APOTEX INC.

Workplace Material Safety Data Sheet

NFPA

Canadian Classifications			
WHMIS	Apotex Haz. Class	Protective Clothing	TDG Air/Road/Rail
Not regulated under WHMIS: Covered by Food & Drug Act.	2		

Section 1. Product Identification and Uses

Common/Trade name	**Apo-Tramadol HCl Tablets 50 mg**	**CI#**	TRAMADOL25125
Synonyms	Tramadol Hydrochloride Tablets **Brand Name** Ultram	**DSL#**	Not on the DSCL list.
Chemical name	Not applicable.	**CAS#**	Not applicable.
Chemical formula	Not applicable.	**Code**	42617
Chemical family	Not available.	**Molecular weight**	Not applicable.
Supplier	TorPharm Etobicoke, Ontario M9W 6Y3 Canada Tel. (416) 675-0338	**Chemical structure**	Not applicable.
Material uses	Pharmaceutical industry: Dosage form Therapeutic category: analgesic.	**Manufacturer**	Apotex Inc. 50 Steinway Blvd Etobicoke, Ontario Canada M9W 6Y3 Tel. (416) 675-0338
Emergency phone	**(416)-749-9300** ext. 5555 For general information call ext. 8483 (8 AM-4 PM)	**DIN**	Not available.

Section 2. Hazards Identification

Potential Acute Health Effects Not expected to be hazardous under normal handling conditions.

Potential Chronic Health Effects Possible hypersensitization.

WHMIS CLASS D-2B: Material causing other toxic effects (TOXIC).

Not regulated under WHMIS: Covered by Food & Drug Act.

Section 3. First Aid Measures

[illegible]	Flush with copious quantities of water. If irritation persists, obtain medical advice.
Skin contact	Not expected to result in hazardous effects.
Hazardous skin contact	Flush with copious amounts of water. Seek medical attention if irritation persist.
Slight inhalation	Not expected to result in hazardous effects.

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Hazard inhalation	Remove from exposure. Persons developing serious hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration (use protective mask with one-way valve). If breathing is difficult give oxygen.
Slight ingestion	Not expected to be hazardous. It is good practice to rinse mouth thoroughly with water and drink a cup of water to minimize discomfort.
Hazardous ingestion	Never give anything by mouth if victim is rapidly losing consciousness, or is unconscious or convulsing. Rinse mouth thoroughly with water. If breathing has stopped, trained personnel should begin artificial respiration (use protective mask with one-way valve), or if the heart has stopped, cardiopulmonary resuscitation (CPR) immediately. Seek medical attention. Overdosage: Serious potential consequences of overdosage are respiratory depression and seizure. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with Tramadol the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Section 4. Composition and Information on Ingredients

Name	CAS #	% (v./w)
Tramadol hydrochloride	73806-49-2	50

Toxicity values of the hazardous ingredients

Tramadol
TDLo: 16 mg/kg/4D (intermittent-woman)
LD50: 228 mg/kg (oral-rat)

TLV	Not available.

Section 5. Fire Fighting Measures

The product is:	Combustible.
Autoignition temperature	Not available.
Fire degradation products	These products are carbon oxides (CO, CO2), nitrogen oxides (NO, NO2...).
Flash points	Not available.
Flammable limits	Not available.
Fire extinguishing procedures	Extinguisher media: water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials. Special fire fighting procedures: As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing.
Flammability	Not available
	Remark No additional remark.
Risks of explosion	Risks of explosion of the product in presence of mechanical impact: No. Risks of explosion of the product in presence of static discharge: Not available.
	Remark No additional remark.

Section 6. Accidental Release Measures

Vacuum or sweep up spillage. Avoid dust. Place spillage in appropriate labeled solid pharmaceutical waste class 261A container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site. Follow appropriate Safe Work Practice.

Use a shovel to put the material into a appropriate labeled waste disposal container. Finish cleaning by spreading water on the contaminated surface. Label and dispose as pharmaceutical waste class 261A. Follow appropriate Safe Work Practices.

Protective Clothing Pictograms in case of large spill and/or high exposure levels

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Protective clothing in case of large spill	Covering uniform. Gloves. 

Section 7. Handling and Storage

Precautions	In case of insufficient ventilation, wear suitable respiratory equipment. Avoid breathing dust. Wash thoroughly after handling. Dispose of as pharmaceutical waste Class 261A.
Storage	Store at room temperature (15-30°C) , in a dry place, out of direct sunlight, in a tightly closed container.

