Pfizer XANAX™

1. NAME OF THE MEDICINAL PRODUCT
XANAX 0.25 mg tablets
XANAX 0.50 mg tablets
XANAX 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
XANAX 0.25 mg tablets
Each tablet contains: *Active ingredient:* alprazolam 0.25 mg.

XANAX 0.50 mg tablets
Each tablet contains: *Active ingredient:* alprazolam 0.50 mg.

XANAX 1 mg tablets
Each tablet contains: *Active ingredient:* alprazolam 1 mg.

3. PHARMACEUTICAL FORM
Tablets and oral drops, solution
ORAL USE.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
XANAX is indicated for the management of **anxiety disorder.**
XANAX is also effective for the management of **panic disorders** with or without phobic avoidance. It is also indicated to block or relieve the symptoms of panic attacks and phobia episodes in patients with agoraphobia and panic attacks.
Benzodiazepines are indicated only in the presence of a severe, debilitating disorder or poses a severe distress for the patient.

4.2 Posology and method of administration
XANAX optimal dosage should be individualized basing on the symptom severity and individual response of the patient.
Dosage indications here reported should meet the requirements of most patients. Should a higher dosage be necessary, the dose should be gradually increased in order to avoid risks of side effects. In these cases it is advisable to increase the evening dose prior to the daily one.
In general patients never treated with psichopharmaceutical drugs require lower doses than patients already treated with antianxiety agents or sedative agents, antidepressants, hypnotic agents or to patients with chronic alcoholism.
It is recommended always to use the lowest dose, to avoid the risk of residual sedation or ataxia.
Should side effects occur already with the administration of the first dose, a decrease of the dosage is recommended.
The treatment should be as short as possible.
Patients should be regularly reassessed and the need for continued treatment should be carefully evaluated, particularly if the patient does not show any symptoms.

Anxiety:
Treatment should be started with a dose of 0.25 to 0.50 mg given 3 times daily. The dose may be increased depending on the patient's needs up to a maximum daily dose of 4 mg, given in divided doses for a time period not over 8–12 weeks, including a gradual discontinuation time.
In particular cases it may be necessary to extend the period of treatment over the maximum time of treatment; in that case this should not occur without any reassessment of the patient.
In elderly patients, in patients with severe liver disease or in patients with physical debilitating diseases, the usual starting dose is 0.25 mg, given 2 or 3 times daily. This may be increased if needed and tolerated. The treatment can be done even using the drop form: 10 drops correspond to 0.25 mg of alprazolam, 20 drops to 0.50 mg.

Agoraphobia and panic disorder:
Treatment for patients with agoraphobia associated with panic attacks with or without phobic avoidance, should be initiated with a dose of 0.5-1 mg given before bedtime, for one or two days. The dose should be then adjusted according to each single patient. The dose may be increased at intervals of 3 and 4 days in increments of no more than 1 mg. Dosage increase can be done first at noon, then in the morning and finally in the afternoon/evening till the achievement of a therapy regimen on a 3 or 4 times per day schedule for a maximum period of 8 month.
In an international multicentre study which involved a high number of patients, the average daily dose was of 5.7 mg; only in some rare cases it was necessary to increase the dose to 10 mg per day.

Therapy discontinuation
The dosage should be reduced slowly in keeping with good medical practice.
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.

4.3 Contraindications
XANAX is contraindicated in patients with known hypersensitivity to the benzodiazepines and their derivatives and in patients with narrow-angle glaucoma who are receiving an appropriate therapy. The drug may be used in patients with open-angle glaucoma who are receiving an appropriate therapy. It is contraindicated in patients with severe respiratory failure. Severe liver disease. Do not administer to children, during the first trimester of pregnancy and lactation. Severe myasthenia. Nocturnal apnea syndrome.

4.4 Special warnings and precautions for use
Tolerability
A certain loss in efficacy to the hypnotic effects of benzodiazepines may develop after continuous use for some weeks.

Dependence
Use of benzodiazepines may lead to physical and psychological dependence to these drugs. The risk of dependence increases with the dose and duration of treatment; it appears to be greater in patients with history of substance or alcohol abuse.
Once physical dependence developed, the abrupt discontinuation will be accompanied by withdrawal symptoms.
These could include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms could be identified: derealisation, depersonalisation, hyperacusia, drowsiness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or seizures.

Insomnia or rebound anxiety
After discontinuation of the treatment, a transient syndrome could develop, in which symptoms that led to the treatment with benzodiazepines recur in a worsened form. It can be accompanied by other reactions, including mood changes, anxiety, restlessness or sleep disorders. Since the risk of withdrawal symptoms is greater after the abrupt discontinuation of the treatment, it is suggested to gradually reduce the dosage.

