dosage and Administration (3.2), Warnings and Precautions (5.3)]*.**

1. DOSAGE FORMS AND STRENGTHS

XANAX® XR 0.5 mg
XANAX® XR 1 mg
XANAX® XR 2 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is Alprazolam.

For the full list of excipients, see section 11, DESCRIPTION.

Excipient with known effect

Each tablet XANAX® XR 0.5 mg, 1 mg & 2 mg contains 221.7 mg lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take Xanax XR.

PHARMACEUTICAL FORM

Sustained-release tablets

2 INDICATIONS AND USAGE

- XANAX XR is indicated for the treatment of anxiety associated with depression.
- XANAX XR is also indicated for the treatment of panic disorder, with or without phobic avoidance.

XANAX XR Tablets (alprazolam) are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual (DSM-III-R) 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 six 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 clammy hands; dry mouth; dizziness or light-headedness; nausea, diarrhea, or other abdominal distress, flushes or chills; frequent urination, trouble swallowing or 'lump in throat'); VIGILANCE AND SCANNING (feeling keyed up or on edge, exaggerated startle response, difficulty concentrating or 'mind going blank" because of anxiety, trouble falling or staying asleep, irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

This claim is supported on the basis of two positive studies with XANAX XR conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder [see CLINICAL STUDIES (14].

Panic disorder (DSM-IV) is an illness characterized by recurrent panic attacks. The panic attacks, at least initially, are unexpected. Later in the course of this disturbance certain situations, e.g., driving a car or being in a crowded place, may become associated with having a panic attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia). The diagnosis requires four such attacks within a four week period, or one or more attacks followed by at least a month of persistent fear of having another attack The panic attacks must be characterized by at least four of the following symptoms: dyspnea or smothering sensations, dizziness, unsteady feelings, or faintness; palpitations or tachycardia; trembling or shaking; sweating; choking, nausea or abdominal distress; depersonalization or derealization; paresthesias, hot flashes or chills;

chest pain or discomfort; fear of dying; fear of going crazy or of doing something uncontrolled. At least some of the panic attack symptoms must develop suddenly, and the panic attack symptoms must not be attributable to some known organic factors. Panic disorder is frequently associated with some symptoms of agoraphobia.

The longer-term efficacy of XANAX XR has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dosage

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.

	Posology of Alprazolam XR Tablets	
Indication or Population	**Usual Starting Dose** (if side effects occur, dose should be lowered)	**Usual Dose Range**
Anxiety	1 mg daily in one or two doses	0.5 to 4 mg daily, in one or two doses
Depression	1 mg daily in one or two doses	0.5 to 4.5 mg daily, in one or two doses
Panic Disorders	0.5 to 1.0 mg given at bedtime or 0.5 mg two times daily	Dose should be adjusted to patient response, with increments no greater than 1 mg/day every 3 to 4 days. [In clinical trials the mean maintenance dose was between 5 and 6 mg/day, given as a single daily dose or divided into two doses daily, with occasional patients needing up to 10 mg/day]

Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

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.*[see* DOSAGE AND ADMINISTRATION *(3.2)]*

3.2 Discontinuation or Dosage Reduction of XANAX XR

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided [*see WARNINGS, PRECAUTIONS (5), DRUG ABUSE AND DEPENDENCE (9)*].

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.

3.3 Dosage Recommendations in Geriatric Patients
In elderly patients the usual starting dosage 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 *[see Use in Specific Populations (8.5), Clinical Pharmacology (12.2)]*.

3.4 Dosage Recommendations in Patients with Hepatic Impairment

In patients with hepatic impairment or in patients with debilitating disease, the usual starting dosage of XANAX XR is 0.5 mg once daily. This may be gradually increased if needed and tolerated *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.2)]*.

