SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the drug Product:

1.1 Name of the Medicinal Product::
LORI -- Diazepam Injection B.P.

1.2 Strength (Composition):
5 mg / ml- 2 ml

1.3 Pharmaceutical dosage form:
Solution for Injection.

2. Qualitative and Quantitative composition :

Sr. No	Particulars	Grade	Qty / ml	Function
1	Diazepam	B.P.	5.0 mg	Active
2	Propylene glycol	B.P.	0.7 ml	Co-solvent
3	Sodium benzoate	B.P.	2.05 mg	Buffer
4	Benzoic acid	B.P.	0.45 mg	Buffer
5	Sodium hydroxide	B.P.	q.s.	For pH adjustment
6	Benzyl alcohol	B.P.	1.5% w/v	Preservative
7	Water for Injections	B.P.	q.s. to 1 ml	Vehicle

3. Pharmaceutical form :
A clear colourless solution.

4. Clinical Particulars:

4.1 Therapeutic indications:
Diazepam has anticonvulsant, sedative and muscle relaxant properties. It is used in the treatment of anxiety and tension states, as a sedative and premedicant, in the control of muscle spasm and in the management of alcohol withdrawal symptoms. Control of status epilepticus, epiletic and febrile convulsions.

4.2 Dosage and administration:
Where continuous intravenous infusion is necessary it is suggested that 2 ml Diazepam Injection is mixed with at least 200 ml of infusion fluid such as Sodium Chloride Injection or Dextrose Injection and that such solutions should be used immediately. There is evidence that Diazepam is adsorbed onto plastic infusion bags and giving sets. It is therefore recommended that glass bottles should be used for the administration of Diazepam by intravenous infusion. Diazepam injection should not be mixed with other drugs. *In severe anxiety or acute muscle spasm:* Diazepam 10 mg may be given intravenously or intramuscularly and repeated after 4 hours.

In tetanus: 100 to 300 micrograms per kg body weight may be given intravenously and repeatedly every 1 to 4 hours; alternatively, a continuous infusion of 3 to 10 mg per kg every 24 hours may be used or similar doses may be given by nasoduodenal tube.

In status epilepticus: 150 to 250 micrograms per kg is given by intramuscular or intravenous injection and repeated if required after 30 to 60 minutes.

Once the patient is controlled, recurrence of seizures may be prevented by a slow infusion providing 3 mg per kg over 24 hours.
In minor surgical procedures and dentistry: the usual dose is 100 to 200 micrograms per kg by injection adjusted to the patient's requirements.
Children: Benzyl alcohol may cause toxic reactions and anaphylactic reactions in infants and children upto 3 years old; and it must not be given to premature babies or neonates.
In status epilepticus, epileptic or febrile convulsions: 200 to 300 mcg per kg body weight is given by intravenous injection. The dose can be repeated, if necessary, after 30 to 60 minutes. Sedation or muscle relaxation: Upto 200 mcg per kg body weight may be given parenterally.
Elderly patients: Doses should not exceed half those normally recommended.
NOT RECOMMONDED FOR NEONATES
IMPORTANT: In order to reduce the likelihood of adverse effects during intravenous administration the injection should be given slowly (1.0 ml solution per minute). It is advisable to keep the patient supine for at least an hour after administration. Except in emergencies, a second person should always be present during intravenous use and facilities for resuscitation should always be available.
It is recommended that patients should remain under medical supervision until at least one hour has elapsed from the time of injection. They should always be accompanied home by a responsible adult, with a warning not to drive or operate machinery for 24 hours.
Intravenous injection may be associated with local reactions and thrombophlebitis and venous thrombosis may occur. In order to minimize the likelihood of these effects, intravenous injections of Diazepam should be given into a large vein of the antecubital fossa.

4.3 Contra-indications:

Contra-indications: Known sensitivity to Diazepam. Acute pulmonary insufficiency. Respiratory depression, severe liver dysfunction. Diazepam Injection should not be used in phobic or obsessional states as there is insufficient evidence of efficacy and safety in this situation, nor should it be used in the treatment of depression or anxiety associated with depression due to the risk of suicide being precipitated in this patient group. Diazepam Injection should not be used in the treatment of chronic psychosis. In common with other benzodiazepines, the use of Diazepam may be associated with amnesia and Diazepam Injection should not be used in cases of loss or bereavement as psychological adjustment may be inhibited.

Use in pregnancy: There is no evidence as to safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters unless there are compelling reasons.

In labour, high single doses or repeated low doses have been reported to produce hypotonia, poor suckling and hypothermia in the neonate and irregularities in the foetal heart.

Lactation: Diazepam is excreted in the breast milk and therefore its use during lactation should be avoided.

4.4 Warning and precaution :

As with other benzodiazepines, extreme caution should be used if prescribing Diazepam Injection for patients with personality disorders.

The disinhibiting effects of benzodiazepines may be manifested as the precipitation of suicide in patients who are depressed and show aggressive behaviour towards self and others. This product contains 15mg/ml of benzyl alcohol. There is a risk of benzyl alcohol poisoning with prolonged use of high dose intravenous infusion of diazepam Injection containing benzeyl alcohol.

4.5 Interaction with other drugs:

Diazepam may enhance the effects of other CNS depressants. Their concurrent use should be avoided.

Particular attention should be paid to the potential effects of drug interactions with diazepam in the elderly.

CNS depressants:

Enhanced sedation, or respiratory or cardiovascular depression may occur when diazepam is administered concomitantly with other CNS depressants including other anticonvulsants, anxiolytics/hypnotics, sedative antihistamines, alcohol, neuroleptics, antidepressants, analgesics and anaesthetics.

Anticonvulsants:

Diazepam may increase or decrease plasma concentrations of phenytoin.

Patients should be monitored for signs of increased phenytoin toxicity.

Phenytoin and carbamazepine may reduce plasma levels of diazepam. Increased sedation or respiratory depression may occur with concurrent use of barbiturates. Concomitant sodium valproate may increase plasma levels of diazepam, with associated sedation.

Antidepressants: The plasma levels of some benzodiazepines are increased by fluvoxamine. Concurrent use of selective serotonin receptor antagonists or tricyclic antidepressants may reduce attention and psychomotor performance and affect the ability to perform complex tasks (e.g. driving).

Antipsychotics: Plasma concentrations of zotepine may be increased. Severe hypotension, collapse, loss of consciousness, respiratory depression, and potentially fatal respiratory arrest have been reported in a few patients taking benzodiazepines and clozapine. Salivary hypersecretion has also occurred.

Caution is advised when initiating clozapine therapy in patients taking diazepam. There is an increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines are given with intramuscular olanzapine.

Sodium oxybate

Concomitant use of sodium oxybate (gamma hydroxybutyrate, GHB) should be avoided as benzodiazepines enhance the effects of this substance.

Antibacterials: The metabolism of diazepam is inhibited by isoniazid, and to a lesser extent, by erythromycin. The effect of diazepam may be increased and prolonged. Known inducers of hepatic enzymes such as rifampicin may increase the clearance of diazepam.

Antivirals: Concomitant use of amprenavir and ritonavir should be avoided, as they have been shown to reduce the clearance of benzodiazepines and may prolong their actions, with risk of extreme sedation and respiratory depression.

Alcohol: The sedative effects of diazepam may be enhanced when the product is used in combination with alcohol.

Gastric acid suppressants: The metabolism of diazepam may be inhibited by cimetidine, omeprazole and esomeprazole, resulting in increased plasma concentrations.

4.6 Pregnancy and lactation:

Use in pregnancy: There is no evidence as to safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters unless there are compelling reasons.

In labour, high single doses or repeated low doses have been reported to produce hypotonia, poor suckling and hypothermia in the neonate and irregularities in the foetal heart.

Lactation: Diazepam is excreted in the breast milk and therefore its use during lactation should be avoided.

4.7 Effects on ability to drive and use machine:

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased. Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

- 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.

4.8 Adverse reactions :

The most common side-effects are drowsiness, lightheadedness,
unsteadiness and ataxia. Respiratory depression has occasionally been reported. Apnoea may occur rarely following intravenous injection.

Other side-effects include, bradycardia, hypotension, gastrointestinal and visual adisturbances, skin rashes, thrombophlebitic, amnesia urinary retention, headaches, confusion, vertigo, changes in libido, blood dyscrasias and jaundice.

4.9 Overdoses:

Treatment is symptomatic. Flumazenil is a specific IV antidote for use in emergency situations. Patients requiring such intervention should be monitored closely in hospital.

Treatment should be kept to a minimum and only given under close medical supervision, as would normally be the case for Diazepam Injection. Little is known regarding the efficacy of benzodiazepines in long term use.

5. Pharmacological properties

5.1 Pharmacodynamic properties:

Diazepam is a benzodiazepine tranquillizer with anticonvulsant, sedative, muscle relaxant and amnesic properties. It is used in the treatment of anxiety and tension states, as a sedative and pre-medicant, in the control of muscle spasm as in tetanus, and in the management of alcohol withdrawal symptoms. It is of value in patients undergoing orthopedic procedures endoscopy and cardioversion.

5.2 Pharmacokinetic Properties:

Diazepam is metabolised to two active metabolites, one of which, desmethyldiazepam, has an extended half-life. Diazepam is therefore a long acting benzodiazepine and repeated doses may lead to accumulation. Diazepam is metabolised in the liver and excreted via the kidney. Impaired hepatic or renal function may prolong the duration of action of diazepam. It is recommended that elderly and debilitated patients receive initially one half the normal recommended dose.

During prolonged administration, for example in the treatment of tetanus, the dosage should generally be reduced after 6-7 days, to reduce the likelihood of accumulation and prolonged CNS depression.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to those included in other sections.

6. Pharmaceutical particulars:

6.1 List of excipients:

Propylene glycol	B.P.
Sodium benzoate	B.P.
Benzoic acid	B.P.
Sodium hydroxide	B.P.
Benzyl alcohol	B.P.
Water for Injections	B.P.

6.2 Incompatibilities:

Diazepam Injection should not be mixed with other drugs in the same infusion solution or the same syringe.

6.3 Shelf – life:

24 Months.

6.4 Special precautions for storage:

Store below 25°C, protected from light. Do not freeze.

6.5 Nature and contents of container:

2 ml amber ampoules with Blue band snap off.

6.6 Special Precaution for Handling and Disposal:

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

7. Marketing authorization holder:

NEON LABORATORIES LIMITED
Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093.

8. Marketing authorization number :

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9. Date of first authorization/ Renewal of the authorization :

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10. Date of revision of the text:
