1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

ATIVAN SL 1 mg (sublingual tablet)

ATIVAN SL 2 mg (sublingual tablet)

COMPOSITION

Each sublingual tablet of ATIVAN SL 1 mg contains 1 mg of lorazepam.

Excipients:

Lactose, maize starch, magnesium stearate, microcrystalline cellulose

Contains sugar: Lactose 21,10 mg

Each sublingual tablet of ATIVAN SL 2 mg contains 2 mg of lorazepam.

Excipients:

FD & C Blue No. 1 Lake (C.I. 42090), lactose, maize starch, magnesium stearate, microcrystalline cellulose

Contains sugar: Lactose 28,631 mg

CATEGORY AND CLASS

A 2.6 Tranquillisers

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Lorazepam is a benzodiazepine. It has anxiolytic, sedative and hypnotic properties. The exact mechanism of action of benzodiazepines has not been elucidated; however, benzodiazepines appear to work through several mechanisms. Benzodiazepines presumably exert their effects by binding to specific receptors at several sites within the central nervous system, thereby potentiating the effects of synaptic or presynaptic inhibition mediated by gamma-aminobutyric acid or directly affecting the action potential generating mechanisms.

Pharmacokinetic Properties

Lorazepam is well absorbed when given sublingually. Peak concentrations in plasma occur approximately 1 to 2 hours following administration. The elimination half-life of unconjugated lorazepam in human plasma is approximately 12 to 16 hours. At clinically relevant concentrations, lorazepam is approximately 90 % bound to plasma proteins. The plasma levels of lorazepam are proportional to the dose given.

Excessive accumulation has not been observed following multi-dose therapy in young healthy subjects. Conjugation with glucuronic acid to form the inactive glucuronide is the major metabolic pathway of lorazepam. It has no active metabolites. Seventy to seventy five percent of the dose is excreted as the glucuronide in the urine. Lorazepam is not hydroxylated to any significant extent, nor is it a substrate for N-dealkylating enzymes of the

cytochrome P450 system.

Haemodialysis did not have any significant effect on the pharmacokinetics of intact lorazepam but substantially removed the inactive glucuronide from the plasma.

INDICATIONS

ATIVAN SL is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

ATIVAN SL is indicated for the following:

1. As a premedicant to relieve anxiety and diminish recall events associated with major or minor diagnostic procedures.
2. Management of severe, acute anxiety episodes.

ATIVAN SL is indicated only when the disorder has not responded to non-drug therapy, and is severe, disabling, or subjecting the individual to unacceptable distress.

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

CONTRAINDICATIONS

ATIVAN SL is contraindicated in patients with:

1. Sleep apnoea syndrome.

2. Respiratory insufficiency.
3. Safety in pregnancy has not been established.
4. History of hypersensitivity to benzodiazepines.

WARNINGS AND SPECIAL PRECAUTIONS

Patients should be advised that since their tolerance for alcohol and other central nervous system depressants will be diminished in the presence of ATIVAN SL, these substances should either be avoided or taken in reduced dosage.

It is recommended that patients receiving ATIVAN SL remain under observation for 24 hours after receiving the last dose. When ATIVAN SL is used for short procedures on an outpatient basis, the patient should be accompanied by a responsible adult when discharged from the institution.

ATIVAN SL is not intended for the primary treatment of psychotic illness or depressive disorders. ATIVAN SL should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients).

Pre-existing depression may emerge during benzodiazepine use.

The use of benzodiazepines may have a disinhibiting effect and may release suicidal tendencies in depressed patients.

The need for continued therapy with ATIVAN SL should be determined periodically. Benzodiazepine therapy should be discontinued gradually.

Anxiety may be a symptom of several other disorders. The possibility should be considered that the complaint may be related to an underlying physical or psychiatric disorder for which there is more specific treatment.

In patients where gastrointestinal or cardiovascular disorders coexist with anxiety, it should be noted that ATIVAN SL has not been shown to be of significant benefit in treating the gastrointestinal or cardiovascular component.

Caution should be used in the treatment of patients with acute narrow-angle glaucoma or myasthenia gravis.

Patients with impaired renal or hepatic functions should be monitored frequently and have their dosage adjusted carefully to patient response. Lower doses are indicated in these patients. The same precautions apply to elderly or debilitated patients and patients with severe respiratory insufficiency.

The use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency.

Some patients taking benzodiazepines have developed blood dyscrasia, and some have

had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended when long-term therapy is clinically necessary.

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses and inappropriate behaviour have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the medicine should be discontinued. Although hypotension has occurred infrequently, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.

In patients with anxiety accompanying depression, the possibility of attempted suicide should be borne in mind and large quantities of ATIVAN SL should not be prescribed.

Oesophageal dilatation occurred in rats treated with lorazepam for more than one year at 6 mg/kg per day. The no-effect dose was 1,25 mg/kg per day (approximately 6 times the maximum human therapeutic dose of 10 mg per day). The effect was reversible only when the treatment was withdrawn within two months of first observation of the phenomenon. The clinical significance of this is unknown. However, use of ATIVAN SL for prolonged periods and in geriatric patients requires caution and there should be frequent monitoring for symptoms of upper GI disease.

Paediatric use:

The safety and effectiveness of ATIVAN SL in children has not been established and such use is not recommended.

Laboratory test interactions:

No interference with laboratory tests has been identified or reported with the use of ATIVAN SL.

Abuse and dependence:

ATIVAN SL should be used with extreme caution in patients with a history of alcohol or drug abuse.

The use of benzodiazepines may lead to physical and psychological dependence. When used at appropriate doses for short-term treatment of anxiety, the dependence potential is low. The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorder. Therefore use in individuals who are drug addicts or alcoholics should be avoided. If physical dependence develops, abrupt termination of treatment may be accompanied by withdrawal symptoms. Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating and the occurrence of rebound phenomena whereby the symptoms that led to the treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which

the medicine was prescribed. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, tinnitus, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, involuntary movements, vomiting, hallucination and convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other medicines that lower the convulsive threshold such as antidepressants.

Withdrawal symptoms, especially the more serious ones, are more common in those patients who have received high doses over an extended period of time. However, withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels, especially when discontinuation is abrupt. Since the risk of withdrawal/rebound phenomena is greater after abrupt discontinuation, the medicine should be discontinued gradually.

Duration of treatment:

The duration of treatment should be as short as possible (see DOSAGE AND DIRECTIONS FOR USE), but should not exceed 8 to 12 weeks in case of anxiety, including tapering 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 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.

Effects on ability to drive and use machines

Patients should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from ATIVAN SL. Patients should be warned not to drive or undertake activities requiring maximum attentiveness for 24 hours after taking ATIVAN SL.

Excipients

Lactose/fructose warning:

ATIVAN SL contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ATIVAN SL.

INTERACTIONS

The benzodiazepines, including ATIVAN SL, produce additive central nervous system depressant effects when co-administered with other central nervous system depressants, e.g., alcohol, barbiturates, anti-psychotics, sedative-hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants and anaesthetics.

There have been reports of marked sedation, excessive salivation and ataxia when ATIVAN

SL and clozapine were given concomitantly.

There have been reports of excessive stupor, significant reduction in respiratory rate, and, in one patient, hypotension when ATIVAN SL and loxapine were given concomitantly.

HUMAN REPRODUCTION

Use during pregnancy:

Benzodiazepines should not be used during pregnancy. If the medicine is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the medicine if she intends to become or suspects that she is pregnant.

Benzodiazepines may cause foetal damage when administered to pregnant women. An increased risk of congenital malformation associated with the use of anxiolytic medicines such as chlordiazepoxide, diazepam and meprobamate has been suggested in several studies.

In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines for several weeks or more preceding delivery and have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnoea, feeding problems and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

Neonates appear to conjugate lorazepam slowly, the glucuronide being detectable in the urine for more than seven days. Glucuronidation of lorazepam may competitively inhibit the conjugation of bilirubin, leading to hyperbilirubinaemia in the newborn.

ATIVAN SL is not recommended for obstetrical use.

Use during lactation:

There is evidence that ATIVAN SL is excreted in pharmacologically insignificant amounts in human breast milk. ATIVAN SL should not be administered to nursing women.

DOSAGE AND DIRECTIONS FOR USE

Treatment should be started at the lowest recommended dose. The maximum dose should not be exceeded.

ATIVAN SL, when placed under the tongue, will dissolve in approximately 20 seconds. The patient should not swallow for at least 2 minutes to allow sufficient time for absorption.

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. Generally, the duration of treatment should not exceed 8 to 12 weeks, including tapering. Extension of the treatment period should not take place without re-evaluation of the need for continued therapy. Treatment should be discontinued gradually.

For elderly or debilitated patients, the initial daily dose should not exceed 2 mg in order to avoid oversedation or ataxia.

Elderly or debilitated patients or patients with impaired renal or hepatic function or severe respiratory insufficiency generally require lower or less frequent doses. These patients should be monitored frequently, and dosages should be adjusted carefully according to patient response.

Premedication:

The usual recommended adult dose is 2 mg the night before procedure and/or 1 to 2 hours pre-procedure. If a heightened sedative effect is desired, a dose of 0,05 mg/kg to a maximum of 4 mg may be used. In the case of local anaesthesia and diagnostic procedures requiring patient co-operation, concomitant use of an analgesic may be appropriate.

Acute anxiety states:

The recommended acute dosage is 4,0 mg.

SIDE EFFECTS

Adverse reactions, when they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use, or upon decreasing the dose.

Most frequently reported adverse reactions include the following:

Daytime drowsiness, sedation, dizziness, muscle weakness and ataxia.

Less frequently reported adverse reactions associated with benzodiazepines, including ATIVAN SL, include the following:

Vertigo, headache, confusion, mental depression, fatigue, slurred speech or dysarthria, changes in libido, tremor, visual disturbances, reduced alertness, numbed emotions, nausea, appetite changes, sleep disturbance, dermatological reactions, gastrointestinal symptoms, urinary retention or incontinence, changes in salivation and amnesia.

Some patients may experience a paradoxical excitation which may lead to hostility, aggression and disinhibition.

Respiratory depression and hypotension occasionally occur with high dosage (see WARNINGS AND SPECIAL PRECAUTIONS).

Rebound anxiety and insomnia may be the result of tolerance to the effects of ATIVAN SL or part of a withdrawal syndrome.

Rarely reported adverse reactions include the following:

Blood dyscrasias, jaundice, abnormal liver function tests and hypersensitivity reactions.

Transient anterograde amnesia or memory impairment has been reported in association with

the use of benzodiazepines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

In the management of overdosage, it should be borne in mind that multiple medicines may have been taken.

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy. In more serious cases, and especially when other central nervous system depressant medicines or alcohol were ingested, symptoms may include ataxia, hypotension, hypotonia, respiratory depression, stage one (1) to three (3) coma, and very rarely, death.

Treatment

If ingestion was recent, induced vomiting and/or gastric lavage should be undertaken when appropriate, followed by general supportive care, monitoring of vital signs and close observation of the patient. If there is no advantage in emptying the stomach, activated charcoal may be effective in reducing absorption. Hypotension, though unlikely, may be controlled with noradrenalin. Lorazepam is poorly dialyzable.

The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the management of benzodiazepine overdosage. Flumazenil product information should be

consulted prior to use.

IDENTIFICATION

ATIVAN SL 1 mg: White to off-white, round, flat, bevelled edged tablets plain on one side and imprinted “1” on the other side.

ATIVAN SL 2 mg: Pale blue, round, flat, bevelled edged tablet impressed “2” on one side.

PRESENTATION

30 or 90 tablets are packed in a round amber glass bottle sealed with a white polypropylene, wadded cap, together with silica gel sachet. The glass bottle is packed into an outer cardboard carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C, in a cool dry place.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ATIVAN SL 1 mg: R/2.6/319

ATIVAN SL 2 mg: R/2.6/320

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Dates of registration:

ATIVAN SL 1 mg: 09 April 1985

ATIVAN SL 2 mg: 10 May 1985

Date of the most recent amendment to the professional information as approved by the Authority: 25 June 1999

Namibia:	NS3
ATIVAN SL 1 mg:	90/2.6/00806
ATIVAN SL 2 mg:	90/2.6/00808

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