4 CONTRAINDICATIONS

XANAX XR is contraindicated in patients:

- with known hypersensitivity to alprazolam or other benzodiazepines. Angioedema has been reported *[see Adverse Reactions (6.2)]*.
- taking strong cytochrome P450 3A (CYP3A) inhibitors (e.g., ketoconazole, itraconazole), except ritonavir [see Warnings and Precautions (5.6), Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including XANAX XR, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe XANAX XR concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of XANAX XR than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking XANAX XR, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when XANAX XR is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined *[see Drug Interactions (7.1)]*.

5.2 Abuse, Misuse, and Addiction

The use of benzodiazepines, including XANAX XR, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death *[see DRUG ABUSE AND DEPENDENCE – Abuse (9.2)]*.

Before prescribing XANAX XR and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of XANAX XR, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of XANAX XR along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

5.3 Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAX XR or reduce the dosage (a patient-specific plan should be used to taper the dose) *[see DOSAGE AND ADMINISTRATION (3.2]*.

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including XANAX XR, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of XANAX XR after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) *[see DRUG ABUSE AND DEPENDENCE – Dependence (9.3)]*.

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months *[see DRUG ABUSE AND DEPENDENCE – Dependence (9.3)]*.

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to XANAX XR. These include a spectrum of withdrawal symptoms; the most important is seizure *[see Drug Abuse and Dependence (9.3)]*. Even after relatively short-term use at doses of $\leq$ 4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received XANAX, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

In a controlled clinical trial in which 63 patients were randomized to alprazolam 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.

Interdose Symptoms
Early morning anxiety and emergence of anxiety symptoms between doses of XANAX 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.

5.4 Effects on Driving and Operating Machinery
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 concomitant use of alcohol and other CNS depressant drugs during treatment with XANAX XR *[see Drug Interactions (7.1)]*.

5.5 Neonatal Sedation and Withdrawal Syndrome
Use of XANAX XR during the later stages of pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding difficulties) in the neonate. Observe newborns for signs of sedation and neonatal withdrawal syndrome and manage accordingly *[see Use in Specific Populations (8.1)]*.

5.6 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.

Strong CYP3A Inhibitors
XANAX XR is contraindicated in patients receiving strong inhibitors of CYP3A such as azole antifungal agents *[see Contraindications (4)]*.— Ketoconazole and itraconazole have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively.

Dosage adjustment is necessary when XANAX XR and ritonavir are initiated concomitantly or when ritonavir is added to a stable dosage of XANAX XR [see Drug Interactions (7.1)].

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam: nefazodone, fluvoxamine, and cimetidine [see Drug Interaction (7.1), Clinical Pharmacology (12.3)]. Use caution and consider dose reduction of XANAX XR, as appropriate, during co-administration with these drugs.

5.7 Patients with Depression

Benzodiazepines may worsen depression. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered in patients with depression.

5.8 Mania

Episodes of hypomania and mania have been reported in association with the use of alprazolam tablets in patients with depression *[see Adverse Reactions (6.1)]*.

5.9 Risks in Patients with Impaired Respiratory Function

There have been reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. Closely monitor patients with impaired respiratory function. If signs and symptoms of respiratory depression, hypoventilation, or apnea occur, discontinue XANAX XR.

5.10 Excipients

Each XANAX® XR 0.5 mg, 1 mg & 2 mg sustained release tablet contains 221.7 mg lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take Xanax XR.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks from Concomitant Use with Opioids *[see Warnings and Precautions (5.1)]*
- Abuse, Misuse, and Addiction *[see Warnings and Precautions (5.2)]*
- Dependence and Withdrawal Reactions *[see Warnings and Precautions (5.3)]*
- Effects on Driving and Operating Machinery *[see Warnings and Precautions (5.4)]*
- Neonatal Sedation and Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Patients with Depression *[see Warnings and Precautions (5.7)]*
- Risks in Patients with Impaired Respiratory Function *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The information included in the section on Adverse Reactions Observed in Short-Term, Placebo-Controlled Trials with XANAX XR is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

<u>Adverse Reactions Observed in Short-Term, Placebo-Controlled Trials of XANAX XR</u>

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 17% of the 531 patients who received XANAX XR in placebo-controlled clinical trials for panic disorder had at least one adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug-related (I e. , leading to discontinuation in at least 1% of the patients treated with XANAX XR at a rate at least twice that of placebo) are shown in Table 1.

Table 1: Adverse ReactionsLeading to Discontinuation in ≥1% of XANAX XR-treated Patients and at least twice the Rate of Placebo-treated Patients in Placebo-Controlled Trials

	Percentage of Patients Discontinuing Due to Adverse Reactions	
	XANAX XR (n=531)	**Placebo (n=349)**
Nervous system disorders		
Sedation	7.5	0.6
Somnolence	3.2	0.3
Dysarthria	2.1	0
Coordination abnormal	1.9	0.3
Memory impairment	1.5	0.3
General disorders/administration site conditions		
Fatigue	1.7	0.6
Psychiatric disorders		
Depression	2.5	1.2

n=number of patients

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

Table 2 shows the incidence of adverse reactions that occurred during 6- and 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 reactions 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.

Table 2: Adverse Reactions Occuring in ≥ 1% in XANAX-treated Patients and Greater than Placebo-treated Patients in 6 and 8 week Placebo-Controlled Trials Panic Disorder

	XANAX XR (n=531)	Placebo (n=349)
Nervous system disorders		
Sedation	45%	23%
Somnolence	23%	6%
Memory impairment	15%	7%
Dysarthria	11%	3%
Coordination abnormal	9%	1%
Mental impairment	7%	6%
Ataxia	7%	3%
Disturbance in attention	3%	1%
Balance impaired	3%	1%
Dyskinesia	2%	1%
Hypoesthesia	1%	<1%
Hypersomnia	1%	0%
General disorders/administration site conditions		
Fatigue	14%	9%
Lethargy	2%	1%
Psychiatric disorders		
Depression	12%	9%
Libido decreased	6%	2%
Disorientation	2%	0%
Confusion	2%	1%
Depressed mood	1%	<1%
Metabolism and nutrition disorders		
Appetite increased	7%	6%
Anorexia	2%	0%
Gastrointestinal disorders		
Constipation	8%	4%
Nausea	6%	3%
Investigations		
Weight increased	5	4
Injury, poisoning, and procedural complications		
Road traffic accident	2%	0%
Reproductive system and breast disorders		
Dysmenorrhea	4%	3%
Sexual dysfunction	2%	1%
Musculoskeletal and connective tissue disorder		
Arthralgia	2%	1%

	XANAX XR (n=531)	Placebo (n=349)
Myalgia Pain in limb	2% 1%	1% 0%
Respiratory, thoracic, and mediatinal disorders Dyspnea	2%	0%

Other Adverse Reactions Observed During the Premarketing Evaluation of XANAX XR
Following is a list of other adverse Reaction reported by 531 patients with panic disorder treated with XANAX XR. Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: those occurring in at least l/l00 patients (frequent); those occurring in less than l/100 patients but at least l/1000 patients (infrequent); those occurring in fewer than l/1000 patients (rare).

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, asthenia, 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; *Infrequen*t: 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, nightmare; *Infrequent:* abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, 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: *Infrequent*: hypotension

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

Table 3 shows the incidence of discontinuation-emergent adverse reactions 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 2 times greater than the incidence in placebo-treated patients.

Table 3: Discontinuation-Emergent Symptom Incidence Reported in ≥5% of XANAX XR-treated Patients and at least twice the Rate of Placebo-treated Patients in Short-Term, Placebo-Controlled Trials

	P	
	XANAX XR n=422 (%)	**Placebo n=261 (%)**
Nervous system disorders		
Tremor	28.2	10.7
Headache	26.5	12.6
Hypoesthesia	7.8	2.3
Paraesthesia	7.1	2.7
Psychiatric disorders		
Insomnia	24.2	9.6
Nervousness	21.8	8.8
Depression	10.9	5.0
Derealization	8.0	3.8
Anxiety	7.8	2.7
Depersonalization	5.7	1.9
Gastrointestinal disorders		
Diarrhea	12.1	3.1
Respiratory, thoracic and mediastinal disorders		
Hyperventilation	8.5	2.7
Metabolism and nutrition disorders		
Appetite decreased	9.5	3.8
Musculosketal and connective tissue disorders		
Muscle twitching	7.4	2.7
Vascular disorders		
Hot flushes	5.9	2.7

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam *[see Warning and Precautions (5.2), Drug Abuse and Dependence (9.3)]*. .

