Lorazepam Injection USP 2mg/1ml, 20mg/10ml, 40mg/10ml

1. Name of the medicinal product

Lorazepam Injection USP 2mg/1ml Taj Pharma

Lorazepam Injection USP 20mg/10ml Taj Pharma

Lorazepam Injection USP 40mg/10ml Taj Pharma

2. Qualitative and quantitative composition

a) Lorazepam Injection USP 2mg/1ml
Each ml contains:

Lorazepam	2mg
Polyethylene glycol	0.18ml
Benzyl alcohol	

b) Lorazepam Injection USP 20mg/10ml
Each ml contains:

Lorazepam	2mg
Polyethylene glycol	0.18ml
Benzyl alcohol	

c) Lorazepam Injection USP 40mg/10ml
Each ml contains:

Lorazepam	4mg
Polyethylene glycol	0.18ml
Benzyl alcohol	

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

Clear, colourless solution supplied in clear glass ampoules.

4. Clinical particulars

4.1 Therapeutic indications

Pre-operative medication or premedication for uncomfortable or prolonged investigations, e.g. bronchoscopy, arteriography, endoscopy.

The treatment of acute anxiety states, acute excitement or acute mania.

The control of status epilepticus.

4.2 Posology and method of administration

Posology

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible.

Treatment in all patients should be withdrawn gradually to minimise possible withdrawal symptoms (See section 4.4).

Method of administration

Ativan Injection can be given intravenously or intramuscularly. However, the intravenous route is to be preferred. Care should be taken to avoid injection into small veins and intra-arterial injection.

Absorption from the injection site is considerably slower if the intramuscular route is used and as rapid an effect may be obtained by oral administration of lorazepam.

Ativan should not be used for long-term chronic treatment.

Preparation of the injection

Ativan Injection is slightly viscid when cool.

Intramuscular administration:

A 1:1 dilution of Ativan Injection with normal saline or Sterile Water for Injection BP is recommended in order to facilitate intramuscular administration.

Intravenous administration:

For intravenous administration, Ativan Injection should always be diluted with saline or Sterile Water for Injection BP as a 1:1 dilution.

Ativan Injection is presented as a 1ml solution in a 2ml ampoule to facilitate dilution.

Ativan Injection should not be mixed with other drugs in the same syringe.

Dosage:

1. Premedication:

Adults: 0.05mg/kg (3.5mg for an average 70kg man). By the intravenous route the injection should be given 30-45 minutes before surgery when sedation will be evident after 5-10 minutes and maximal loss of recall will occur after 30-45 minutes. By the intramuscular route the injection should be given 1-$1^1/_2$ hours before surgery when sedation will be evident after 30-45 minutes and maximal loss of recall will occur after 60-90 minutes.

Paediatric population: Ativan Injection is not recommended in children under 12.

2. Acute Anxiety

Adults: 0.025-0.03mg/kg (1.75-2.1mg for an average 70kg man). Repeat 6 hourly.

Paediatric population: Ativan Injection is not recommended in children under 12.

3. Status epilepticus

Adults: 4mg intravenously

Paediatric population: 2mg intravenously

Elderly: The elderly may respond to lower doses and half the normal adult dose may be sufficient.

Patients with Renal or Hepatic impairment:

Lower doses may be sufficient in these patients (See section 4.4). Use in patients with severe hepatic insufficiency is contraindicated.

Elderly and debilitated patients

For elderly and debilitated patients reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated (see section 4.4 Special warnings and precautions for use)

4.3 Contraindications

• Acute pulmonary insufficiency

• Hypersensitivity to benzodiazepines, including lorazepam or to any of the excipients listed in section 6.1.

• Sleep apnoea syndrome

• Myasthenia gravis

• Severe hepatic insufficiency

Ativan Injection is not recommended for out-patient use unless the patient is accompanied.

4.4 Special warnings and precautions for use

Prior to use, Ativan Injection may be diluted for IM administration and should always be diluted for IV administration with equal amounts of compatible diluent (see section 4.2). Intravenous injection should be administered slowly except in the control of status epilepticus where rapid injection is required.

The possibility that respiratory arrest may occur or that the patient may have partial airway obstruction should be considered. Therefore, equipment necessary to maintain a patent airway and to support respiration/ventilation should be available and used where necessary.

The use of benzodiazepines, including lorazepam, may lead to physical and psychological dependence.

Severe anaphylactic/anaphylactoid reactions have been reported with the use of benzodiazepines. Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of benzodiazepines. Some patients taking benzodiazepines have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with a benzodiazepine should not be rechallenged with the drug.

It is recommended that patients receiving Ativan Injection should remain under observation for at least eight hours and preferably overnight. When Ativan Injection is used for short procedures on an outpatient basis, the patient should be accompanied when discharged.

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished in the presence of Ativan Injection. Alcoholic beverages should not be consumed for at least 24 to 48 hours after receiving Ativan Injection.

