

**APPROVED PACKAGE INSERT**

**SCHEDULING STATUS:**

S5

**PROPRIETARY NAMES AND DOSAGE FORM:**

XANOR<sup>®</sup> 0,25 mg tablet

XANOR<sup>®</sup> 0,5 mg tablet

XANOR<sup>®</sup> 1,0 mg tablet

XANOR<sup>®</sup> 2,0 mg tablet

XANOR<sup>®</sup> SR 0,5 mg tablet

XANOR<sup>®</sup> SR 1,0 mg tablet

XANOR<sup>®</sup> SR 2,0 mg tablet

**COMPOSITION:**

Each XANOR 0,25 mg tablet contains 0,25 mg alprazolam and 0,1125 mg Sodium benzoate (preservative)

Each XANOR 0,5 mg tablet contains 0,5 mg alprazolam and 0,1125 mg Sodium benzoate (preservative)

Each XANOR 1,0 mg tablet contains 1,0 mg alprazolam and 0,1125 mg Sodium benzoate (preservative)

Each XANOR 2,0 mg tablet contains 2,0 mg alprazolam and 0,225 mg Sodium benzoate (preservative)

Each XANOR SR tablet contains 0,5 mg; 1,0 mg; or 2,0 mg alprazolam

XANOR contains the following inactive ingredients:

XANOR tablets: Colloidal silicon dioxide, docusate sodium with sodium benzoate, lactose hydrous, magnesium stearate, microcrystalline cellulose and starch with erythrosine sodium or FD and C blue as colourants.

XANOR SR tablets: Cellulose methylhydroxypropyl, lactose anhydrous, magnesium stearate, and silicon colloidal dioxide with FD & C blue as colourant.

**PHARMACOLOGICAL CLASSIFICATION:**

A 2.6. Tranquillisers

## **PHARMACOLOGICAL ACTION:**

### **Pharmacodynamic properties:**

Alprazolam is an anxiolytic agent of the benzodiazepine group. Benzodiazepines, including alprazolam, are thought to bind to central nervous system benzodiazepine receptors, thereby increasing the affinity of the receptor for gamma-aminobutyric acid (GABA). GABA, an inhibitory neurotransmitter, modulates the activity of other neurotransmitter systems, including the noradrenergic system.

### **Pharmacokinetic properties:**

The pharmacokinetics of alprazolam are linear over the recommended dosage range, with plasma concentrations being proportional to dose given. Alprazolam is almost completely bioavailable following oral administration. The bioavailability and pharmacokinetic characteristics of XANOR tablets or XANOR SR tablets are comparable, except for a slower rate of absorption of alprazolam from XANOR SR tablets. The slower absorption rate for XANOR SR tablets results in peak plasma alprazolam concentrations that are approximately one-half that of an equivalent dose of XANOR tablets; peak concentrations occur within one to two hours after a single dose of XANOR tablets, and 5 to 11 hours after a single dose of XANOR SR tablets.

Steady-state plasma concentrations are achieved within three to four days of continuous dosing with either dosage form. When equivalent daily doses are given, steady-state peak and trough plasma alprazolam concentrations for XANOR SR tablets given once or twice a day are comparable to XANOR tablets given three or four times a day.

Alprazolam and its metabolites are excreted primarily in the urine. The predominant metabolites are alpha-hydroxy-alprazolam, 4-hydroxy alprazolam, and a benzophenone derived from alprazolam. Although they possess some pharmacological activity, the plasma levels of these metabolites are extremely low during chronic dosing. *In vitro*, alprazolam is bound (80 %) to human serum protein.

The plasma elimination half-life of alprazolam has been found to be about 11 to 15 hours in healthy adults. A comparable elimination half-life for XANOR SR tablets indicates that the metabolism and elimination of alprazolam are the same for both dosage forms. Alprazolam clearance has been reported to be delayed in patients with impaired hepatic and renal function, alcoholism, in elderly or obese patients, and by the co-administration of certain medicines.

## **INDICATIONS:**

XANOR is indicated for the treatment of:

- SHORT-TERM RELIEF OF SYMPTOMS OF ANXIETY
- TREATMENT OF ANXIETY DISORDERS

Anxiety disorder is a condition corresponding most closely to the latest APA Diagnostic and Statistical Manual [DSM] diagnosis of generalised anxiety disorder.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Diagnostic criteria for Generalised Anxiety Disorder:

A. Generalised, persistent anxiety is manifested by symptoms from three of the following four categories:

1. Motor tension:

Shakiness, jitteriness, jumpiness, trembling, muscle aches, tension, eyelid twitch, inability to relax, furrowed brow, strained face, restlessness and easily startled.

2. Autonomic hyperactivity:

Heart pounding or racing, sweating, cold clammy hands, dry mouth, light-headedness, dizziness, paraesthesias, upset stomach, diarrhoea, discomfort in the pit of the stomach, hot or cold spells, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

3. Apprehensive expectation:

Fear, anxiety, worry, rumination, and anticipation of misfortune to self and others.

4. Vigilance and scanning:

Hyper attentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", impatience and irritability.

B. The anxious mood has been continuous for at least one month.

C. Not due to another mental disorder, such as Depressive Disorder or Schizophrenia.

D. At least 18 years of age.

- ANXIETY ASSOCIATED WITH DEPRESSION
- MIXED ANXIETY-DEPRESSION
- DEPRESSION

Depression can be variously described as neurotic depression, reactive depression, major depressive disorder, etc., depending upon local psychiatric nosology. Usage has not been established in depression

with psychiatric features, in bipolar disorders or in "endogenous" depression (i.e., severely depressed inpatients).

- **PANIC DISORDERS**

This includes panic disorder with or without agoraphobia. The essential feature of panic disorder is the unexpected panic attack, a sudden onset of intense apprehension, fear, or terror.

Panic disorder is an illness characterised by recurrent panic attacks. Later in the course of this disturbance, certain issues, 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).

Diagnostic criteria for Panic Disorder:

A. At least three panic attacks within a three-week period in circumstances other than during marked exertion or in a life-threatening situation. The attacks are not precipitated by exposure to a circumscribed phobic stimulus.

B. Panic attacks are manifested by discrete periods of apprehension or fear, and at least four of the following symptoms appear during each attack:

dyspnoea; palpitations; chest pain or discomfort; choking or smothering sensations; dizziness, vertigo, or unsteady feelings; feelings of unreality; paraesthesias (tingling in hands or feet); hot and cold flushes; sweating; faintness; trembling or shaking; smothering sensations, dizziness.

XANOR is indicated for use of up to six months duration for anxiety and depression and for up to eight months in the treatment of panic disorder with or without some phobic avoidance. The effectiveness for long-term use, exceeding six months has not been established.

**CONTRAINDICATIONS:**

XANOR is contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of these formulations.

XANOR is not recommended for patients whose primary diagnosis is schizophrenia

Concomitant administration with antiretroviral protease inhibitors, ketoconazole, as the elimination of XANOR is delayed several fold.

**WARNINGS and SPECIAL PRECAUTIONS:**

XANOR usage has not been established in certain types of depression. See INDICATIONS.

Implemented in line with Regulation 9 and MCC Guidance, Package inserts for human medicines, January 2014

XANOR must be used with caution in patients with impaired renal or hepatic function, pulmonary disease or limited pulmonary reserve.

The safety and efficacy of XANOR has not been established in children under the age of 18 years.

XANOR produces additive CNS depressant effects when co-administered with alcohol or other medicines producing CNS depression.

Habituation and emotional/physical dependence may occur with XANOR. 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. Caution should be particularly used when prescribing XANOR to patients who are prone to abuse drugs (e.g. alcoholics and drug addicts) because of their predisposition to habituation and dependence.

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of XANOR. 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 XANOR and special care must be taken in the treatment of epileptic patients. See DOSAGE AND DIRECTIONS FOR USE section for dose reduction during withdrawal period.

XANOR should be avoided in psychotic patients and patients suffering from mental depression unless there is a marked component of anxiety in their illness.

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 XANOR in treating patients with panic disorders as is exercised with the use of any psychotropic medicines in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Effects on ability to drive and use machinery:**

Caution patients about using XANOR while operating motor vehicles or other dangerous activities until it is established that they do not become impaired while taking XANOR.

### **INTERACTIONS:**

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 XANOR tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Pharmacokinetic interactions can occur when XANOR is administered along with medicines that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450III A4) may increase the concentration of XANOR and enhance its activity. Data from clinical and *in vitro* studies with XANOR, and clinical studies with medicines metabolised similarly to XANOR provide evidence for varying degrees of interaction and possible interaction with XANOR for a number of medicines. Based on the degree of interaction and the type of data available, the following recommendations are made:

- Caution and consideration of dose reduction is recommended when XANOR is co-administered with nefazodone, fluvoxamine, and cimetidine.
- Caution is recommended when XANOR is co-administered with fluoxetine, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.

### **PREGNANCY AND LACTATION:**

#### **Pregnancy:**

The safety of XANOR during pregnancy and lactation has not been established. The potential for congenital malformations in children of patients who have received XANOR during pregnancy exists.

XANOR should not be administered during labour. Given during labour, it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking.

#### **Lactation:**

XANOR should not be administered to mothers breastfeeding their infants, since XANOR is excreted in human breast milk.

### **DOSAGE AND DIRECTIONS OF USE:**

Patients should be periodically re-assessed and dosage adjustments made, as appropriate.

Implemented in line with Regulation 9 and MCC Guidance, Package inserts for human medicines, January 2014

The optimum dose of XANOR tablets should be individualised based upon the severity of the symptoms and individual patient response. In patients who require higher doses, dosage should be increased cautiously to avoid adverse effects.

When higher dosage is required, the evening dose should be increased before the daytime dose. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquillisers, antidepressants or hypnotics or those with a history of chronic alcoholism. It is recommended that the general principle of using the lowest effective dose be followed in elderly or debilitated patients to preclude the development of ataxia or over sedation.

XANOR SR tablets may be administered once daily, preferably in the morning.

The XANOR SR tablets should be taken intact; they should not be chewed, crushed or broken.

<b>XANOR tablets</b>	<b>Usual Starting Dose*</b>	<b>Usual Dose Range</b>
Anxiety	0,25 to 0,5 mg given 3 times daily	0,5 to 4,0 mg daily, given in divided doses
Mixed anxiety/depression Anxiety associated with depression	0,5 mg given 3 times daily	1,5 to 4,5 mg daily, given in divided doses
Panic Disorders	0,5 - 1,0 mg given at bedtime or 0,5 mg three times daily	The dose should be adjusted to patient response. Dosage adjustments should be in increments no greater than 1 mg every three to four days. With XANOR tablets, additional doses can be added until a three times daily or four times daily schedule is achieved. The mean dose in a large multi-clinic study was $5,7 \pm 2,27$ mg with occasional patients requiring a maximum of 10 mg daily.
Geriatric Patients or in the presence of debilitating disease	0,25 mg given two or three times daily.	0,25 to 0,75 mg daily, given in divided doses; to be gradually increased if needed and tolerated.

<b>XANOR SR tablets</b>	<b>Usual Starting Dose*</b>	<b>Usual Dose Range</b>
Anxiety	1 mg daily, in one or two doses	0,5 to 4,0 mg daily, in one or two doses
Mixed anxiety/depression Anxiety associated with 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 - 1,0 mg given at bedtime or 0,5 mg two times daily	In clinical trials the mean maintenance dose was between 5 and 6 mg per day given as a single daily dose or divided into two doses daily, with occasional patients needing up to 10 mg per day. The dose should be adjusted to patient response, with dose increments of no greater than 1 mg in the daily dose every three to four days.
Geriatric Patients	0,5 to 1,0 mg daily, given in one or two doses	0,5 to 1 mg daily; may be gradually increased if needed and tolerated.

\* If side effects occur, the dose should be lowered. See WARNINGS and SPECIAL PRECAUTIONS.

To discontinue treatment in patients taking XANOR tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANOR be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction (see WARNINGS and SPECIAL PRECAUTIONS).

**SIDE EFFECTS:**

The table below contains adverse events categorized as follows utilizing the incidence rates: Very common  $\geq 1/10$  ( $\geq 10\%$ ); Common  $\geq 1/100$  and  $< 1/10$  ( $\geq 1\%$  and  $< 10\%$ ); Uncommon  $\geq 1/1000$  and  $< 1/100$  ( $\geq 0,1\%$  and  $< 1\%$ ), Rare  $\geq 1/10\ 000$  and  $< 1/1000$  ( $\geq 0,01\%$  and  $< 0,1\%$ ); Very rare  $< 1/10\ 000$  ( $< 0,01\%$ ).

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

<b>MedDRA System Organ Class</b>	<b>Frequency</b>	<b>Undesirable Effects</b>
<b>Metabolism and nutrition disorders</b>	<i>Common</i>	Decreased appetite
<b>Psychiatric disorders</b>	<i>Common</i>	Confusional state, depression, irritability, libido decreased
	<i>Uncommon</i>	Aggression, insomnia, loss of libido, mood disorder, nervousness
	<i>Rare</i>	Hallucinations, agitation, rage
<b>Nervous system disorders</b>	<i>Very common</i>	Sedation, somnolence
	<i>Common</i>	Ataxia, balance impaired, coordination abnormal, dizziness, headache, memory impairment, dysarthria, hypersomnia, lethargy
	<i>Uncommon</i>	Amnesia, increased activity, tremor
	<i>Rare</i>	Intellectual impairment, slurred speech
<b>Eye disorders</b>	<i>Common</i>	Vision blurred
	<i>Rare</i>	Increased intraocular pressure
<b>Gastrointestinal disorders</b>	<i>Common</i>	Constipation, nausea, dry mouth
	<i>Uncommon</i>	Diarrhoea, vomiting
<b>Hepatobiliary disorders</b>	<i>Rare</i>	Abnormal liver function
<b>Skin and subcutaneous tissue disorders</b>	<i>Rare</i>	Dermatitis
<b>Musculoskeletal and connective tissue disorders</b>	<i>Uncommon</i>	Muscle twitching, muscle weakness
<b>Renal and urinary disorders</b>	<i>Uncommon</i>	Enuresis, urinary frequency
	<i>Rare</i>	Urinary retention
<b>Reproductive system and breast disorders</b>	<i>Uncommon</i>	Menstrual irregularities
	<i>Rare</i>	Sexual dysfunction

<b>General disorders and administration site conditions</b>	<i>Common</i>	Fatigue
<b>Investigations</b>	<i>Uncommon</i>	Jaundice, weight decreased, weight increased

**Post-marketing Surveillance:**

The following post-marketing events have been reported with XANOR:

<b>MedDRA System Organ Class</b>	<b>Frequency</b>	<b>Undesirable Effects</b>
<b>Endocrine disorders</b>	Less frequent	Hyperprolactinaemia
<b>Psychiatric disorders</b>	Less frequent	Hypomania, mania (see WARNINGS), hallucination, anger, aggression, hostility, agitation, libido disorder, abnormal thinking, psychomotor hyperactivity
<b>Nervous system disorders</b>	Less frequent	Dystonia
	Less frequent	Autonomic nervous system imbalance
<b>Gastrointestinal disorders</b>	Less frequent	Gastrointestinal disorder
<b>Hepatobiliary disorders</b>	Less frequent	Hepatitis, abnormal hepatic function, jaundice
<b>Skin and subcutaneous tissue disorders</b>	Less frequent	Dermatitis
	Less frequent	Angioedema
<b>Renal and urinary disorders</b>	Less frequent	Incontinence, urinary retention
<b>Reproductive system and breast disorders</b>	Less frequent	Sexual dysfunction, irregular menstruation
<b>General disorders and administration site conditions</b>	Less frequent	Peripheral oedema
<b>Investigations</b>	Less frequent	Increased intraocular pressure

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Symptoms of overdose with XANOR are extensions of its pharmacological action and include drowsiness, slurred speech, motor in-coordination, coma and respiratory depression. Serious sequela are rare unless other medicines and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive

of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

**IDENTIFICATION:**

XANOR 0,25 mg tablets are white, ovoid shaped, embossed with "Upjohn 29" on the one side and scored on the other side.

XANOR 0,5 mg tablets are pink, ovoid shaped, embossed with "Upjohn 55" on the one side and scored on the other side.

XANOR 1,0 mg tablets are lavender, ovoid shaped, embossed with "Upjohn 90" on the one side and scored on the other side.

XANOR 2,0 mg tablets are white capsule shaped, three scored tablets, embossed with "U94".

XANOR SR 0,5 mg tablets are light blue, round deep oval shape, embossed with "P & U 57".

XANOR SR 1,0 mg tablets are white, round deep oval shape, embossed with "P & U 59".

XANOR SR 2,0 mg tablets are light blue, pentagonal deep oval shape, embossed with "P & U 66".

**PRESENTATION:**

XANOR 0,25 mg and 1,0 mg are packed in blister packs of 30 and 100 tablets.

XANOR 0,5 mg is packed in blister packs of 30 and 100 tablets and in bottles containing 500 tablets.

XANOR 2,0 mg is packed in bottles containing 30 and 100 tablets.

XANOR SR tablets are packed in foil blisters of 60 tablets.

**STORAGE INSTRUCTIONS:**

Store at or below 30 °C. Keep tablets packed in bottles tightly closed.

Keep tablets in the carton until use. Protect from light. Keep out of reach of children.

**REGISTRATION NUMBERS:**

XANOR 0,25 mg tablets: M/2.6/233

XANOR 0,5 mg tablets: M/2.6/234

XANOR 1,0 mg tablets: M/2.6/235

XANOR 2,0 mg tablets: 27/2.6/96

XANOR SR 0,5 mg tablets: 29/2.6/0504

XANOR SR 1,0 mg tablets:29/2.6/0505

XANOR SR 2,0 mg tablets: 29/2.6/0506

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:**

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

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