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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of alprazolam tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Endocrine disorders: Hyperprolactinemia
General disorders and administration site conditions: Edema peripheral
Hepatobiliary disorders: Hepatitis, hepatic failure, jaundice
Investigations: Liver enzyme elevations
Psychiatric disorders: Hypomania, mania
Reproductive system and breast disorders: Gynecomastia, galactorrhea, menstruation irregular
Skin and subcutaneous tissue disorders: Photosensitivity reaction, angioedema, Stevens-Johnson syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with XANAX XR

Table 4 includes clinically significant drug interactions with XANAX XR *[see Clinical Pharmacology (12.2)]*.

Table 4: Clinically Significant Drug Interactions with XANAX XR

Opioids	
Clinical implication	The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at gamma-aminobutyric acid ($GABA_A$) sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Prevention or management	Limit dosage and duration of concomitant use of XANAX XR and opioids, and monitor patients closely for respiratory depression and sedation *[see Warnings and Precautions (5.1)]*.
Examples	Morphine, buprenorphine, hydromorphone, oxymorphone, oxycodone, fentanyl, methadone, alfentanil, butorpenol, codeine, dihydrocodeine, meperidine, pentazocine, remifentanil, sufentanil, tapentadol, tramadol.

CNS Depressants	
Clinical implication	The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other CNS depressants.
Prevention or management	Limit dosage and duration of XANAX XR during concomitant use with CNS depressants *[see Warnings and Precautions (5.4)]*.
Examples	Psychotropic medications, anticonvulsants, antihistaminics, ethanol, and other drugs which themselves produce CNS depression.
Strong Inhibitors of CYP3A (except ritonavir)	
Clinical implication	Concomitant use of XANAX XR with strong CYP3A inhibitors has a profound effect on the clearance of alprazolam, resulting in increased concentrations of alprazolam and increased risk of adverse reactions *[see Clinical Pharmacology (12.2)]*.
Prevention or management	Concomitant use of XANAX XR with a strong CYP3A4 inhibitor (except ritonavir) is contraindicated *[see Contraindications (4), Warnings and Precautions (5.6)]*.
Examples	Ketoconazole, itraconazole, clarithromycin
Moderate or Weak Inhibitors of CYP3A	
Clinical implication	Concomitant use of XANAX XR with CYP3A inhibitors may increase the concentrations of XANAX XR, resulting in increased risk of adverse reactions *[see Clinical Pharmacology (12.2)]*.
Prevention or management	Avoid use and consider appropriate dose reduction when XANAX XR is coadministered with a moderate or weak CYP3A inhibitor *[see Warnings and Precautions (5.5)]*.
Examples	Nefazodone, fluvoxamine, cimetidine, erythromycin
CYP3A Inducers	
Clinical implication	Concomitant use of CYP3A inducers can increase alprazolam metabolism and therefore can decease plasma levels of alprazolam *[see Clinical Pharmacology (12.2)]*.
Prevention or management	Caution is recommended during coadministration with alprazolam.
Examples	Carbamazepine, phenytoin

