NEW ZEALAND DATA SHEET

1. PRODUCT NAME

XANAX® 0.25 mg, 0.5 mg and 1.0 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.25 mg tablet contains 0.25 mg alprazolam

Each 0.5 mg tablet contains 0.5 mg alprazolam

Each 1.0 mg tablet contains 1.0 mg alprazolam

Excipients with known effects:

- Lactose monohydrate
- Sodium benzoate

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

XANAX 0.25mg tablets are white, scored, ovoid shaped tablets coded "Upjohn 29". Length 9.1 mm, Width 5.5 mm, Thickness 3.5 mm.

XANAX 0.5mg tablets are pink coloured, scored, ovoid shaped tablets coded "Upjohn 55". Length 9.1 mm, Width 5.5 mm, Thickness 3.5 mm.

XANAX 1.0mg tablets are lavender coloured, scored, ovoid shaped tablets coded "Upjohn 90". Length 9.1 mm, Width 5.5 mm, Thickness 3.5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XANAX (alprazolam) is indicated for the treatment of:

1. **Anxiety states (anxiety neuroses).**
   Symptoms which occur in such patients include anxiety, tension, fear, insomnia, apprehension, restlessness, concentration difficulties, irritability and/or autonomic hyperactivity resulting in a variety of somatic complaints.

2. **Mixed anxiety-depression**.
   Symptoms of both anxiety and depression occur concurrently in such patients.

3. **Neurotic or reactive depression.**
Such patients primarily exhibit a depressed mood or a pervasive loss of interest or pleasure. Other characteristics include anxiety, appetite disturbances, changes in weight, cognitive disturbances, decreased energy, feeling of worthlessness or guilt, insomnia, somatic complaints, or thoughts of death or suicide.

4. **Anxiety states, mixed anxiety-depression, or neurotic depression** associated with other diseases such as the chronic phase of alcohol withdrawal and functional or organic disease, particularly certain gastrointestinal, cardiovascular, or dermatological disorders.

The effectiveness of XANAX in the treatment of anxiety, anxiety associated with depression and neurotic (reactive) depression for long-term use exceeding six months has not been established by systematic clinical trials.

The physician should periodically reassess the usefulness of the drug for the individual patient.

4.2 Dose and method of administration

Dose

The optimum dose should be individualised, based upon the severity of the symptoms and individual patient response. The usual dose will meet the needs of most patients. In patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquilizers, antidepressants or hypnotics. It is recommended that the general principle of using the lowest effective dose be followed, especially in elderly or debilitated patients to preclude the development of ataxia or oversedation.

Indication or population	**Usual starting dosage** (if side effects occur dose should be lowered)	***Usual dosage range***
Anxiety	0.25 to 0.5 mg, given three times daily	0.5 to 4.0 mg daily, given in divided doses
Depression	0.5 mg, given three times daily	1.5 to 4.5 mg daily, given in divided doses
Geriatric patients or in the presence of debilitating disease	0.25 mg, given two to three times daily	0.5 to 0.75 mg daily, given in divided doses; to be gradually increased if needed and tolerated

Duration of Treatment

Data are available to support usage of up to 6 months for anxiety and depression.

The risk of dependence may increase with dose and duration of treatment, therefore, the lowest possible effective dose and duration should be used and the need for continued treatment reassessed frequently (see section 4.4 **Special warnings and precautions for use**).

Discontinuation of Treatment

To discontinue alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

Use in Children

Safety and efficacy have not been established in children under 18 years of age.

4.3 Contraindications

XANAX is contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam or to any component of the product's formulation.

4.4 Special warnings and precautions for use

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including alprazolam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use 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 alprazolam 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. Advise both patients and caregivers about the risks of respiratory depression and sedation when alprazolam is used with opioids (see section 4.5 Interactions with other medicines and other forms of interactions).

Renal and Hepatic Impairment

Caution is recommended when treating patients with impaired renal or hepatic function.

