Material Safety Data Sheet

CLORAZEPATE DIPOTASSIUM TABLETS
3.75/7.5/15 mg

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING	
Material	Clorazepate Dipotassium Tablets
Empirical Chemical Formula	$C_{16}H_{11}ClK_2N_2O_4$
Synonyms	Tranxene, Nevracten
Manufacturer	Ohm Laboratories, Inc., 1385 Livingston Ave. North Brunswick, NJ, 08907, USA.
Distributor	Ranbaxy Pharmaceuticals Inc., 9431, Florida Mining Blvd. East, Jacksonville, FL, 32257

2. COMPOSITION / INFORMATION ON INGREDIENTS		
Ingredients	CAS Number	Percentage
Clorazepate Dipotassium	57109-90-7	3.75 mg – 1.97% 7.5 mg – 3.94% 15 mg – 7.87%
Non-Hazardous Ingredients	–	3.75 mg – 98.03% 7.5 mg – 96.06% 15 mg – 92.13%

3. HAZARDS IDENTIFICATION	
Fire and Explosion	Expected to be non-combustible.
Health	Principal routes of exposure are by accidental skin and eye contact and inhalation of generated dusts. Prolonged use of benzodiazepines can lead to alcoholism-like dependence. Benzodiazepines can cause involuntary movements and difficulties in moving the muscles of the face. Arteriosclerosis, kidney, liver and respiratory conditions can be aggravated. They also cause an increased risk of some birth defects such as cleft palate. Benzodiazepines may be associated with some cancers. As a result of the physical presentation of the product, the risk to health in the normal handling of the product is expected to be low.
Environment	No information is available about the potential of this product to produce adverse environmental effects.

4. FIRST-AID MEASURES	
Ingestion	If poisoning occurs, contact a doctor or Poisons Information Centre.

Inhalation	If dust is inhaled, remove from contaminated area. Encourage patient to blow nose to ensure clear passage of breathing. If irritation or discomfort persists seek medical attention.
Skin Contact	Remove contaminated clothing. Wash affected areas with plenty of water and soap if available, for several minutes. Seek medical attention if irritation or rash develops and persists.
Eye Contact	Flush eyes with large amounts of running water for 15 minutes. Hold eyelids open. Get immediate medical attention.
NOTES TO PHYSICIANS / HEALTH PROFESSIONALS	
Medical Treatment	Converted in the acid environment of the stomach to desmethyldiazepam. For severe benzodiazepine overdose the stomach should be emptied by aspiration and lavage. Recovery usually follows symptomatic relief. Dialysis is of no value.
Medical Conditions Caused or Aggravated by Exposure	Refer to prescribing information for detail description of medical conditions caused by or aggravated by overexposure to this product
Antidotes	Flumazenil

5. FIRE-FIGHTING MEASURES	
Fire and Explosion Hazards	No apparent fire or explosion hazard for the product, although the packaging is combustible. Emits toxic fumes under fire conditions.
Extinguishing Media	Water spray. Carbon dioxide, dry chemical powder or appropriate foam is recommended.
Special Firefighting Procedures	For single units (packages) – No special requirements needed. For larger amounts (multiple packages/pallets) of product – Since toxic or flammable vapours/fumes might be evolved from fires involving this product and associated packaging, self contained breathing apparatus and full protective equipment are recommended for firefighters. If possible, contain and collect firefighting water for later disposal.
Hazardous Combustion Products	Toxic, corrosive or flammable thermal decomposition products are expected when the product is exposed to fire.

6. ACCIDENTAL RELEASE MEASURES	
Personal Precautions	Wear protective clothing and equipment consistent with the degree of hazard.
Environmental Precautions	For large spills, take precautions to prevent entry into waterways, sewers, or surface drainage systems.
Clean-up Methods	Collect and place it in a suitable, properly labelled container for recovery or

	disposal. Avoid raising dust. Ventilate area and wash spill site after pick-up complete.
Decontamination Procedure	No specific decontamination or detoxification procedures have been identified for this product. Water can be used for clean-up and decontamination operations.

7. HANDLING AND STORAGE	
Safe Handling and Use	Avoid breaking or crushing the tablets.
Storage	No storage requirements necessary for occupational hazards. Follow product information storage instructions to maintain efficacy.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION	
PERSONAL PROTECTIVE EQUIPMENT	
Eye Protection	Wear approved safety glasses with side shields in case of eye contact.
Respirators	If respiratory protective equipment (RPE) is used, the type of RPE will depend upon air concentrations present, required protection factor as well as hazards, physical properties and warning properties of substances present.
Other Equipment or Procedures	Wear appropriate clothing to avoid skin contact.
Work / Hygienic Practices	Wash hands and arms thoroughly after handling.

9. PHYSICAL AND CHEMICAL PROPERTIES	
Physical Form (Appearance)	Shape – Round Color -Blue –3.75 mg, Peach –7.5 mg and Red – 15 mg

10. STABILITY AND REACTIVITY	
Stability	Stable
Conditions to Avoid	n/k, As a precautionary measure, keep away from strong oxidizers.

11. TOXICOLOGICAL INFORMATION

This material contains active pharmaceutical ingredient Clorazepate Dipotassium, the specific information on which is provided below.

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is essential that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Oral Toxicity	Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg; sedation was induced at 32 mg/kg; the LD50 was 1320 mg/kg. In monkeys aggressive behavior was reduced at an oral dose of 0.25 mg/kg; sedation (ataxia) was induced at 7.5 mg/kg; the LD50 could not be determined because of the emetic effect of large doses, but the LD50 exceeds 1600 mg/kg. Twenty-four dogs were given clorazepate dipotassium orally in a 22-month toxicity study; doses up to 75 mg/kg were given. Drug-related changes occurred in the liver; weight was increased and cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved. Eighteen rhesus monkeys were given oral doses of clorazepate dipotassium from 3 to 36 mg/kg daily for 52 weeks. All treated animals remained similar to control animals. Although total leucocyte count remained within normal limits it tended to fall in the female animals on the highest doses.
Inhalation Toxicity	n/k
Skin Effects	n/k
Eye Effects	n/k
Target Organ Effects	Examination of all organs revealed no alterations attributable to clorazepate dipotassium. There was no damage to liver function or structure.
Sensitisation	n/k
Genetic Toxicity	n/k
Carcinogenicity	n/k
Reproductive Effects	Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. Clorazepate dipotassium did not alter the fertility indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young

	by their mothers.
Gastrointestinal Reactions	The side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia, depression, tremor, and slurred speech. There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit. Decrease in systolic blood pressure has been observed.
Hypersensitivity Reactions	
Pharmacological Effects	Pharmacologically, clorazepate dipotassium has the characteristics of the benzodiazepines. It has depressant effects on the central nervous system. The primary metabolite, nordiazepam, quickly appears in the blood stream. The serum half-life is about 2 days. The drug is metabolized in the liver and excreted primarily in the urine. Studies in healthy men have shown that clorazepate dipotassium has depressant effects on the central nervous system. Prolonged administration of single daily doses as high as 120 mg was without toxic effects. Abrupt cessation of high doses was followed in some patients by nervousness, insomnia, irritability, diarrhea, muscle aches, or memory impairment. Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Nordiazepam, the primary metabolite, quickly appears in the blood and is eliminated from the plasma with an apparent half-life of about 40 to 50 hours. Plasma levels of nordiazepam increase proportionally with a clorazepate dipotassium dose and show moderate accumulation with repeated administration. The protein binding of nordiazepam in plasma is high (97-98%). Within 10 days after oral administration of a 15 mg (50 µCi) dose of 14C-clorazepate dipotassium to two volunteers, 62-67% of the radioactivity was excreted in the urine and 15-19% was eliminated in the feces. Both subjects were still excreting measurable amounts of radioactivity in the urine (about 1% of the 14C-dose) on day ten. Nordiazepam is further metabolized by hydroxylation. The major urinary metabolite is conjugated oxazepam (3-hydroxynordiazepam), and smaller amounts of conjugated p-hydroxynordiazepam and nordiazepam are also found in the urine.
Over Dosage	Overdosage is usually manifested by varying degrees of CNS depression ranging from slight sedation to coma. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed immediately. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though rarely reported, may occur with large overdoses. While

	reports indicate that individuals have survived overdoses of clorazepate dipotassium as high as 450 to 675 mg, these doses are not necessarily an accurate indication of the amount of drug absorbed since the time interval between ingestion and the institution of treatment was not always known. Sedation in varying degrees was the most common physiological manifestation of clorazepate dipotassium overdosage. Deep coma when it occurred was usually associated with the ingestion of other drugs in addition to clorazepate dipotassium. Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.**
Contraindications	Clorazepate dipotassium tablets are contraindicated in patients with a known hypersensitivity to the drug, and in those with acute narrow angle glaucoma.

12. ECOLOGICAL INFORMATION
Do not allow product to enter drinking water supplies, waste water or soil.

13. DISPOSAL CONSIDERATIONS	
Disposal Recommendations	Material should be disposed of in keeping with all local and national legislation. Packaging should be disposed of in keeping with all local and national legislation. Handle contaminated containers as product.
Regulatory Requirements	Observe all local and national regulations when disposing of this product.

14. TRANSPORT INFORMATION
The MSDS should accompany all shipments for reference in the event of spillage or accidental release. Only authorized persons trained and competent in accordance with appropriate national and international regulatory requirements may prepare dangerous goods for transport.

Transport Information	n/k

15. REGULATORY INFORMATION	
EU Classification and Labelling	n/k
US OSHA Standard (29 CFR Part 1910.1200)	n/k
OTHER US REGULATIONS	
	n/k

16. OTHER INFORMATION

The above information and recommendations are believed to be correct as on date but does not purport to be all-inclusive and shall be used only as a guide. Nothing herein shall be deemed to create any warranty, express or implied. It is the responsibility of the user to determine the applicability of this information and the suitability of the material or product for any particular purpose.

Ranbaxy shall not be held liable for any damage resulting from handling or from contact with the above product. Ranbaxy reserves the right to revise this MSDS.