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression. Extreme care must be taken in administering Ativan Injection to elderly or very ill patients and to those with limited pulmonary reserve or compromised respiratory function (e.g. chronic obstructive pulmonary disease [COPD]), because of the possibility that apnoea and/or cardiac arrest may occur. Care should also be exercised when administering Ativan Injection to a patient with status epilepticus, especially when the patient has received other central nervous system depressants.

Concomitant use of benzodiazepines and opioids may result in sedation, respiratory depression, coma, and death.

Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Ativan with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Ativan concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

There is no evidence to support the use of Ativan Injection in coma or shock.

Ativan is not intended for the primary treatment of psychotic illness or depressive disorders, and should not be used alone to treat depressed patients. The use of benzodiazepines may have a disinhibiting effect and may release suicidal tendencies in depressed patients.

Pre-existing depression may emerge during benzodiazepine use.

There are no clinical data available for Ativan Injection with regard to abuse or

dependence. However, based upon experience with oral benzodiazepines, doctors should be aware that repeated doses of Ativan Injection over a prolonged period of time may lead to physical and psychological dependence. The risk of dependence on Ativan is low when used at the recommended dose and duration, but increases with higher doses and longer term use. The risk of dependence is further increased in patients with a history of alcoholism or drug abuse, or in patients with significant personality disorders. Therefore, use in individuals with a history of alcoholism or drug abuse should be avoided.

Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, **the drug should always be discontinued gradually** - using the oral preparation if necessary.

Symptoms reported following discontinuation of oral 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 treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug 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; hallucinations; convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold, such as antidepressants.

It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimise anxiety should they occur.

Withdrawal symptoms (e.g. rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with a long duration of action are being used, it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Abuse of benzodiazepines has been reported.

Anxiety or insomnia 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.

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

As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy.

Patients with impaired renal or hepatic function should be monitored frequently and have their dosage adjusted carefully according to patient response. Lower doses may be sufficient in these patients. The same precautions apply to elderly or debilitated

patients and patients with chronic respiratory insufficiency.

As with all CNS-depressants, the use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency. Therefore, use in these patients is contraindicated.

Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.

Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines. This effect may be advantageous when Ativan is used as a premedicant.

Paradoxical reactions have been occasionally reported during benzodiazepine use (see section 4.8). Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

Although hypotension has occurred only rarely, 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.

Ativan Injection contains the excipients polyethylene glycol and propylene glycol. There have been reports of propylene glycol toxicity (e.g. lactic acidosis, hyperosmolality, hypotension) and polyethylene glycol toxicity (e.g. acute tubular necrosis) during administration of Ativan Injection, including at higher than recommended doses. Central nervous system toxicity, including seizures, as well as unresponsiveness, tachypnoea, tachycardia and diaphoresis have also been associated with propylene glycol toxicity. Those prone to propylene glycol accumulation and its potential adverse effects include patients with impaired alcohol and aldehyde dehydrogenase enzyme systems, those with renal or hepatic disease; and paediatric patients.

Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse event, and death in paediatric patients including neonates characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies (“gasping syndrome”). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Use only if it is necessary and if there are no alternatives possible. If given in high volumes, should be used with caution and preferably for short term treatment in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis)

Premature and low-birth weight infants may be more likely to develop toxicity.

Benzyl Alcohol containing products should not be used in pre-term or full-term neonates unless strictly necessary.

Elderly patients

Lorazepam should be used with caution in elderly due to the risk of sedation and/or musculoskeletal weakness that can increase

the risk of falls, with serious consequences in this population. Elderly patients should be given a reduced dose (see section 4.2 Posology).

4.5 Interaction with other medicinal products and other forms of interaction
Not recommended: Concomitant intake with alcohol

The sedative effects may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

The benzodiazepines, including Ativan Injection, produce additive CNS depressant effects including respiratory depression, when co-administered with other medications which themselves produce CNS depression, e.g. opioids, barbiturates, antipsychotics, sedatives/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants and anaesthetics (see section 4.4).

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Ativan with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Concurrent administration of lorazepam with sodium valproate may result in reduced clearance (20 to 40%) and increased concentrations of lorazepam. Therefore clinical monitoring is advised and lorazepam dosage should be reduced when appropriate.

Concurrent administration of lorazepam with probenecid may result in reduced clearance, increased elimination half-life and increased concentrations of lorazepam. Therefore clinical monitoring is advised and lorazepam dosage should be reduced when appropriate.

An enhancement of the euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines which are metabolised only by conjugation.

The addition of scopolamine to Ativan Injection is not recommended, since their combination has been observed to cause an increased incidence of sedation, hallucination and irrational behaviour.

Concomitant use of clozapine and lorazepam may produce marked sedation, excessive salivation, and ataxia.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lorazepam.

There have been reports of apnoea, coma, bradycardia, heart arrest and death with the concomitant use of lorazepam injection solution and haloperidol.

4.6 Fertility, pregnancy and lactation
Pregnancy

Ativan Injection should not be used during pregnancy, especially during the first and last trimesters, unless in the judgement of the physician such administration is clinically justifiable. Benzodiazepines may cause foetal damage when administered to pregnant women.