Dependence

Habituation and emotional/physical dependence may occur with benzodiazepines, including alprazolam. As with all benzodiazepines, the risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse. Drug abuse is a known risk for alprazolam and other benzodiazepines, and patients should be monitored accordingly when receiving alprazolam. Alprazolam may be subject to diversion.

There have been reports of overdose-related deaths when alprazolam is abused with other central nervous system (CNS) depressants including opioids, other benzodiazepines, and alcohol. These risks should be considered when prescribing or dispensing alprazolam. To reduce these risks the smallest appropriate quantity should be used and patients should be advised on the proper storage and disposal of unused drug (see section 4.2 **Dose and method of administration**, section 4.8 **Undesirable effects** and section 4.9 **Overdose**).

Discontinuation

During discontinuation of alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam (see section 4.2, **Dose and method of administration** - Discontinuation of Treatment, and section 4.8 **Undesirable effects**).

Psychiatric Disorders

Panic disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of XANAX in treating patients with panic disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of the prescription.

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

The use of alprazolam has not been established in certain types of depression.

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines produce additive CNS depressant effects, including respiratory depression, when co-administered with opioids, alcohol or other drugs producing CNS depression (see section 4.4 Special warnings and precautions for use).

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 GABAA 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. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, *in vitro* studies with alprazolam, and clinical studies with drugs metabolised similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended.
- Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine, and cimetidine.
- Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.
- Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offsets this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.
- Increased digoxin concentrations have been reported when alprazolam was given, especially in the elderly (over 65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

4.6 Fertility, pregnancy and lactation

PregnancyCategory C

The data concerning teratogenicity and effects on postnatal development and behaviour following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class that *in utero* exposure may be associated with malformations. Later studies with the benzodiazepine class of drugs have provided no clear evidence of any type of defect. Infants exposed to benzodiazepines during late third trimester of pregnancy or during labour have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding

Levels of benzodiazepines, including alprazolam, in breast milk are low. However, nursing should not be undertaken while using benzodiazepines.

Fertility

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about using alprazolam while operating motor vehicles or engaging in other dangerous activities until it is established that they do not become drowsy or dizzy while receiving the drug.

4.8 Undesirable effects

Adverse effects, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

As with other benzodiazepines, adverse effects such as concentration difficulties, confusion, hallucinations, stimulation, and adverse behavioural effects such as irritability, agitation, rage and aggressive or hostile behaviour have been reported rarely.

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients who have borderline personality disorder, a prior history of violent or aggressive behaviour, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

Undesirable effects associated with alprazolam therapy in patients participating in controlled clinical studies are as follows:

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Metabolism and Nutrition Disorders	Common	Decreased appetite
Psychiatric Disorders	Very Common	Depression
	Common	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness
	Uncommon	Drug dependence
Nervous System Disorders	Very Common	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache
	Common	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia, lethargy, tremor
	Uncommon	Amnesia
	Not known	Autonomic manifestations
Eye Disorders	Common	Vision blurred
Gastrointestinal Disorders	Very Common	Constipation, dry mouth
	Common	Nausea

MedDRA System Organ Class	Frequency	Undesirable Effects
	Not known	Various gastrointestinal symptoms
Musculoskeletal, Connective Tissue and Bone Disorders	Uncommon	Muscular weakness
General Disorders and Administration Site Conditions	Very Common	Fatigue, irritability
Investigations	Common	Weight decreased, weight increased

Post-Marketing Experience

The following additional adverse effects have been reported:

MedDRA System Organ Class	Frequency	Undesirable Effects
Endocrine disorders	Not known	Hyperprolactinaemia
Psychiatric disorders	Common	Libido increased
	Uncommon	Mania, hallucination, anger, agitation
	Not known	Hypomania, aggression, hostility, thinking abnormal, psychomotor hyperactivity, drug abuse
Nervous system disorders	Not known	Autonomic nervous system imbalance, dystonia
Gastrointestinal disorders	Not known	Gastrointestinal disorder
Hepatobiliary disorders	Not known	Hepatitis, hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Common	Dermatitis
	Not known	Angioedema, photosensitivity reaction
Renal urinary disorders	Uncommon	Incontinence
	Not Known	Urinary retention
Reproductive system and breast disorders	Common	Sexual dysfunction
	Uncommon	Menstruation irregular
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome
	Not Known	Oedema peripheral
Investigations	Not Known	Intraocular pressure increased

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Signs and Symptoms

Overdosage of benzodiazepines is usually manifested by an extension of their pharmacologic activity, including respiratory depression and central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms may include drowsiness, mental confusion and lethargy, impaired coordination, diminished reflexes, slurred speech, dilated pupils, absent bowel sounds, and tachycardia. In more serious cases symptoms may include ataxia, hypotonia, hypotension, hypothermia, rhabdomyolysis, atrio-ventricular block, coma and very rarely death. Serious sequelae occur when XANAX is taken with other drugs and/or ethanol is concomitantly ingested. Deep coma, marked hypotension and respiratory depression may indicate other drugs have been ingested as well. In terms of duration, most obtunded patients become arousable within 12 to 36 hours following an acute overdose.

Treatment

In the management of overdosage it should be borne in mind that multiple agents may have been taken. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. Following overdosage with XANAX tablets, activated charcoal should be given to reduce absorption. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of CNS actions of benzodiazepines. 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. Please consult the flumazenil product information prior to usage.

Haemoperfusion, forced diuresis and haemodialysis are generally not useful in benzodiazepine intoxication. Ipecac-induced emesis is not recommended due to the potential for CNS depression.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

CNS agents of the 1.4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown.

Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 mg/mL were observed.

Distribution

In vitro, alprazolam is bound (80 percent) to human serum protein.

Biotransformation

The predominant metabolites are ∝-hydroxy alprazolam and a benzophenone derived from alprazolam. The biological activity of ∝-hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as alprazolam.

Elimination

The mean elimination half-life of alprazolam is 12 - 15 hours. Alprazolam and its metabolites are excreted primarily in the urine. The mean percentage excreted over a two week period following a single ^{14}C alprazolam dose was 78.8 +/- 2.1% in urine and 7.02 +/- 0.6% in faeces.

Enzyme Induction

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Special Populations

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. It has not yet been determined if similar changes occur in the pharmacokinetics of alprazolam.

5.3 Preclinical safety data

Carcinogenesis

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

Mutagenesis

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

Effect of Anaesthetic and Sedative Drugs

Nonclinical research has shown that administration of anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with alprazolam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

XANAX 0.25 mg tablets

Colloidal silicon dioxide,
Docusate sodium (85%) with sodium benzoate (15%),
Lactose monohydrate,
Magnesium stearate,
Maize starch,
Microcrystalline cellulose.

XANAX 0.5 mg tablets

Colloidal silicon dioxide,
Erythrosine,
Docusate sodium,
Sodium benzoate,
Lactose monohydrate,
Magnesium stearate,
Maize starch,
Microcrystalline cellulose.

XANAX 1 mg tablets

Colloidal silicon dioxide,
Erythrosine,
Indigo carmine,
Docusate sodium (85%) with sodium benzoate (15%),
Lactose monohydrate,
Magnesium stearate,
Maize starch,
Microcrystalline cellulose.

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

XANAX tablets 0.25 mg, 0.5 mg and 1.0 mg are available in quantities of 50 or 100 (not all presentations available).

6.6 Special precautions for disposal and other handling

None stated.

7. MEDICINE SCHEDULE

Class C5 Controlled Drug

8. SPONSOR

Pfizer New Zealand Ltd
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

30 August 1984

10. DATE OF REVISION OF THE TEXT

27 December 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Addition of "list of excipients"
4.2, 4.4, 4.5 4.8	Addition of abuse, dependence and withdrawal text