Ritonavir	
Clinical implication	Interactions involving ritonavir and alprazolam are complex and time dependent. Short term administration of ritonavir increased alprazolam exposure due to CYP3A4 inhibition. Following long term treatment of ritonavir (> 10 - 14 days), CYP3A4 induction offsets this inhibition. Alprazolam exposure was not meaningfully affected in the presence of ritonavir.
Prevention or management	Reduce XANAX XR dose when a patient is initiated with ritonavir and XANAX XR concomitantly, or when ritonavir is added to a regimen where XANAX XR is stabilized. Increase XANAX XR dosage to the target dosage after 10 to 14 days of dosing ritonavir and XANAX XR concomitantly. No dosage adjustment of XANXR XR is necessary in patients receiving ritonavir for more than 10 to 14 days. Concomitant use of XANAX XR with a strong CYP3A inhibitor, except ritonavir, is contraindicated *[see Contraindications (4), Warnings and Precautions (5.6)]*.
Digoxin	
Clinical implication	Increased digoxin concentrations have been reported when alprazolam was given, especially in geriatric patients (>65 years of age).
Prevention or management	In patients on digoxin therapy, measure serum digoxin concentrations before initiating XANAX XR. Continue monitoring digoxin serum concentration and toxicity frequently. Reduce the digoxin dose if necessary.

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Neonates born to mothers using benzodiazepines during the later stages of pregnancy have been reported to experience symptoms of sedation and neonatal withdrawal *[see Warnings and Precautions (5.5), Clinical Considerations)*]. Overall available data from published observational studies of pregnant women exposed to alprazolam have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Benzodiazepines cross the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to benzodiazepines during pregnancy and labor for signs of sedation, respiratory depression, withdrawal, and feeding problems and manage accordingly *[see Warnings and Precautions (5.5)]*.

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, the majority of recent case-control and cohort studies of benzodiazepine use during pregnancy, which were adjusted for confounding exposures to alcohol, tobacco, and other medications, have not confirmed these findings. At this time, there is no clear evidence that alprazolam exposure in early pregnancy can cause major birth defects. Neonates exposed to benzodiazepines during the late third trimester of pregnancy or during labor have been reported to exhibit sedation and neonatal withdrawal symptoms.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of alprazolam in human breast milk. There are reports of sedation and withdrawal symptoms in breastfed neonates and infants exposed to alprazolam. The effects of alprazolam on lactation are unknown. Because of the potential for serious adverse reactions, including sedation and withdrawal symptoms in breastfed neonates and infants, advise patients that breastfeeding is not recommended during treatment with XANAX XR.

8.3 Pediatric Use

Safety and effectiveness of XANAX XR have not been established in pediatric patients.

8.4 Geriatric Use

XANAX XR-treated geriatric patients had higher plasma concentrations of alprazolam (due to reduced clearance) compared to younger adults receiving the same doses. Therefore, dosage reduction of XANAX XR is recommended in geriatric patients *[see Dosage and Administration (3.3) and Clinical Pharmacology (12.2)]*.

8.5 Hepatic Impairment

Patients with alcoholic liver disease exhibit a longer elimination half-life (19.7 hours), compared to healthy subjects (11.4 hours). This may be caused by decreased clearance of alprazolam in patients with alcoholic liver disease. Dosage reduction of XANAX XR is recommended in patients with hepatic impairment *[see Dosage and Administration (3.4), Clinical Pharmacology (12.2)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

XANAX XR contains alprazolam, a controlled substance.

9.2 Abuse

XANAX XR is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders *[see Warnings and Precautions (5.2)]*.

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

9.3 Dependence

<u>Physical Dependence</u>

XANAX XR may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use *[see Warnings and Precautions (5.3)]*.

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue XANAX XR or reduce the dosage *[see Dosage and Administration (3.2), Warnings and Precautions (5.3)]*.

Acute Withdrawal Signs and Symptoms

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue, gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome associated with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to XANAX XR may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of XANAX XR may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

10 OVERDOSAGE

10.1 Clinical Experience

Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported in association 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.

10.2 Management of Overdose

As in all cases of drug overdosage, 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. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

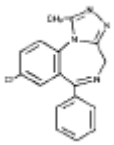
Flumazenil, may be useful in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory 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 should be consulted prior to use.

11 DESCRIPTION

XANAX XR contains 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-4*H*-*s*-triazolo [4,3-α] [1,4] benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$ which corresponds to a molecular weight of 308.76.

