PACKAGE INSERT

1999 -01- 26

SCHEDULING STATUS: S5

PROPRIETARY NAME (AND DOSAGE FORM):

ZOPAX 1,0 Tablets

COMPOSITION:

Each tablet contains 1,0 mg alprazolam.

Preservatives:	Methylparaben	0,09% m/m
	Propylparaben	0,009% m/m

PHARMACOLOGICAL CLASSIFICATION:

A 2.6 Tranquillisers

PHARMACOLOGICAL ACTION:

Alprazolam is an anxiolytic agent of the benzodiazepine group. It is believed that benzodiazepines enhance or facilitate the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain and mediates both pre- and post-synaptic inhibition in all regions of the central nervous system, following interaction between the benzodiazepine and a specific neuronal membrane receptor.

Following oral administration, alprazolam is readily absorbed from the gastrointestinal tract, usually within 1 to 2 hours. The half-life in plasma is 12 to 15 hours. Alprazolam is 70 to 80% bound to plasma protein. Steady-state plasma concentrations are usually attained within a few days. Alprazolam undergoes oxidative metabolism to metabolites and is eliminated as glucuronide conjugates primarily in the urine.

INDICATIONS:

ZOPAX is indicated for the management of anxiety disorders and the short-term relief of symptoms of anxiety. Anxiety associated with depression is also responsive to **ZOPAX.**

ZOPAX is also indicated for the treatment of panic disorders for up to eight months. The doctor should periodically re-assess the usefulness of **ZOPAX** for the individual patient.

ZOPAX is only indicated when the anxiety is severe, disabling or subjecting the individual to extreme stress.

CONTRA-INDICATIONS:

The safety of **ZOPAX** (alprazolam) in pregnancy has not been established. **ZOPAX should not be administered during pregnancy. Do not administer 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.**

ZOPAX (alprazolam) should not be administered to nursing mothers, since alprazolam is excreted in human breast milk.

ZOPAX (alprazolam) is contra-indicated in patients with known hypersensitivity to the benzodiazepines and in acute narrow angle glaucoma.

ZOPAX (alprazolam) is not recommended for use in patients whose primary diagnosis is schizophrenia, psychotic patients and patients suffering from mental depression or suicidal tendencies, unless there is a marked component of anxiety in their illness.
ZOPAX (alprazolam) is contra-indicated in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency, sleep apnoea, myasthenia gravis, porphyria and in children.

WARNINGS:

There is potential for abuse and dependence. Withdrawal symptoms may occur after periods of ordinary therapeutic doses. Individuals who are prone to abuse medicines such as alcoholics and drug addicts or patients on other central nervous system depressants, should be under careful surveillance while receiving a benzodiazepine because of the predisposition of such patients to habituation and dependence.

Patients receiving **ZOPAX** (alprazolam) should be advised not to drive or operate machinery, or climb dangerous heights until it is established that they do not become drowsy or dizzy while receiving **ZOPAX.** In these situations, impaired decision making could lead to accidents.

DOSAGE AND DIRECTIONS FOR USE:

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 8 - 12 weeks, including a tapering off process.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

A maximum dosage of 4 mg should not be exceeded, except in the treatment of panic disorders. The optimum dosage of **ZOPAX** (alprazolam), should be individualized 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 a higher dosage is required, the evening dose should be increased before the day-time doses. In general, patients who have not previously received psychotropic medications, will require 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. Patients should be periodically re-assessed and dosage adjustments made as appropriate.

Discontinuation therapy:
The dosage should be reduced slowly to reduce withdrawal symptoms. It is suggested that the daily dosage of **ZOPAX** be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction.

	Usual starting dosage*	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 associated with anxiety	0,5 mg given three times daily	1,5 mg to 4,0 mg daily given in divided doses
*Geriatric patients or in the presence of debilitating disease	0,25 mg given two or three times daily	0,5 to 0,75 mg daily given in divided doses to be gradually increased if needed and tolerated
Panic-related disorders	0,5 to 1,0 mg given at bedtime	The dose should be adjusted to patient response. Dosage adjustments should be in increments no greater than 1 mg every 3 to 4 days. Additional doses can be added until a three times daily of four times daily schedule is achieved

* If side-effects occur, the dose should be lowered.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Drowsiness, sedation and ataxia are the most frequent side-effect of alprazolam use. These effects generally decrease on continued administration and are a consequence of central nervous system depression.

Less frequent side-effects include vertigo, headache, confusion, mental depression, slurred speech or dysathria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastro-intestinal disturbances, changes in salivation, amnesia and paradoxical excitation and dis-inhibition. Jaundice, blood disorders and hypersensitivity reactions have been reported less frequently.

Respiratory depression and hypotension occur with high dosage.

Precautions

Alprazolam is not recommended for the primary treatment of psychotic illness. Alprazolam should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients). Alprazolam should be used with extreme caution in patients with history of alcohol or drug abuse.

Dependence

There is a potential for abuse and the development of physical and psychic dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: de-realisation, depersonalisation, hyperacousia, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound effects
A transient syndrome whereby the symptoms that led to treatment with alprazolam recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment it is recommended that the dosage is decreased gradually.

Duration of treatment: The duration of treatment should be as short as possible (see Dosage), but should not exceed 8 - 12 weeks, including tapering off-process. Extension beyond these periods should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms, should they occur while the product is being discontinued.

Caution is required in elderly patients or debilitated patients who may be more prone to adverse effects. Caution is required in patients with impaired liver or kidney function.
Sedation or respiratory and cardiovascular depression may be enhanced by other medicines with central nervous system depressant properties; these include alcohol, antidepressants, antihistamines, general anaesthetics, other hypnotics or sedatives, neuroleptics and opioid analgesics.

Interactions
ZOPAX (alprazolam) produces additive central nervous system depressant effects when co-administered with medicines such as barbiturates, alcohol or other central nervous system depressants. Patients should be cautioned regarding the additive effect of alcohol.

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased on average of 31% and 20% respectively by the concomitant administration of **ZOPAX** (alprazolam). Pharmacokinetic interactions of **ZOPAX** with other have been reported. The clearance of **ZOPAX** can be delayed by the co-administration of cimetidine or macrolide antibiotics.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See "Side-effects and Special Precautions".
Overdosage can produce central nervous system depression and coma.
Treatment is symptomatic and supportive.
The antidote flumazenil may be administered.

IDENTIFICATION:

White to off-white, round, flat, bevelled tablets, smooth on one side with central breakline on the other side.

PRESENTATION:

Blister strips of 10 tablets packaged in 5 x 10's.

STORAGE INSTRUCTIONS:

Store below 30°C and protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

30/2.6/0358

NAME AND BUSINESS ADDRESS OF APPLICANT:

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