If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the drug if she intends to become, or suspects that she is, pregnant.

Use of Ativan Injection during the late phase of pregnancy may require ventilation of the infant at birth.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period.

Symptoms such as 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.

There are insufficient data regarding obstetrical safety of parenteral Ativan, including use in caesarean section. Such use, therefore, is not recommended.

Benzyl alcohol can cross the placenta, see section 4.4..

Breast-feeding

Since benzodiazepines are found in breast milk, Ativan Injection should not be given to breast- feeding mothers unless the expected benefit to the woman outweighs the potential risk to the infant.

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. Therefore, patients should not drive or operate machinery within 24-48 hours of administration of Ativan Injection and should be advised not to take alcohol (see section 4.5).

4.8 Undesirable effects

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to <**	**Uncommon ≥ 1/1,000 to <**	**Frequency not known (cannot be estimated from the**

		1/10	1/100	available data)
Blood and lymphatic system disorders				Thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders				Hypersensitivity reactions, anaphylactic/oid reactions
Endocrine disorders				SIADH
Metabolism and nutrition disorders				Hyponatremia
Psychiatric disorders		Confusion depression, unmasking of depression	Change in libido, decreased orgasm	Disinhibition, euphoria, suicidal ideation/attempt, paradoxical reactions, including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations
Nervous system disorders	Sedation, drowsiness	Ataxia, dizziness		Extrapyramidal symptoms, tremor, dysarthria/slurred speech, headache, convulsions/seizures, amnesia, coma, impaired attention/concentration, balance disorder
Eye disorders				Visual disturbances (including diplopia and blurred vision)
Ear and labyrinth disorders				Vertigo
Vascular disorders				Hypotension, lowering in blood pressure
Respiratory, thoracic and mediastinal disorders				Respiratory depression, apnea, worsening of sleep apnea, worsening of obstructive pulmonary disease
Gastrointestinal disorders			Nausea	Constipation
Hepatobiliary disorders				Jaundice
Skin and				Angioedema

subcutaneous tissue disorders				, allergic skin reactions, alopecia
Musculoskeletal and connective tissue disorders		Muscle weakness		
Reproductive system and breast disorders			Impotence	
General disorders and administration site conditions	Fatigue	Asthenia		Hypothermia
Investigations				Increase in bilirubin, increase in liver transaminases, increase in alkaline phosphatase

± Benzodiazepine effects on the CNS are dose-dependent, with more severe CNS depression occurring with high doses.

β The extent of respiratory depression with benzodiazepines is dose-dependent, with more severe depression occurring with high doses.

Tolerance at the injection site is generally good although, rarely, pain and redness have been reported after Ativan Injection.

Transient anterograde amnesia or memory impairment may occur using therapeutic doses, the risk increasing at higher doses (see section 4.4).

Paediatric population

Paradoxical reactions may be more likely to occur in children and the elderly (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

4.9 Overdose

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

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 CNS-depressant drugs or alcohol are ingested, symptoms may include ataxia, hypotension, hypotonia, respiratory depression, cardiovascular depression, coma and, very rarely, death.

Propylene glycol toxicity and polyethylene glycol toxicity have been reported following higher than recommended doses of Ativan Injection (see section 4.4).

Treatment of overdosage is mainly supportive including monitoring of vital signs and close observation of the patient. An adequate airway should be maintained and assisted respiration used as needed.

Hypotension, though unlikely, may be controlled with noradrenaline. Lorazepam is poorly dialysable.

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. The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in tricyclic antidepressant overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives.

Ativan is a benzodiazepine with anxiolytic, sedative, hypnotic, anticonvulsant and muscle relaxant properties.

5.2 Pharmacokinetic properties

Absorption

Ativan Injection is readily absorbed when given intramuscularly. Peak plasma concentrations occur approximately 60-90 minutes following intramuscular administration.

Metabolism

Ativan is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There is minimal risk of accumulation after repeated doses, giving a wide margin of safety.

There are no major active metabolites.

Elimination

The elimination half-life is about 12-16 hours when given intramuscularly or intravenously.

5.3 Preclinical safety data

Lorazepam glucuronide, the major metabolite of lorazepam, has no demonstrable CNS activity in animals.

Carcinogenicity

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

Mutagenicity

A study of the mutagenic activity of lorazepam on *Drosophila melanogaster* indicated that this agent was mutationally inactive.

Impairment of fertility

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

Effect of anesthetic and sedative drugs

Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with lorazepam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of

these nonclinical findings to human use is unknown.

6. Pharmaceutical particulars

6.1 List of excipients
Polyethylene glycol 400

Benzyl alcohol

Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
1 year.

6.4 Special precautions for storage
Store and transport refrigerated (2°C to 8°C).

Keep ampoule in the outer carton to protect from light.

6.5 Nature and contents of container
1ml solution in 2ml ampoules (Type I glass) with a one-point-cut opening, position marked by red spot in pack sizes of 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.Manufactured in India by:
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