

New Zealand Data Sheet

ATIVAN

Lorazepam tablets 0.5 mg, 1.0 mg and 2.5 mg

Presentation

0.5 mg: pale blue tablet, 4.8 mm round, flat, bevelled-edge, with "0.5" impressed on one side.

1 mg: (white, round scored tablet, plain on one side and debossed 1 L' on the scored face with break bar between the 1 and L)

2.5 mg: (yellow, round, plain on one side" debossed with '2.5 L' on scored face, with E.Z split break bar separating the 2.5 and L):

Uses

Actions

The exact mechanism of action of benzodiazepines has not yet 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 either by potentiating the effects of synaptic or pre-synaptic inhibition mediated by gamma-aminobutyric acid or by directly affecting the action potential generating mechanisms.

Pharmacokinetics

ATIVAN is readily absorbed when given orally. Peak concentrations in plasma occur approximately 2 hours following administration. The half-life of ATIVAN in human plasma is approximately 12-16 hours. At clinically relevant concentrations, ATIVAN is approximately 90% bound to plasma proteins.

Lorazepam is metabolised in the liver, mainly to the inactive glucuronide of lorazepam. Seventy to seventy-five per cent of the dose is excreted as the glucuronide in the urine. The glucuronides of lorazepam have no demonstrable CNS activities in animals, and there are no active metabolites of ATIVAN.

The plasma levels of ATIVAN are proportional to the dose given. There is no evidence of excessive accumulation of ATIVAN on administration up to 6 months nor is there any indication of induction of drug-metabolising enzymes

under these conditions. ATIVAN is not a substrate for N-dealkylating enzymes of the cytochrome P450 system nor is it hydroxylated to any significant extent.

Studies comparing young and elderly subjects have shown that the pharmacokinetics of ATIVAN remain unaltered with advancing age. No changes in absorption, distribution, metabolism and excretion were reported in patients with hepatic disease (hepatitis, alcoholic cirrhosis). As with other benzodiazepines, the pharmacokinetics of lorazepam may change in patients with impaired renal function and the medication should be used with caution.

Indications

ATIVAN (lorazepam) is useful in the therapy of most disorders in which anxiety is a major component. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Treatment of moderate to severe anxiety.

Treatment of insomnia associated with anxiety.

Pre-medication before surgery.

Dosage and Administration

ATIVAN is administered orally. For optimal results, dose, frequency of administration and duration of therapy should be individualised according to patient response. A short course of up to three weeks is recommended. The physician should periodically reassess the usefulness of the medication for the individual patient. Dosage should be individualised for maximum beneficial effect. In patients previously treated with anxiolytic agents, higher initial dosages of ATIVAN may be indicated.

The average daily dosage for treatment of anxiety is 2-3 mg administered in divided doses, however, this may range between 1 and 10 mg.

Dosages higher than 10 mg daily have been successfully employed in hospitalised cases, especially as adjunctive therapy in psychosis and severe depression.

For insomnia due to anxiety or transient situational stress, a single daily dose of 1-2 mg may be given, usually at bedtime.

For elderly or debilitated patients, an initial dosage of 1 or 2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated.

The need for continued therapy with ATIVAN in patients who have been taking medication for several weeks should be evaluated, periodically.

For pre-surgical medication, a dosage of 2-4 mg of ATIVAN is recommended the night before surgery and/or 1-2 hours prior to the surgical procedure.

Contraindications

ATIVAN is contraindicated in:

Patients with a known hypersensitivity to benzodiazepines.

Patients with chronic obstructive airways disease with incipient respiratory failure.

Patients with sleep apnoea.

Warnings and Precautions

As with all patients taking CNS-depressant medications, patients receiving ATIVAN 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 therapy. Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of ATIVAN.

Following the prolonged use of ATIVAN at therapeutic doses withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use of ATIVAN (see Dependence).

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of ATIVAN is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Although hypotension has occurred only rarely, ATIVAN should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

ATIVAN could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired Renal/Liver Function and Blood Dyscrasias

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended.

Depression, Psychosis and Schizophrenia

ATIVAN is not recommended as primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients, and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

Paradoxical reactions such as acute rage, stimulation or excitement may occur. Should such reactions occur, ATIVAN should be discontinued.

Geriatric or debilitated patients

Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion which may increase the possibility of a fall.

Impaired Respiratory Function

Caution in the use of ATIVAN is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased arterial oxygen tension.

Epilepsy

Abrupt withdrawal of benzodiazepines in patients with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Abuse

Caution must be exercised in administering ATIVAN to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence

The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines especially in those with drug seeking behaviour. Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms can range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (eg feelings of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have also been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, ATIVAN should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses taken for relatively short periods.

Carcinogenesis and Mutagenesis

No evidence of carcinogenic potential emerged in rats or mice during an 18-month study with oral lorazepam. An investigation of the mutagenic activity of lorazepam on *Drosophila melanogaster* indicated that it was mutationally inactive.

Paediatric Use

The safety and effectiveness of lorazepam has not been established in children less than 16 years of age.

Use in Pregnancy

Category C.

Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.

The use of benzodiazepines during the first trimester of pregnancy should almost always be avoided. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

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 new born.

Non-Teratogenic Effects - The use of benzodiazepines during the late phase of pregnancy or at delivery may require ventilation of the infant at birth.

Impairment of Fertility - A pre-implantation study in rats was performed with oral lorazepam at a 20 mg/kg dose which showed no impairment of fertility.

Use During Lactation

Caution should be exercised when ATIVAN is given to breast feeding women. ATIVAN is excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant.

Effects on Ability to Drive and Use Machines

As with all patients taking CNS-depressant medications, patients receiving ATIVAN 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 therapy. Abilities may be impaired on the day following use.

Adverse Effects

More Common Reactions

The more common adverse reactions, if they occur, are usually observed at the beginning of therapy and generally decreases in severity or disappears on continued medication or upon decreasing the dose.

Nervous System: anterograde amnesia, dizziness, sedation.

Musculo-Skeletal: unsteadiness, weakness.

Less Common Reactions

Autonomic Manifestations: dry mouth, hypersalivation.

Dermatological: rash.

Gastrointestinal: nausea, vomiting.

Miscellaneous: change in appetite.

Nervous System: disorientation, headache, sleep disturbances.

Ocular: eye-function disturbances.

Psychiatric: agitation, depression. Paradoxical reactions such as stimulation, excitement or rage rarely occur (see Warnings and Precautions).

Interactions

The benzodiazepines, including ATIVAN, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics.

The cytochrome P450 system has not been shown to be involved in the disposition of ATIVAN and, unlike many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with ATIVAN.

The anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, have been reported with benzodiazepine administration.

No interference with laboratory tests have been identified or reported with the use of lorazepam.

Overdosage

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, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma, and very rarely proves fatal.

Treatment

In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

Following overdosage with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airways protected if the patient is comatose. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

CONTROLLED DRUG C5

Package Quantities

Tablets, 0.5 mg: glass bottles of 100 or 250 (not marketed).

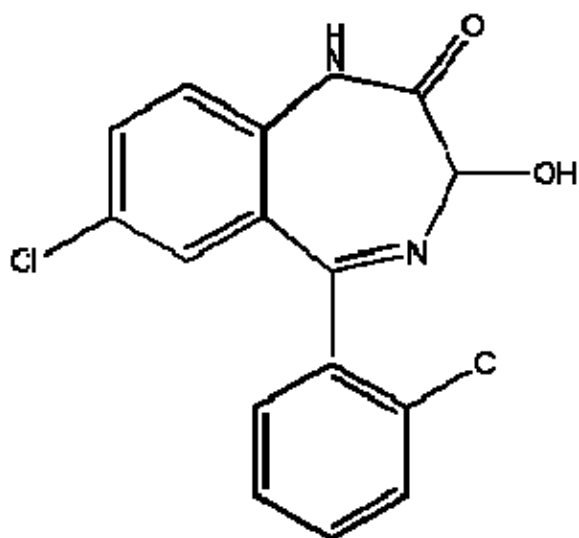
1 mg: glass bottles of 250

2.5 mg: glass bottles of 100s

Further Information

Chemical structure

Lorazepam (ATIVAN), an antianxiety agent, is a 1,4 benzodiazepine with the chemical name 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one. Its structural formula is:-



Lorazepam is a nearly white powder which is almost insoluble in water and slightly soluble in alcohol and chloroform. The molecular weight is 321.2.

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