The structural formula is represented below:



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 sustained -release tablet, for oral administration, contains 0.5 mg, 1 mg or 2 mg of alprazolam. The inactive ingredients are: lactose, methylhydroxypropylcellulose, magnesium stearate, and colloidal anhydrous silica, . In addition, the 0.5 mg and 2 mg tablets contain FD&C blue No. 2 Aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alprazolam is a 1,4 benzodiazepine. Alprazolam exerts its effect for the treatment of panic disorder through binding to the benzodiazepine site of gamma aminobutyric acid-A ($GABA_A$) receptors in the brain and enhances GABA-mediated synaptic inhibition.

12.2 Pharmacokinetics

The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam) are linear, and concentrations are proportional up to 10 mg XANAX XR given once daily.

<u>Absorption</u>

Following oral administration of XANAX XR in the morning, peak plasma concentration of alprazolam (C_{max}) occurs in about 10 hours postdose. Compared to morning dosing, alprazolam C_{max} increased by 30% and the T_{max} decreased by an hour following dosing at night.

The mean absolute bioavailability of alprazolam following administration of XANAX XR is approximately 90%, and the relative bioavailability compared to XANAX is about 100%. The bioavailability and pharmacokinetics of alprazolam following administration of XANAX XR are similar to that for XANAX, with the exception of a slower rate of absorption.

Effect of Food

A high-fat meal given up to 2 hours before dosing with XANAX XR increased the mean C_{max} by about 25%. The effect of this meal on T_{max} depended on the timing of the meal, with a reduction in T_{max} by about 1/3 for subjects eating immediately before dosing and an increase in T_{max} by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life ($t_{½}$) were not affected by eating.

Distribution
The apparent volume of distribution of alprazolam is similar for XANAX XR and XANAX. Alprazolam is 80% bound to human serum protein, and albumin accounts for the majority of the binding.

Elimination
The mean plasma elimination half-life of alprazolam following administration of XANAX XR ranges from 10.7 to 15.8 hours in healthy adults.

Metabolism
Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major active metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. The plasma circulation levels of the two active metabolites after both Xanax XR and Xanax are less than 10% and 4% of the parent, 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. The low concentrations and low potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam indicate that they unlikely contribute much to the effects of alprazolam. 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, indicating that the metabolism of alprazolam is not affected by absorption rate.

Excretion
Alprazolam and its metabolites are excreted primarily in the urine.

Specific Populations

Geriatric Patients
The mean $T_{1/2}$ of alprazolam was 16.3 hours (range: 9.0 to 26.9 hours) in healthy elderly subjects compared to 11.0 hours (range: 6.3 to 15.8 hours, n=16) in healthy adult subjects.

Obese Patients
The mean $T_{1/2}$ of alprazolam was 21.8 hours (range: 9.9 to 40.4 hours) in a group of obese subjects.

Patients with Hepatic Impairment
The mean $T_{1/2}$ of alprazolam was 19.7 hours (range: 5.8 to 65.3 hours) in patients with alcoholic liver disease.

Racial or Ethnic Groups
Maximal concentrations and $T_{1/2}$ of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Smoking
Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug Interaction Studies

In Vivo Studies
Most of the interactions that have been documented with alprazolam are with drugs that modulate CYP3A4 activity.

Compounds that are inhibitors or inducers of CYP3A would be expected to increase or decrease plasma alprazolam concentrations, respectively. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.66 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold *[see Contraindications (4), Warnings and Precautions (5.6), Drug Interactions (7.1)]*. Other studied drugs include:.

Cimetidine: Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 82%, decreased clearance by 42%, and increased $T_{1/2}$ by 16%.

Fluoxetine: Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased $T_{1/2}$ by 17%, and decreased measured psychomotor performance.

Oral Contraceptives: Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased $T_{1/2}$ by 29%.

Carbamazepine: The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90±0.21 mL/min/kg to 2.13±0.54 mL/min/kg and the elimination $T_{1/2}$ was shortened (from 17.1±4.9 to 7.7 ±1.7 hour) following administration of 300 mg per day carbamazepine for 10 days *[see Drug Interactions (7.1)]*. However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000-1200 mg per day); the effect at usual carbamazepine doses is unknown.