Duration of treatment
The duration of treatment should be as short as possible (see Posology) and in case of anxiety it should not extend over 8–12 weeks, including a period of tapering. The prolongation of therapy beyond this period should be undertaken only with prior reassessment of the clinical situation. At the beginning of the treatment, it is advisable to inform the patient that it will have a limited duration and explain in detail how the dosage should be gradually reduced.
Furthermore, it is important for the patient to be informed of the possibility of occurrence of rebound effects, thus minimizing the patient's anxiety regarding these symptoms should they occur at the drug discontinuation.
When treated with benzodiazepines with a long duration of effect, the patients should be informed that it is not advisable to replace the drug abruptly with another benzodiazepine with a short effect because withdrawal symptoms could occur.

Discontinuation of treatment
As any other benzodiazepine, XANAX dosage should be gradually reduced, since abrupt or too quick discontinuation may lead to the occurrence of withdrawal symptoms.
These could include mild dysphoria and insomnia or they may occur as major syndromes with muscular and abdominal cramps, vomit, sweating and tremors.
There have been reports of occasional withdrawal seizures upon rapid decrease or abrupt discontinuation of treatment with alprazolam.
These symptoms, particularly the most severe ones, are generally more common in patients treated with a massive dose for prolonged periods. However, withdrawal symptoms have been reported even after sudden discontinuation of the administration of therapeutic doses of benzodiazepines. Therefore, the abrupt discontinuation should be avoided and a gradual dose reduction is prescribed (see Posology).
During the phase of drug discontinuation in patients with panic disorders, some symptoms may be observed that are related to the re-occurrence of panic attacks that simulate those occurring in case of withdrawal.

Amnesia
Benzodiazepines could induce an anterograde amnesia. This occurs more often several hours after the ingestion of the drug. Therefore, in order to reduce this risk, the patients should be assessed to have an uninterrupted sleep for 7–8 hours (see Undesirable effects).

Psychiatric and paradoxical reactions
As with all benzodiazepines, paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, alteration of behaviour could occur. Should any of the above events occur, alprazolam should be discontinued. These reactions are more common in children and elderly persons.

Specific groups of patients
Benzodiazepines should not be administered to children without careful assessment of the real need of the treatment; the duration of the treatment should be as short as possible. In elderly patients a low-dose therapy should be employed (see Posology). A lower dosage is also recommended for patients with chronic respiratory deficiency because of the risk of respiratory depression.
Usual precautions are recommended for the treatment of patients with impaired liver and/or kidney function, while in patients with severe liver and/or kidney failure, benzodiazepines are not indicated because they could precipitate an encephalopathy.
Benzodiazepines are not recommended for the primary treatment of psychotic disease. Benzodiazepines should not be used alone for the treatment of depression or anxiety or anxiety associated to depression (suicide can be precipitated in these patients).

The combination with other psychotropic drugs requires a particular caution and alertness by the physician in order to prevent unexpected interaction effects to occur. As it occurs with other psychotropic drugs, in patients with severe depression or with tendency to suicide alprazolam should be administered with due precautions and prescribed in an adequate package.
Since in panic disorders a concomitant depression disorder is observed (primary or secondary) with an increased number of suicides in patients untreated, it is important that the same precautions are adopted when using XANAX for the treatment of patients with panic disorders as with the use of any other psychotropic drug for the treatment of depressed patients or those with suspected ideation or attempted suicide.
Benzodiazepines should be used with extreme care in patients with history of drug or alcohol abuse.
Patients with normal alcohol and/or substances abuse, when treated with benzodiazepines should be kept under a strict medical control, because of their predisposition to habituation and dependence.
For this reason, patients should be warned of the risks related to the concomitant intake of alcohol or other drugs having a depressant action on the CNS.
Keep far from the reach and sight of children

4.5 Interactions with other medicinal products and other forms of interactions
The concomitant alcohol intake should be avoided, because the sedative effect can be increased when the drug is taken along with alcohol. This affects negatively the ability to drive or use machines.
Concomitant use with depressant agents of CNS: the depressant effect on CNS could be enhanced with the concomitant administration of anti-psychotic drugs (neuroleptics), hypnotic substances, anxiolytic/sedative agents, antidepressants, narcotic analgesics, antiepileptics, anesthetics, antihistamines and sedative drugs.
As with narcotic analgesics increased euphoria could occur leading to an increase in psychological dependence.
The activity of benzodiazepines could be increased by compounds which inhibit certain liver enzymes (in particular cytochrome P 450).
This can also be applied, though in a lower degree, to benzodiazepines that are metabolised only via conjugation.
The steady-state plasma concentrations of imipramine and desipramine has been reported to be increased of 31% and 20%, respectively, with the concomitant administration of XANAX at doses up to 4 mg/day.
Kinetic interactions between benzodiazepines and other drugs have been described. For instance, clearance of alprazolam and other drugs can be reduced with the concomitant administration of cimetidine or macrolide antibiotics.
The clinical meaning of these effects was not defined.