Section 8. Exposure Controls/Personal Protection

Engineering Controls	Exposure to this material can be controlled in many ways. The measures appropriate for a particular worksite depend on how this material is used and on the extent of exposure. This general information can be used to help develop specific control measures. Ensure that control systems are properly designed and maintained. Comply with occupational, environmental, fire, and other applicable regulations. Engineering methods to control hazardous conditions are preferred. Methods include mechanical (local exhaust) ventilation, process or personnel enclosure and control of process conditions. Administrative controls and personal protective equipment may also be required. Supply sufficient replacement air to make up for air removed by exhaust system.
Personal Protection	Covering uniform. Gloves.
Protective Clothing (Pictograms)	
	PERSONAL PROTECTIVE EQUIPMENT : Under normal work conditions, the use of personal protective equipment is not expected to be required. However major spills should require the use of designated personal protective equipment. If engineering controls and work practices are not effective in controlling exposure to this material, then wear suitable personal protective equipment including approved respiratory protection. Have appropriate equipment available for use in emergencies such as spills or fire. If the physical state of the finished product is altered by crushing, grinding or breakage, appropriate PPE may be required including dust respirator. Refer to the CSA Standard Z94.4-M1982, "Selection, Care, and Use of Respirators," available from the Canadian Standards Association, Rexdale, Ontario, M9W 1R3. RESPIRATORY PROTECTION GUIDELINES : Under normal work conditions, the use of personal protective equipment is not expected to be required. However major spills should require the use of designated personal protective equipment. EYE/FACE PROTECTION : Not required under normal working conditions. SKIN PROTECTION : The use of gloves is required for Good Manufacturing Practices (GMP) compliance. RESISTANCE OF MATERIALS FOR PROTECTIVE CLOTHING : Guidelines : GOOD: Natural, butyl or styrene-butadiene rubber (SBR), neoprene, nitrile, polyvinyl chloride (PVC), polyurethane, nitrile+PVC, neoprene+SBR, neoprene+natural rubber, SBR/neoprene NOTE: Resistance of specific materials can vary from product to product. Evaluate resistance under conditions of use and maintain clothing carefully. EXPOSURE CONTROLS/PERSONAL PROTECTION COMMENTS : Remove contaminated clothing promptly. Launder before rewearing. Inform laundry personnel of contaminant's hazards. Do not eat, drink or smoke in work areas. Wash hands thoroughly after handling this material. Maintain good housekeeping.
Exposure Limits	Not available.

Section 9. Physical and Chemical Properties

Physical state and appearance	Solid. (Film-coated, capsule-shaped tablets)	**Odor**	Not available.
pH (1% soln/water)	Not available.	**Taste**	Not available.
Odor threshold	Not available.	**Color**	White.
Volatility	Not applicable.		

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Melting point/ Freezing point	Not available.
Boiling point	Not available.
Specific gravity	Not available.
Vapor density	Not available.
Vapor pressure	Not available.
Water/oil dist. coeff.	Not available.
Ionicity (surface active agent)	Not available.
Critical temperature	Not available.
Instability temperature	Not available.
Conditions of instability	Not available.
Dispersion properties	See solubility.
Evaporation rate	Not applicable.
Solubility	Soluble in water.

Section 10. Stability and Reactivity

Stability	Normally stable.
Hazardous decomp. products	Not available.
Degradability	Not available.
Corrosivity	Not corrosive
	Remark No additional remark.
Reactivity/ Incompatibility	Not available.
	Remark No additional remark.

Section 11. Toxicological Information

Routes of entry	As the product is a solid dosage form, the major route of entry is ingestion. Other routes of entry, including inhalation, skin and eye contact may occur only under certain circumstances.
Toxicity data	**Tramadol** RTECS#: GV8925000 TDLo: 16 mg/kg/4D (intermittent-woman) LD50: 228 mg/kg (oral-rat)
	Remark The toxicological properties have not been thoroughly investigated.
Long-term effects	Target organ: Centaral nervous system Possible hypersensitization. Carcinogenicity: A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice (dosing orally up to 30 mg/kg for approximately two years, although the study was not done with the Maximum Tolerated Dose). This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study. Reproductive Toxicity: No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. Teratogenicity: There are no adequate and well-controlled studies in pregnant women. Tramadol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pragnancy category C. Tramadol has been shown to be embryotoxic and fetotoxic in mice, rats and rabbits at maternally toxic doses 3 to 15 times the maximum human dose or higher (120 mg/kg in mice, 25 mg/kg or higher in rats and 75 mg/kg or higher in rabbits), but was not teratogenic at these dose levels. No harm to the fetus due to tramadol was seen at

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doses that were not maternally toxic.
Mutagenicity: Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

Remark

Medical conditions aggravated by exposure: Hypersensitivity to material, in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

Short-term effects and Signs & Symptoms of overexposure

Possible eye, skin, gastrointestinal and/or respiratory tract irritation.
Dosage: Tramadol should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, Tramadol 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.
The most frequently reported adverse reactions were in the central nervous system and gastrointestinal system.
A variety of other adverse events were reported infrequently in patients taking tramadol during clinical trials: Coordination disturbance: Paresthesia; Cognitive dysfunction; Euphoria; Nervousness; Sleep disorder Hallucinations; Tremor; Amnesia; Difficulty in concentration; Abnormal gait Gastrointestinal Abdominal pain; Anorexia; Flatulence Musculoskeletal Hypertonia Respiratory Dyspnea Skin Rash Urticaria, Vesicles Special Senses Visual disturbance Dysgeusia Urogenital Urinary retention; Dysuria; Menstrual disorder Urinary frequency; Menopausal symptoms. A causal relationship between tramadol and these events has not been determined. However, the most significant events are listed below as alerting information to the physician: Body as a whole: Suicidal tendency.
Cardiovascular: Abnormal ECG, hypertension, myocardial ischemia, palpitations.
Central Nervous System: Migraine.
Gastrointestinal: Gastrointestinal bleeding, hepatitis, stomatitis.
Laboratory abnormalities: Creatinine increase, elevated liver enzymes, hemoglobin decrease, proteinuria.
Sensory: Cataracts, deafness, tinnitus.
Overdose: Cases of overdose with tramadol have been reported. Estimates of ingested dose in foreign fatalities have been in the range of 3 to 5 g. A 3 g intentional overdose by a patient in the clinical studies produced emesis and no sequelae. The lowest dose reported to be associated with fatality was possibly between 500 and 1000 mg in a 40 kg woman, but details of the case are not completely known.

Remark

The above adverse effects are based on clinical studies.

Section 12. Ecological Information

Ecotoxicity	Not available.
BOD5 and COD5	Not available.
Products of Biodegradation	Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.
Toxicity of the Products of Biodegradation	The products of degradation are less toxic than the product itself.
Special Remarks on the Products of Biodegradation	No additional remark.

Section 13. Disposal Considerations

Waste Disposal

Collect in sealed containers and place in appropriate labeled pharmaceutical solid waste class 261A container according to internal and external standards and procedures. Follow all appropriate safe work procedures and federal, provincial and local regulations for disposal. Use only licensed disposal and waste hauling companies.

Section 14. Transport Information TDG, IATA, IMDG

Not controlled under TDG (Canada).

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Not applicable (PIN and PG).

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Special Provisions for Transport	Not applicable.

Section 15. Other Regulatory Information and Pictograms

USA Classifications

NATIONAL FIRE PROTECTION ASSOCIATION (NFPA) HAZARD INDEX

NFPA-HEALTH-blue :2-Hazardous to health.
NFPA-FLAMMABILITY-red :1-Materials that must be preheated before ignition can occur.
NFPA-REACTIVITY-yellow :0-Normally stable.

National Fire Protection Association (U.S.A.)

Health
Fire Hazard
Reactivity
Specific Hazard

Hazardous Material Information System (U.S.A.)

Health Hazard	2
Fire Hazard	1
Reactivity	0
Personal Protection * - Chronic hazard indicator X - See Section 8	X

HCS (Hazardous Communication System) (OHSA, U.S.A.)

Not an HCS controlled material in USA.

DOT (Department of Transportation) (U.S.A) (Pictograms)

Not a DOT controlled material (United States).

European Classifications

DSCL (Dangerous Substances Classifications) (Europe) (Pictograms)

DSCL Risk (R) and Safety (S) Phrases

This product is not classified according to the EU regulations.

ADR (European Agreement of Dangerous goods by Road) (Pictograms)

Not controlled under ADR (Europe).

Other Regulations

Not available.

Section 16. Other Information

References

The Merck Index, twelfth edition
HSBD & RTECS Database
RxList Monographs
Physicians Desk Reference

MSDS:

Validation date: (year.month)

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Other Special Considerations	SAMPLING AND ANALYSIS : Use appropriate instrumentation and sampling strategy (location, timing, duration, frequency, and number of samples). Interpretation of the sampling results is related to these variables and the analytical method. OSHA method IMISC136 has been published, but is not validated.

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