Ritonavir: Interactions involving HIV protease inhibitors (eg, ritonavir) and alprazolam are complex and time dependent. Short-term low doses of ritonavir (4 doses of 200 mg) increased mean AUC of alprazolam by about 2.5-fold, and did not significantly affect C_{max} of alprazolam. The elimination $T_{1/2}$ was prolonged (30 hours versus 13 hours). However, upon extended exposure to ritonavir (500 mg, twice daily for 10 days), CYP3A induction offset this inhibition. Alprazolam AUC and C_{max} was reduced by 12% and 16%, respectively, in the presence of ritonavir. The elimination $T_{1/2}$ of alprazolam was not significantly changed *[see Warnings and Precautions (5.6)]*.

Sertraline: A single dose of alprazolam 1 mg and steady state dose of sertraline (50 to 150 mg per day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam.

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 in doses up to 4 mg per day.

Warfarin: Alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

In Vitro Studies
Data from in vitro studies of alprazolam suggest a possible drug interaction of alprazolam with paroxetine. The ability of alprazolam to induce human hepatic enzyme systems has not been determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in rats or mice administered alprazolam for 2 years at doses up to 30 and 10 mg/kg/day, respectively. These doses are 29 times and 4.8 times the maximum recommended human dose of 10 mg/day based on mg/m^2 body surface area, respectively.

Mutagenesis

Alprazolam was negative in the in vitro Ames bacterial reverse mutation assay and DNA Damage/ Alkaline Elution Assay and in vivo rat micronucleus genetic toxicology assays.

Impairment of Fertility

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg per day, which is approximately 5 times the maximum recommended human dose of 10 mg per day based on mg/m^2 body surface area.

13.2 Animal Toxicology and/or Pharmacology

When rats were treated with alprazolam at oral doses of 3 mg/kg, 10 mg/kg, and 30 mg/kg per day (3 to 29 times the maximum recommended human dose based on mg/m^2 body surface area) 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.

14 CLINICAL STUDIES

The efficacy of XANAX XR in the treatment of panic disorder in adults was established in two 6-week, flexible-dose, placebo-controlled studies in adult patients meeting DSM-III criteria for panic disorder. In these studies, patients were treated with XANAX XR in a dose range of 1 mg to 10 mg once per day. The effectiveness of XANAX XR was assessed on the basis of changes in various measures of panic attack frequency, on various measures of the Clinical Global Impression, and on the Overall Phobia Scale. In all, there were 7 primary efficacy measures in these studies, and XANAX XR was superior to placebo on all 7 outcomes in both studies. The mean dose of XANAX XR at the last treatment visit was 4.2 mg per day in the first study and 4.6 mg per day in the second.

In addition, there were two 8-week, fixed-dose, placebo-controlled studies of XANAX XR in patients with panic disorder, involving fixed XANAX XR doses of 4 and 6 mg/day, on a once-a-day basis, that did not show a benefit for either dose of XANAX XR.

Analyses of the relationship between treatment outcome and gender did not suggest any differential responsiveness on the basis of gender.

15 HOW SUPPLIED/STORAGE AND HANDLING

Blister packs containing 30 sustained -release tablets.

XANAX® XR **0.5 mg** - round blue convex tablets debossed with "P&U 57".
XANAX® XR **1 mg** - round white convex tablets debossed with "P&U 59".
XANAX® XR **2 mg** -pentagonal blue tablets debossed with "P&U 66". .

Shelf life: The expiry date of the product is indicated on the packaging materials.

Storage: Store below 30ºC.

16 LICENSE HOLDER:

Pfizer PFE Pharmaceuticals Israel Ltd.,9 Shenkar St., Herzliya Pituach 46725.

17 LICENSE NUMBERS:

XANAX® XR 0.5 mg: 110-49-28804
XANAX® XR 1 mg: 110-50-28805
XANAX® XR 2 mg: 110-51-28806

Revised in 04/2021 in accordance with MOHs guidelines.