

# New Zealand Data Sheet

## 1. ATIVAN 0.5 mg, 1.0 mg and 2.5 mg

Lorazepam tablets 0.5 mg, 1.0 mg and 2.5 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5mg, 1.0mg or 2.5mg of lorazepam

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic 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.

### 4.2 Dose and method of 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.

### **4.3 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.

Lorazepam should not be used as monotherapy to treat depression, or symptoms of anxiety associated with depression, due to a risk of suicide (see section 4.4).

### **4.4 Special warnings and precautions for use**

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.

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).

#### ***Duration of Treatment***

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks).

For patients with anxiety and/or insomnia the duration of treatment should not exceed 4 weeks (including tapering off process).

Continuous long-term use of ATIVAN is not recommended, but intermittent use may be appropriate.

Where long-term therapy is considered essential, the patient should be regularly reviewed.

## ***Tolerance***

There is evidence that tolerance develops to the sedative effects of benzodiazepines. 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.

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. Therefore, benzodiazepines should be used with caution and the prescription size should be limited, in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

## ***Psychiatric and/or paradoxical reactions***

As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been described.

- Amnestic symptoms: anterograde amnesia with appropriate or inappropriate behavior;
- Confusional states: disorientation, derealisation, depersonalization and/or clouding of consciousness; and

- Agitational states: sleep disturbances, restlessness, irritability, aggression and excitation.

Lorazepam should be discontinued if confusion or agitation occurs.

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.

Lower doses should be used in elderly patients (see Dosage and Administration).

### ***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.

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.

### ***Concomitant use with alcohol/CNS depressants***

The concomitant use of lorazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of lorazepam which may include severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

### ***Risks from Concomitant Use with Opioids***

Concomitant use of benzodiazepines, including lorazepam, 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 ATIVAN 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 ATIVAN is used with opioids (see section 4.5).

### ***Paediatric Use***

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

### ***Paediatric neurotoxicity***

Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans. Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6).

#### **4.5 Interaction with other medicines and other forms of interaction**

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 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.

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.

#### **4.6 Fertility, pregnancy and lactation**

##### ***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.

##### ***Risk summary statement***

Anaesthetic and sedative agents can be part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

##### ***Preclinical data***

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal

apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

### ***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.

### **4.7 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.

### **4.8 Undesirable 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 section 4.4).

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**

#### ***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.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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.

### **5.2 Pharmacokinetic properties**

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 enzyme 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.

### **5.3 Preclinical safety data**

#### ***Animal toxicology and/or pharmacology***

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Microcrystalline cellulose, lactose monohydrate, magnesium stearate and polacrillin potassium, indigo carmine (0.5mg only), iron oxide yellow (2.5 mg only) and quinolone yellow (2.5mg only).

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

0.5 mg: 48 months

1 mg: 20 months

2 mg: 24 months

## **6.4 Special precautions for storage**

Store below 25°C. Protect from light.

## **6.5 Nature and contents of container**

0.5 mg: glass bottles of 100s and 250s (both not marketed).

1 mg: glass bottles of 250s

2.5 mg: glass bottles of 100s

## **6.6 Special precautions for disposal**

Not applicable.

## **7. MEDICINE SCHEDULE**

CONTROLLED DRUG C5

## **8. SPONSOR**

Pharmacy Retailing (NZ) Limited  
Trading as Healthcare Logistics  
58 Richard Pearse Drive  
Airport Oaks  
Auckland, New Zealand  
Telephone (09) 9185 100  
Email: [aspen@aspenpharma.co.nz](mailto:aspen@aspenpharma.co.nz)

## **9. DATE OF FIRST APPROVAL**

14 February 1974

## **10. DATE OF REVISION OF THE TEXT**

19 May 2017

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
	Update to the SPC-style format  Safety update in 4.4, 4.5, 4.6 and 5.3 due MARC request