4.6 Pregnancy and lactation
Because of the risk of potential congenital malformations already observed with the use of other benzodiazepines, XANAX should not be administered during the first trimester of pregnancy.
If the drug is prescribed to a woman of child bearing potential, she has to be warned to consult her physician regarding the discontinuation of the drug if she intends to become pregnant or suspects that she is pregnant.

If, because of serious medical reasons, the drug is administered in the last period of pregnancy or during childbearing at high doses, effects on the newborn such as hypothermia, hypotonia and moderate respiratory depression could be observed due to the pharmacological activity of the drug.
Further, newborns, born from mothers who have been chronically administered benzodiazepines during the last weeks of pregnancy, may develop a physical dependence and a certain risk of withdrawal symptoms during the post-natal period. Since benzodiazepines are excreted into the mother's milk, they should not be administered during lactation.

4.7 Effects on ability to drive and use machines
Sedation , amnesia, alteration of concentration and of muscle function may affect their ability to drive and use machinery. If sleep time is not sufficient, vigilance alteration will be probably increased (see Interactions).
Given the depressant effect of alprazolam on the CNS, patients treated with the drug should be cautioned against activities requiring mental alertness, judgement and physical coordination such as driving or operating machinery, until side effects such as drowsiness or vertigo can be completely excluded.

4.8 Undesirable effects
Potential side effects to XANAX are generally observed at the beginning of therapy and usually disappear upon continued medication use or reduction
In patients treated for anxiety, the undesirable effects more frequently reported include drowsiness, vertigo/light-headedness.
Less frequent effects have been reported, they include blurred vision, headache, depression, insomnia, nervousness, tremor, changes in weight, memory disturbance/amnesia, impaired coordination, ataxia, gastrointestinal symptoms and hyperactivity of the autonomic nervous system.
As with other benzodiazepines, paradoxical reactions such as: stimulation, agitation, difficulty of concentration, confusion, hallucinations and other behavioral reactions may be rarely reported. Furthermore, the following reactions may be observed: numbness of emotions, decreased vigilance, cutaneous reactions.
Rarely, increased intraocular pressure has been reported. Treatment with benzodiazepine anxiolytic drugs, including XANAX, can lead to the following undesirable effects: dystonia, irritability, anorexia, fatigue, language difficulty, jaundice, muscle weakness, alteration of libido, menstrual irregularity, incontinence or micturition difficulties and impaired liver function.
Most common undesirable effects **in patients treated for panic disorder and panic attacks** are: sedation/sleepiness, fatigue, ataxia/impaired coordination and language difficulty. Less common undesirable effects are: mood changes, gastrointestinal symptoms, dermatitis, memory disorders, sexual dysfunctions, alteration in cognition and confusion.

Amnesia
Though to date for XANAX no cases have been reported, benzodiazepines could cause an anterograde amnesia. This may occur even at a therapeutic dosage and the risk increases with higher levels. Amnestic effects may be associated to behavioural alterations (see Special warnings and precautions of use)

Depression
A pre-existing depression disorder can be unmasked by the use of benzodiazepines.

Psychiatric and paradoxical reactions
Benzodiazepines or benzodiazepine-like compounds could cause reactions such as, restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, behavioural alterations.
These reactions could be rather severe: they are more likely to occur in children and elderly persons.

Dependence
The use of benzodiazepines (even at a therapeutic dosage) could lead to physical dependence: the discontinuation of the treatment may lead to rebound or withdrawal reactions (see Special warnings and precautions of use). Psychological dependence may also occur. Abuse of benzodiazepines has been reported.

4.9 Overdose
Manifestations of overdose include increased pharmacological activity in particular ataxia and somnolence.
As with other benzodiazepines, an overdose should not pose a life-threatening risk, except when concomitant CNS depressants (alcohol included) are involved.
When treating overdose of any drug, it should be borne in mind that multiple agents may have been simultaneously intaken.
Following an oral overdose of benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage should be made while protecting the airways, if the patient is consciousless.
If voiding the stomach does not produce any improvements, active charcoal should be administered in order to reduce the drug absorption. A special attention should be paid to respiratory and cardiovascular functions during emergency treatment. Manifestations of overdose of benzodiazepines usually include various degrees of depression of the central nervous system, ranging from clouding of consciousness to coma. In mild cases, the symptoms include: clouding of consciousness, mental confusion and lethargy. In most severe cases, the symptoms could include: ataxia, hypotonia, hypotension, respiratory depression, seldom coma and very seldom fatality.
"Flumazenil" can be useful as an antidote.

