AUSTRALIAN PRODUCT INFORMATION
LORAZEPAM VIATRIS (LORAZEPAM) tablets

1. NAME OF THE MEDICINE

Lorazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lorazepam VIATRIS immediate release tablets contain the active ingredient lorazepam.

Each Lorazepam VIATRIS 1 mg tablet contains 1 mg of lorazepam.

Each Lorazepam VIATRIS 2.5 mg tablet contains 2.5 mg of lorazepam.

Lorazepam is a white or almost white crystalline powder.

Lorazepam VIATRIS contains lactose, for the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Lorazepam VIATRIS 1 mg immediate release tablets are white, round, flat, beveled and scored with the inscription “1.0” on one side.

Lorazepam VIATRIS 2.5 mg immediate release tablets are white, round, flat, beveled and scored tablets.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. The physician should periodically reassess the usefulness of the drug for the individual patient.

Pre-surgical medication taken the night before surgery and/or 1-2 hours prior to the surgical procedure.

4.2. DOSE AND METHOD OF ADMINISTRATION

Lorazepam VIATRIS is administered orally. For optimal results, dose, frequency of administration and duration of therapy should be individualised according to patient response. Dosage should be individualised for maximum beneficial effect. In patients previously treated with anxiolytic agents, higher initial dosages of Lorazepam VIATRIS 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.

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

For patients with anxiety and/or insomnia, the duration of treatment should not exceed 4 weeks, including tapering off process (See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Duration of Treatment).

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 Lorazepam VIATRIS 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 Lorazepam VIATRIS is recommended the night before surgery and/or 1-2 hours prior to the surgical procedure.

Lorazepam VIATRIS is not recommended for children.

4.3. CONTRAINDICATIONS

- 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 in patients with depression, or symptoms of anxiety associated with depression, due to a risk of suicide (See section SPECIAL WARNING AND PRECAUTIONS FOR USE).

4.4. SPECIAL WARNING AND PRECAUTIONS FOR USE

As with all patients taking CNS-depressant medications, patients receiving lorazepam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from lorazepam therapy. Abilities may be impaired on the day following use.

Following the prolonged use of lorazepam 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 lorazepam (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 lorazepam is not recommended.

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 those with drug seeking behaviour.

After as little as one week of therapy withdrawal symptoms can appear following the cessation of recommended doses (eg rebound insomnia following cessation of a hypnotic benzodiazepine).

Although hypotension has occurred only rarely, lorazepam 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.

Lorazepam 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).

Use in renal or hepatic impairment
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
Lorazepam 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.

CNS 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 behaviour;
• 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, lorazepam 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 lorazepam 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

Use in the elderly
Lower doses should be used in elderly patients (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Abuse
Caution must be exercised in administering lorazepam 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, Lorazepam 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.

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Paediatric Neurotoxicity
Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration resulting in longer exposure to the drug.

Effects on Laboratory Tests
No interference with laboratory tests have been identified or reported with the use of lorazepam.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The benzodiazepines, including Lorazepam, 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 lorazepam and, unlike many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with Lorazepam.

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.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on 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 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.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

Use in lactation
Caution should be exercised when lorazepam is given to breast feeding women. Lorazepam 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 lorazepam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from lorazepam therapy. Abilities may be impaired on the day following use.

4.8. ADVERSE EFFECTS (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 SPECIAL WARNING AND PRECAUTIONS FOR USE).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials
No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

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

Distribution

The plasma levels of lorazepam are proportional to the dose given. There is no evidence of excessive accumulation of lorazepam on administration up to 6 months nor is there any indication of induction of drug-metabolising enzymes under these conditions. Lorazepam is not a substrate for N-dealkylating enzymes of the cytochrome P450 system nor is it hydroxylated to any significant extent.

Metabolism

Lorazepam is metabolised in the liver, mainly to the inactive glucuronide of lorazepam.

Excretion

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 lorazepam.

Studies comparing young and elderly subjects have shown that the pharmacokinetics of lorazepam 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

Genotoxicity

An investigation of the mutagenic activity of lorazepam on Drosophila melanogaster indicated that it was mutationally inactive.

Carcinogenicity

No evidence of carcinogenic potential emerged in rats or mice during an 18-month study with oral lorazepam.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lorazepam 1 mg and 2.5 mg tablets contain the following inactive ingredients: maize starch, microcrystalline cellulose, sodium starch glycollate Type A, lactose monohydrate, povidone, crospovidone, magnesium stearate, polacrilin potassium.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C. Protect from light and store in original container.

6.5. NATURE AND CONTENTS OF CONTAINER

Lorazepam tablets are available in PA/Al/PVC/Al blister packs.

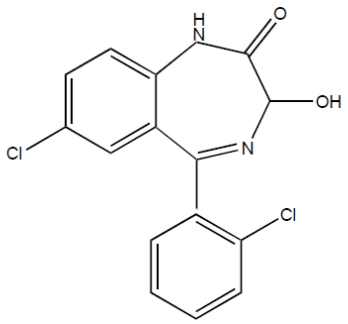
1 mg & 2.5 mg in blister packs of 50 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:



Chemical name: 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one

Molecular formula: $C_{15}H_{10}Cl_2N_2O_2$

Molecular weight: 321.2

CAS Number: 846-49-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

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9. DATE OF FIRST APPROVAL

18th July 2019

10. DATE OF REVISION

11 September 2024

Summary table of changes

Section Changed	Summary of new Information
4.4	Added information on paediatric neurotoxicity under “Paediatric use”
4.6	New warnings in pregnant women and young children