SAFETY DATA SHEETS

This SDS packet was issued with item:

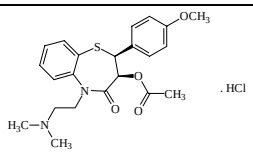
078491305

N/A

APOTEX
ADVANCING GENERICS

Material Safety Data Sheet

Section 1. Product Identification and Uses

Common/Trade name	**Diltiazem hydrochloride**	**DSL#**	On the DSL list.
Synonyms	Diltiazem chloridrate	**CAS#**	33286-22-5
Chemical name	1,5-Benzothiazepin-4(5H)-one,2,3-dihydro-3-(acetyloxy)-5-(2-(dimethylamino)ethyl-2-(4-methoxyphenyl)HCl, Cis-(+)	**Molecular weight**	451.02 g/mole
Chemical family	Benzothiazepine	**Chemical formula**	$C_{22}H_{26}N_2O_4S.HCl$
Supplier	Nicholas Piramal India Limited Nicholas Piramal Tower Ganpatrao Kadam Marg Lower Parel, Mumbai 400 013 Tel: 91-22-30466666	**Chemical structure**	
Material uses	Pharmaceutical active ingredient. Therapeutic category: Vasodilator (coronary) (calcium channel blocker)	**Manufacturer**	Not available.
Emergency phone	**(416)-749-9300** ext. 5555 For general information call ext. 8483 (8 AM-4 PM)	**DIN**	Not applicable.

Section 2. Hazards Identification

Potential Acute Health Effects	Possible eye, skin, gastrointestinal and/or respiratory tract irritation.
Potential Chronic Health Effects	Possible hypersensitization. Possible teratogen based on animals studies.
WHMIS	WHMIS CLASS D-2A: Material causing other toxic effects (VERY TOXIC).

Remark

Covered by Food & Drug Act and therefore not regulated under WHMIS

Apotex Hazard Classification (For Apotex internal practices only)	This material has been assigned hazard class: **2**

Section 3. First Aid Measures

Eye contact	IMMEDIATELY flush eyes with running water for at least 15 minutes, keeping eyelids open. Take care not to rinse contaminated water into the non-affected eye. Always seek medical attention for accidents involving the eyes.
Skin contact	Flush the contact area with lukewarm running water.
Hazardous skin contact	Flush the contact area with lukewarm running water for at least 15 minutes. Remove contaminated clothing, taking care not to spread the chemical. Seek medical attention if irritation persists.
Slight inhalation	Allow the victim to rest in a well ventilated area. If symptoms persist, obtain medical advice.
Hazardous inhalation	Take proper precautions to ensure your own safety before attempting rescue. Remove source of contamination or move victim to fresh air. 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.

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Slight ingestion	Flush out mouth with water.
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. In the event of an oral overdose, treatment may include the following: 1. Employ supportive measures in addition to gastrointestinal decontamination. 2. For hypotension, administer vasopressors. 3. For bradycardia, administer atropine. If there is no response to vagal blockade, administer isoproterenol cautiously. 4. For high-degree AV block, treat as for bradycardia. Fixed high-degree AV block should be treated with cardiac pacing. 5. For cardiac failure, administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics. 6. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination, but peritoneal or hemodialysis is NOT effective. (PDR 2005)

Section 4. Hazardous Ingredients

Name	CAS #	% (w/w)
Diltiazem hydrochloride	33286-22-5	100

Toxicity values of the hazardous ingredients

Refer to Sec. 11.

TLV Not established.

Section 5. Fire Fighting Measures

The product is:	May be combustible.
Autoignition temperature	Not available.
Fire degradation products	Decomposition products may include the following materials: carbon oxides (CO, CO_2), nitrogen oxides (NO, NO_2 etc.), sulfur oxides (SO_2, SO_3 etc.), halogenated compounds, hydrogen chloride.
Flash points	Not applicable.
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	This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity. Emits toxic fumes under fire conditions.
	Remark No additional remark.
Risks of explosion	Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Fine airborne dust can be ignited by static discharge.
	Remark No additional remark.

Section 6. Accidental Release Measures

Spill and leak	Vacuum or sweep up spillage. Avoid dust. Place spillage into an appropriate labeled waste disposal container. Wash contaminated clothing before reuse. Ventilate area and wash spill site. Follow appropriate Safe Work Practices.

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

Protective clothing in case of large spill	Hooded Full suit -Tyvek coveralls or equivalent. Powered Air Purifying Respirator with combination particulate/organic vapour cartridge. Gloves.

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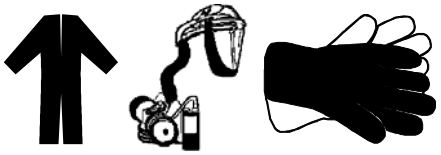


Section 7. Handling and Storage

Precautions

Use with adequate dust control. In case of insufficient ventilation, wear suitable respiratory equipment. Avoid inhalation, skin and eye contact. Pregnant women should avoid exposure to this product.

Storage

Store in suitable labelled containers. Keep containers tightly closed when not in use and when empty. Protect from damage. Store in a cool, dry, well-ventilated area, out of direct sunlight.

Section 8. Exposure Controls/Personal Protection

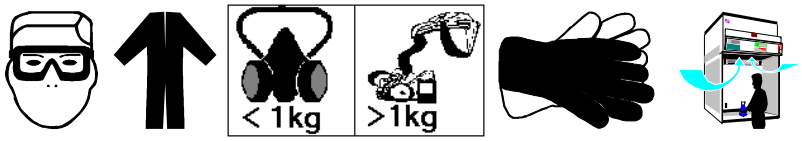
Engineering Controls

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

Splash goggles. Full suit with hood, or disposable/washable coveralls. Half facepiece Air Purifying Respirator with combination particulate/organic vapour cartridge (less then 1 kg). Powered Air Purifying Respirator (PAPR) with combination particulate/organic vapour cartridge (greater then 1 kg). Nitrile gloves (impervious). Chemical fume hood.

Protective Clothing (Pictograms)



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 respiratory protection is required, institute a complete respiratory protection program, including selection, fit testing, training, maintenance and inspection. Refer to the CSA Standard Z94, "Selection, Care, and Use of Respirators".
RESPIRATORY PROTECTION GUIDELINES:
Where Local Exhaust Ventilation (LEV) at dust generating process points exists, respiratory protection may not be required.
When working with quantities less than 1 kg and in the absence of appropriate Local Exhaust Ventilation (LEV) with dusty processes, a half facepiece Air Purifying Respirator with combination particulate/organic vapour cartridge and goggles is recommended.
When working with quantities greater than 1 kg and in the absence of Local Exhaust Ventilation (LEV) with dusty processes, a Powered Air Purifying Respirator (PAPR) with combination particulate/organic vapour cartridge and helmet/hood or Supplied Air Respirator (SAR) is recommended.
The specific respirator selected must be based on contamination levels found in the work place, the specific operation and not exceed the working limits of the respirator.
When performing cleaning activities refer to appropriate cleaning solution MSDS.
EYE/FACE PROTECTION: Splash goggles/safety glasses.
PROTECTIVE CLOTHING/SKIN PROTECTION: Glove selection must take into account any solvents and other hazards present. The selection of gloves for a specific activity must be based on the material's properties and on possible permeation and degradation that may occur under the circumstances of use. Potential allergic reactions can occur with certain glove materials (e.g. Latex) and therefore these should be avoided. Full environmental suit with hood. and/or other resistant protective clothing when working in dusty areas. Have a safety shower/eye-wash fountain readily available in the immediate work area.
EXPOSURE CONTROLS/PERSONAL PROTECTION COMMENTS: In the event clothing becomes contaminated, remove promptly. Launder before use. 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.
PREGNANCY PRECAUTION:
Pregnant women should avoid exposure to this product unless:
True Barrier Technology or appropriate engineering controls exists or:
When working with quantities less than 1 kg and in the absence of appropriate Local Exhaust Ventilation (LEV) with dusty processes, a full facepiece Air Purifying Respirator with combination particulate/organic vapour cartridge and goggles is worn.
When working with quantities greater than 1 kg and in the absence of Local Exhaust Ventilation (LEV) with dusty processes, a Powered Air Purifying Respirator (PAPR) with combination particulate/organic vapour cartridge and helmet/hood or Supplied Air Respirator (SAR) is worn.

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Section 9. Physical and Chemical Properties

Physical state and appearance	Solid. (Crystalline powder.)	**Odor**	Odorless.
pH	4.3 - 5.3 (1% water solution)	**Taste**	Bitter.
Odor threshold	Not available.	**Color**	White to off-white.
Volatility	Not available.		
Melting point/ Freezing point	207-212°C		
Boiling point	Not available.		
Specific gravity	Not available.		
Vapor density	Not available.		
Vapor pressure	Not available.		
Partition Coefficient:	n-octanol/water: 2.7		
Ionicity (surface active agent)	Not available.		
Critical temperature	Not available.		
Instability temperature	Not available.		
Conditions of instability	No additional remark.		
Dispersion properties	See solubility.		
Evaporation rate	Not available.		
Solubility	Freely soluble in water. Freely soluble in methyl alcohol, chloroform and formic acid. Slightly soluble in absolute ethanol. Practically insoluble in benzene. Insoluble in ether.		

Section 10. Stability and Reactivity

Stability	The product is stable.
Hazardous decomp. products	When heated to decomposition material emits toxic fumes of NOx, SOx and HCl. Emits toxic fumes under fire conditions.
Degradability	Not available.
Corrosivity	Not corrosive
	Remark No additional remark.
Reactivity/ Incompatibility	Strong oxidizing agents. Avoid exposure to light.
	Remark Not additional remark.

Section 11. Toxicological Information

Routes of entry	Ingestion. Inhalation. Eye contact. Skin contact.
Toxicity data	RTECS#: DL0310000 TDLo: 36 mg/kg/13 Days Intermittent (oral-man) TDLo: 18 mg/kg (oral-woman) TDLo: 8.400 mg/kg (oral-woman) LDLo: 21 mg/kg (oral-man) LD50: 560 mg/kg (oral-rat) LD50: 508 mg/kg (oral-mouse) Other toxicity data: Skin Rat: LD50: 271 mg/kg Irritancy Data: Human/skin: Moderate; Human/eye: Irritating

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Long-term effects

Possible hypersensitization.
Target organs: cardiovascular system.
Carcinogenicity: Not listed by IARC, NTP, ACGIH, or OSHA.
A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity.
Reproductive Toxicity: No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.
Teratogenicity: Category C. Diltiazem was injected intraperitoneally during organogenesis in pregnant mice, rats and rabbits. At 80 mg and 12.5 mg per kg, respectively, in rats and rabbits, malformations of the limbs and tail were found. No malformations occurred in the mouse. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg a day) resulted in embryo and fetal lethality. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths. No congenital anomalies were reported among nine infants whose mothers were treated with diltiazem during the first trimester of pregnancy. Major congenital anomalies were reported in 4 of 27 infants of women who had received prescriptions for diltiazem during the first trimester of pregnancy in another study. The limited data do not permit determination of the statistical significance, the specificity of the observed associations, or possible effects of confounding factors. Diltiazem decreases myometrial activity in the rat and has been used successfully to stop human preterm labor.
Mutagenicity: There was no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria.
Sensitization data: Dermal hypersensitivity reactions have been reported with therapeutic use of diltiazem.

Remark

Medical conditions aggravated by exposure: Hypersensitivity to material, heart problems and low blood pressure.

Short-term effects and Signs & Symptoms of overexposure

Possible eye, skin, gastrointestinal and/or respiratory tract irritation.
The usual oral adult dose of diltiazem hydrochloride is 30 mg three or four times a day, gradually increased to a maximum of 360 mg per day.
Adverse effects may include headache; nausea; difficulty breathing, coughing, or wheezing; constipation; diarrhea; dizziness or lightheadedness; swelling of feet, ankles, or lower legs; flushing or feelings of warmth; skin rash; and unusual tiredness or weakness. Possible allergic reaction to material if inhaled, ingested or in contact with skin.
Symptoms of overdose may include a slow heart rate. low blood pressure, heart block, and cardiac failure.

Remark

The above adverse effects are based on clinical studies.

Section 12. Ecological Information

Ecological Information Not available.

Section 13. Disposal Considerations

Waste Disposal For internal Apotex waste disposal: Collect in sealed containers and place in appropriate labeled pharmaceutical solid waste class 261A.
For external waste disposal: 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).

UN Not applicable (PIN and PG).

Special Provisions for Transport Not applicable.

Section 15. Other Regulatory Information and Pictograms

NATIONAL FIRE PROTECTION ASSOCIATION (NFPA) HAZARD INDEX

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

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

Health

Fire Hazard

Reactivity

Specific Hazard

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

Health Hazard	*	1
Fire Hazard		1
Reactivity		0
Personal Protection		X

* - Chronic hazard indicator
X - See Section 8

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

HCS CLASS: Harmful.

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

Not a DOT controlled material (United States).

EU Classification and Labelling

R22- Harmful if ingested. R33- Danger of cumulative effects. R36/37/38- Irritating to eyes, respiratory system and skin. R63- Possible risk of harm to the unborn child. S36- Wear suitable protective clothing.

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

Not controlled under ADR (Europe).

Other Regulations

This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all of the information required by the CPR.

Section 16. Other Information

References

The Merck Index
HSBD & RTECS Database

MSDS:

U.S. Pharmacopeia

Validation date: (year.month)

May 4, 2006

Revision date: 8/24/2011.

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Notice to Reader