Animal experiments have indicated that a cardio-circulatory collapse could occur after massive intravenous doses of (over 195 mg/kg; 975-fold the maximum recommended daily human dose).
The animals were treated with positive mechanical ventilation and intravenous infusion of norepinephrine. Other experiments in the animals showed that diuresis or hemodialysis are of little help in treating overdose.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Therapeutic group: Anxiolitics, benziodiazepine derivates
ATC Code: N05BA12
XANAX contains alprazolam, a triazole benzodiazepine analogue as active ingredient.

Alprazolam binds-up to GABA benzodiazepine receptor complex, synergizing the GABA activity, an inhibitory neurotransmitter, resulting in a reduction of the neuronal stimulation. This feature gives the product anxiolytic, hypnotic and sedative properties.
Clinical studies performed in healthy volunteers showed that single doses up to 4 mg produce effects that can be considered as part of its pharmacological activity. Significant effects on cardiovascular and respiratory systems have not been observed.

5.2 Pharmacokinetic properties
Orally administered alprazolam is rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours after the administration.
Plasma levels are proportional to the dose; with doses ranging from 0.5 to 3 mg, peak plasma concentrations from 8 to 37 ng/ml may be observed.
The mean half-life of alprazolam to a healthy adult is of 11.2 hours (interval: 6.3-26.9 hours).
The main metabolites are alpha-hydrossialprazolam and a benzophenone.
The biological activity of hydrossi-alprazolam is of about one half versus alprazolam. Benzofenone is not active. The plasma levels of these metabolites are extremely low, however, their half-lives are the same as that of alprazolam.
Alprazolam and its metabolites are excreted primarily into the urine.
XANAX does not affect the prothrombin time or plasma warfarin level in volunteers administered sodium warfarin orally.
In-vitro alprazolam is about 80% protein bound.
Upon administration to a female pregnant mouse, alprazolam ^{14}C shows that its radioactivity is uniformly distributed to the foetuses

in concentrations of ^{14}C approximately equal to those present in blood and in the skeletal muscle of the mother.
Differences in the kinetics and metabolism of benzodiazepines were observed under different pathologic conditions, including alcoholism and abnormalities of the liver and kidney function as well as in the geriatric patient.
In elderly persons, the mean half-life of alprazolam is of 16,3 hours (range: 9-26.9 hours). In healthy women the simultaneous administration of oral contraceptives increases the half-life of alprazolam (mean half-life: 12.4 hours). The simultaneous administration of cimetidine increases the mean half-life of alprazolam (16.6 hours).
In patients with alcoholic liver disease the half-life of alprazolam varies between 5.8 and 65.3 hours, with an average of 19.7 hours. In obese patients the interval of the half-life of XANAX varies between 9.9 and 40.4 hours, resulting in an average of 21.8 hours.
Considering the similarity of alprazolam with other benzodiazepines, it is expected that the drug may cross the placenta and is excreted into the mother's milk.

5.3 Preclinical data of safety
The results of acute toxicity tests in experimental animals are reported here below:

Animal species	Administration	LD_{50} (mg/kg)
Mouse	i.p.	500
Rat	p.o.	2171
Rat	i.p.	819

In long-term toxicity tests in the rats treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for two 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. Studies in the experimental animals (rats and rabbits) showed that alprazolam is not teratogen and has no influence on fertility.
Carcinogenesis and mutagenesis tests were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:
XANAX 0.25 mg tablets
Excipients: lactose; microcrystalline cellulose; dioctyl sodium sulphosuccinate; sodium benzoate; precipitated silica; maize starch; magnesium stearate.

XANAX 0.50 mg tablets
Excipients: lactose, microcrystalline cellulose; dioctyl sodium sulphosuccinate; sodium benzoate; precipitated silica; maize starch; magnesium stearate; E110; aluminum oxide hydrate.

XANAX 1 mg tablets
Excipients: lactose, microcrystalline cellulose; dioctyl sodium sulphosuccinate; sodium benzoate; precipitated silica; maize starch; magnesium stearate; E132; aluminum oxide hydrate. .

6.3 Shelf-life:
Don't use the product after the expiry date which is stated on the carton after EXP.: The expiry date refers to the last day of that month.

6.4 Special precautions for storage
Keep away from light sources.
Keep vial and blisters in the cardboard box
Store below 30 °C

6.5 Nature and contents of the container
Blister in matt PVC/Al
50 tablets 0.25 mg
50 tablets 0.50 mg
50 tablets 1 mg
30 tablets 0.25 mg
30 tablets 0.50 mg
30 tablets 1 mg
Not all pack sizes may be marketed.

6.6 Instructions for use and handling
No special instructions

10. DATE OF REVISION OF THE TEXT:
December 22, 2006

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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists