SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF FINISHED PHARMACEUTICAL PRODUCT:

NOTIUM (Diazepam Injection BP 10mg/2ml)

1.1 Strength

10 mg/ 2ml

1.2 Pharmaceutical form

A clear colourless to yellow liquid Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Sr. No.	Ingredients	Specification	Quantity per ml	Activity
1.	Diazepam	BP	5.054 mg	Anticonvulsant
2.	Propylene glycol	BP	0.7 ml	Solvent, Stabilizing agent
3.	Benzyl Alcohol	BP	1.5 %	Solvent
4.	Sodium Benzoate	BP	3.8 mg	pH modifier
5.	Benzoic Acid	BP	0.343 mg	Preservative
6.	Water for Injections	BP	q.s	Vehicle

3. PHARMACEUTICAL FORM:

Liquid Injection.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Adults (20 yrs and over)

Treatment of anxiety and tension states in various psycho-reactive disorders. As anti-convulsant in the control of status epilepticus. As adjunctive therapy for the relief of skeletal muscle spasm or tetanus.

As an adjuvant in pre-medication before surgery or in the control of alcohol withdrawal syndrome.

Diazepam is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Adults:

Severe acute anxiety or agitation:

10 mg IV or IM Injection which may be repeated after an interval of not less than 4 hours.

Delirium Tremens:

10-20 mg IV or IM Higher doses may be needed depending on severity of symptoms.

Acute Muscle Spasm:

10 mg IV or IM Injection which may be repeated after an interval of not less than 4 hours.

Tetanus:

Initially an IV dose of 0.1-0.3 mg/kg body weight, repeated at intervals of 14 hours. Continuous IV infusion of 3-10 mg/kg body weight per 24 hours can also be used. The chosen dose should be related to the severity of the case and in extremely severe cases higher doses have been used.

Status epilepticus, convulsions due to poisoning:

10-20 mg IV or IM, repeated if necessary 30-60 minutes later. If indicated, this may be followed by slow intravenous infusion (maximum dose 3 mg/kg body weight over 24 hours)

Pre-operative medication or premedication:

0.2 mg/kg body weight. The usual adult dose is 10-20 mg but higher doses may be necessary according to the clinical response.

Elderly or Debilitated Patients:

Doses should not exceed half those normally recommended.

Children:

Status epilepticus, convulsions due to poisoning, febrile convulsions:

0.2-0.3 mg/kg body weight IV (or IM) or 1 mg per year of life.

Tetanus:

As for adults.

Pre-operative medication or premedication:

0.2 mg/kg body weight.

The Injection should be given slowly (0.5 ml per minute).Diazepam Injection should be given into a large vein of the antecubital fossa, the patient in a supine position throughout the procedure to reduce the possibility of hypotension or apnoea occurring.

4.3 Method of administration

Diazepam Injection BP may be given IV, IM or by IV infusion.

4.4 Contraindications

Diazepam Injection is contraindicated in the following group of patients:

Known hypersensitivity to Diazepam or any other benzodiazepine.

Severe chronic obstructive pulmonary disease.

Acute glaucoma

Myasthenia gravis

Hypoalbuminemia

Neonates

Diazepam should be avoided in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency or sleep apnoea.

4.5 Special warning and Precautions for use.

Special precautions should be exercised with the elderly patients as parenteral administration of Diazepam is more likely to cause apnoea, hypotension, bradycardia or cardiac arrest in geriatric patients.

Diazepam induced disinhibition may precipitate suicide or aggressive behaviour so it should be used with care in patients with personality disorders, mental depression or suicidal tendencies.

Caution should be exercised in patients with impaired hepatic and/or renal functions.

Precautions:

Diazepam is not recommended for the primary treatment of psychotic illness. It should not be used alone to treat depression or anxiety with depression (suicide may be precipitated in such patients). It should be used with extreme caution in patients with history of alcohol or drug abuse.

4.6 Paediatric population

Not applicable.

4.7 Interactions with other FPPs and other forms of interactions

The following interactions have been reported with Diazepam:

Isoniazid : Increases half-life of Diazepam

Rifampicin : Decreases half-life of Diazepam

Anticoagulants : Protein binding of Diazepam reduced

Lithium:Hypothermia

Sodium Valproate : Displaces Diazepam from plasma-protein binding sites

Propranolol and metoprolol : Inhibits metabolism of Diazepam

Digoxin : Raised serum digoxin level

Disulfiram : Prolongs half-life and reduces clearance of Diazepam

Cimetidine & Omeprazole : Inhibits hepatic metabolism of Diazepam

Oral contraceptives : Inhibits biotransformation of benzodiazepines

4.8 Additional information on special populations

Not available.

4.9 Paediatric population

Not available.

4.10 Fertility, Pregnancy and Lactation

Diazepam crosses the placenta and is reported to increase the risk of congenital malformations when used during the first trimester of pregnancy. When used as anti-convulsant, risk-benefit must be considered as recent reports suggest an increased incidence of congenital abnormalities in children whose mothers used anticonvulsants during pregnancy. Chronic usage in pregnancy may cause physical dependence with resulting withdrawal symptoms in the neonate. Use of Diazepam just prior to or during labour may cause neonatal flaccidity. When Diazepam Injection is administered in doses of more than 30 mg within 15 hours before delivery, the neonate may develop apnoea, hypotonia, hypothermia, a reluctance to feed and impaired metabolic response to cold stress. Diazepam is distributed into breast milk and should be avoided in nursing mothers.

4.11 Effects on ability to drive and use machines

Patients treated with Diazepam Injection should not drive or use machinery.

4.12 Undesirable effects

Central Nervous System: Drowsiness, sedation, ataxia, nervousness, irritability, insomnia, extrapyramidal effects, dystonia, impairment of memory, muscle weakness, paresthesias, seizures, vertigo, headache, confusion, mental depression, slurred speech or dysarthria.

Gastrointestinal System:Abdominal cramps, constipation, diarrhoea, dryness of mouth or increased thirst, hepatic dysfunction.

Cardiovascular System:Palpitations, tachycardia, venous thrombosis or phlebitis, hypotension.

Allergic Reactions: Skin rash or itching.

Haematological: Anemia, neutropenia, thrombocytopenia, agranulocytosis.

Others: Changes in libido, tremor, visual disturbances, urinary retention or incontinence, amnesia, paradoxical excitation and disinhibition. Respiratory depression and hypotension may occur with parenteral administration.

4.13 Overdose

Symptoms of overdosage include impairment of consciousness, deep coma and depression of vital brain stem function. Respiration, pulse and blood pressure should be monitored. Oxygen should be administered if respiration is depressed. IV fluids should be administered to promote diuresis.

Hypotension should be controlled. Dialysis is of limited value in the treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties

Diazepam a benzodiazepine, acts as depressant of the central nervous system (CNS), producing all levels of CNS depression from mild sedation to hypnosis to coma depending on dose. The precise sites and mechanisms of action have not been completely established.

Although various mechanisms of action have been proposed, it is believed that benzodiazepines enhance or facilitate the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA) which is one of the major inhibitory neurotransmitters in the brain and mediates both pre- and post synaptic inhibition in all regions of the CNS, following interaction between the benzodiazepines and a specific neuronal membrane receptor.

5.2. Pharmacokinetic properties

Following intramuscular administration of Diazepam into the deltoid muscle, absorption is usually rapid and complete.

Diazepam is highly lipid soluble and crosses the blood-brain barrier, these properties qualify it for intravenous use since it acts promptly and its initial effects decrease rapidly as it is redistributed into fat depots and tissues. Diazepam has a half-life of 30-60 hours.

Diazepam is metabolized by oxidation to active, as well as inactive metabolites before final inactivation as glucuronide conjugates. Accumulation of Diazepam and its active metabolites is significant during repeated dosing. Elimination is slow since metabolites remain in blood for several days or even weeks.

5.3. Preclinical safety data

Not available

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients

Following excipients are used in the formulation of NOTIUM.

Propylene glycol BP

Benzyl Alcohol BP

Sodium Benzoate BP

Benzoic Acid BP

Water for Injections BP

6.2 Incompatibilities

NA

6.3 Shelf life

36 Months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C, protected from light. Do not freeze.

6.5 Nature and contents of container

Each 2ml amber glass USP Type I ampoule is filled, sealed and labeled. 10 such ampoules are to be placed in a transparent tray & inserted along with a leaflet in printed carton. [Cartons with inside printing with KILITCH].

6.6 Special precaution for disposal and other handling

Keep out of reach of children.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESS:

Manufactured By:

KILITCH DRUGS (INDIA) LIMITED.

Plot no- C-301/2, M.I.D.C T.T.C, Industrial Area, Pawane Village, Navi Mumbai - 400 705, Maharashtra, INDIA.

8. MARKETING AUTHORIZATION NUMBERS:

Not applicable.

9. DATE OF FIRST REGISTRATION/ RENEWAL OF THE REGISTRATION:

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable.

11. DOSIMETRY (IF APPLICABLE)

Not Applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable.

The Summary of Product Characteristics (SPC) is satisfactory.