Atomoxetine Hydrochloride Tablets and Capsules

Eli Lilly and Company
Material Safety Data Sheet

Effective Date: 15 Oct 2008

Section 1 - Chemical Product and Company

Manufacturer:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Manufacturer's Emergency Phone:
1-317-276-2000
CHEMTREC:
1-800-424-9300 (North America)
1-703-527-3887 (International)

Common Name: Atomoxetine Hydrochloride Tablets and Capsules

Chemical Name: Benzenepropanamine, N-methyl-gamma-(2-methylphenoxy)-, hydrochloride, (gammaR)-
Chemical Name 2: (-)-N-Methyl-3-phenyl-3-(ortho-tolyloxy)-propylamine hydrochloride
Synonym(s): 139603 Formulation; Tomoxetine; Tomoxetine hydrochloride capsules and tablets; Tomoxetine hydrochloride formulation; Tomoxetine hydrochloride high dose tablets and capsules; Tomoxetine hydrochloride tablets and capsules
Trademarks(s): Atenten; Atentin; Atinten; Cerentra; Compedur; Noriqual; Strattera; Valindra; Xovene
Lilly Item Code(s): B02453; B02455; B02457; B02459; B02490; ND1061; ND1062; ND1063; ND1064; ND1090; ND1101; ND1102; ND1103; ND1104; PU3225; PU3226; PU3227; PU3228; PU3229; PU3238; PU3239; PU3250; PU3251; TA4705; TA4710; TA4725; TA4740; UC9546; UC9547; UC9548; UC9549; UC9550

See attached glossary for abbreviations.

Section 2 - Composition / Information on Ingredients

Ingredient	CAS	Concentration %
Atomoxetine Hydrochloride	82248-59-7	2 - 33
Excipients	NA	71 - 98

Contains no hazardous components (one percent or greater) or carcinogens (one-tenth percent or greater) not listed above.

Exposure Guidelines:
Atomoxetine hydrochloride - LEG 25 micrograms/m3 TWA for 12 hours. LEG 38 micrograms/m3 TWA for 8 hours.

Section 3 - Hazards Identification

Appearance: White to off-white powder finished as capsules or tablets
Physical State: Solid
Odor: Odorless

Emergency Overview

Emergency Overview Effective Date: 04-Apr-2001

Lilly Laboratory Labeling Codes:
Health 3 **Fire** 1 **Reactivity** 0

Primary Physical and Health Hazards: Not hazardous if intact. Corrosive (eyes). Nervous System and Heart Effects.

Caution Statement: Intact Atomoxetine Hydrochloride Tablets and Capsules are not considered to be a health hazard. The contents of Atomoxetine Hydrochloride Tablets and Capsules may cause burns or permanent tissue damage to the eyes. Effects of exposure may include tremors, nervousness, anxiety, nausea, headache, change in blood pressure, and increased heart rate.

Routes of Entry: Inhalation and skin contact.

Effects of Overexposure: Tablets and capsules are intended for human consumption under guidance of a physician. Based on animal/clinical data, atomoxetine hydrochloride may be harmful if ingested, may be fatal if inhaled, may cause burns or permanent tissue damage to the eyes, and is not expected to be irritating to the skin. Effects of overexposure to atomoxetine hydrochloride may include gastrointestinal effects (nausea, vomiting), fatigue, decreased appetite, dizziness, mood swings, insomnia, and increased blood pressure and heart rate. Rare cases of liver toxicity have been reported. Animal studies with atomoxetine hydrochloride have reported liver effects, dilated pupils, and tremors.

Medical Conditions Aggravated by Exposure:
Atomoxetine hydrochloride - Individuals with cardiovascular disease, glaucoma, or on monoamine oxidase inhibitor (MAOI) therapy.

Carcinogenicity:
Atomoxetine hydrochloride - Not listed by IARC, NTP, ACGIH, or OSHA.

Section 4 - First Aid Measures

Eyes: Hold eyelids open and flush with a steady, gentle stream of water for 15 minutes. See an ophthalmologist (eye doctor) or other physician immediately. Immediate rinsing may prevent permanent damage.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Do not induce vomiting. Call a physician or poison control center. If available, administer activated charcoal (6-8 heaping teaspoons) with two to three glasses of water. Do not give anything by mouth to an unconscious person. Immediately transport to a medical care facility and see a physician.

Notes to Physician:
Atomoxetine - An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

Section 5 - Fire Fighting Measures

Flash Point: Not applicable
UEL: No applicable information found
LEL: No applicable information found

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon.

Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Hazardous Combustion Products: May emit toxic chloride fumes when exposed to heat or fire.

Section 6 - Accidental Release Measures

The following are recommended for manufacturing or other situations where exposure to the capsule contents or tablet powder may occur.

Spills: Vacuum material with appropriate dust collection filter in place. Be aware of potential for dust explosion when using electrical equipment. If vacuum is not available, lightly mist material and remove by sweeping or wet wiping. Wear protective equipment, including eye protection, to avoid exposure (see Section 8 for specific handling precautions).

Section 7 - Handling and Storage

Storage Conditions: Controlled Room Temperature: 15 to 30 C (59 to 86 F).

Section 8 - Exposure Controls / Personal Protection

See Section 2 for Exposure Guideline information.

Intact capsules and coated compressed tablets are not considered hazardous under normal handling procedures and protective equipment is not required. The following are recommended for manufacturing or other situations where exposure to the capsule contents or tablet powder may occur.

Respiratory Protection: Use an approved respirator.

Eye Protection: Chemical goggles and/or face shield.

Ventilation: Laboratory fume hood or local exhaust ventilation.

Other Protective Equipment: Chemical-resistant gloves and body covering to minimize skin contact. If handled in a ventilated enclosure, as in a laboratory setting, respirator and goggles or face shield may not be required. Safety glasses are always required.

Additional Exposure Precautions: In production settings, airline-supplied, hood-type respirators are preferred. Shower and change clothing if skin contact occurs.

Section 9 - Physical and Chemical Properties

Appearance: White to off-white powder finished as capsules or tablets
Odor: Odorless
Boiling Point: No applicable information found
Melting Point: No applicable information found
Density: No applicable information found
pH: No applicable information found
Evaporation Rate: No applicable information found
Water Solubility: Soluble
Vapor Density: No applicable information found
Vapor Pressure: No applicable information found

Section 10 - Stability and Reactivity

Stability: Stable at normal temperatures and pressures.

Incompatibility: May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

Hazardous Decomposition: May emit toxic chloride fumes when heated to decomposition.

Hazardous Polymerization: Will not occur.

Section 11 - Toxicological Information

Acute Exposure

Oral:
Atomoxetine hydrochloride - Rat (fasted), median lethal dose 196 mg/kg.
Rat (fed), median lethal dose estimated greater than 300 mg/kg, mortality, myoclonic jerking.
Dog, 37.5 mg/kg, no deaths, tremors, myoclonic jerking, dilation of the pupils.

Skin:
Atomoxetine hydrochloride - Rabbit, 200 mg/kg, no deaths or toxicity.

Inhalation:
Atomoxetine hydrochloride (racemic mixture) - Rat, median lethal concentration 330 mg/m3 for 4 hours.
Atomoxetine hydrochloride tablets and capsules formulation - The formulated material is not expected to pose an inhalation hazard.

Skin Contact:
Atomoxetine hydrochloride - Rabbit, nonirritant

Eye Contact:
Atomoxetine hydrochloride - Rabbit, corrosive
(Injury was decreased if eyes were rinsed immediately after exposure)

Chronic Exposure

Target Organ Effects:
Atomoxetine hydrochloride - Hepatotoxicity (increased liver weight, hepatocellular vacuolation, increased serum ALT) was reported in male rats given dietary concentrations greater than or equal to 0.01% for 3 or 12 months and in mice given 0.4% in diet for 3 months. No hepatoxicity was observed in dogs administered up to 16 mg/kg/day for 3 or 12 months. Clinical signs (pupillary light response, tremors, dilated pupils) were observed in dogs given less than 8 mg/kg/day for 1 year. Young rats administered up to 50 mg/kg/day from 10 days of age through adulthood matured physically and behaviorally with no major organ toxicity.

Reproduction:
Atomoxetine hydrochloride - Slight fertility effects reported in a 1-generation fertility study in rats. However, fertility findings were not duplicated in a subsequent 2-generation study at equivalent doses and route of administration. Embryo-fetal developmental toxicity studies in rats and rabbits indicate that atomoxetine is not teratogenic or embryotoxic. Study results indicate that atomoxetine administered to young rats causes a slight delay in puberty and in epididymal sperm counts but that these effects have no impact on reproduction.

Sensitization: No applicable information found.

Mutagenicity:
Atomoxetine hydrochloride - Negative in Ames, unscheduled DNA synthesis, sister chromatid exchange, chromosome aberration, mouse micronucleus, mouse lymphoma, and mouse micronucleus (in vivo) assays.

Carcinogenicity:
Atomoxetine hydrochloride - No evidence of carcinogenicity reported in two-year studies at dietary concentrations up to 0.1% (rats) and 0.3% (mice).

Section 12 - Ecological Information

No environmental data for the mixture or formulation. The environmental information for ingredient(s) or related material(s) are presented.

Ecotoxicity Data:
Atomoxetine hydrochloride (concentrations below as atomoxetine free base)
Rainbow trout 96-hour median lethal concentration: 8.8 mg/L
Daphnia magna 48-hour median effective concentration: 5.7 mg/L
Daphnia magna 21-day chronic no observable effect concentration: 0.47 mg/L
Green algae (*P.subcapitata*) 72-hour median effective concentration (biomass): 0.42 mg/L
Green algae *(P.subcapitata*) 72-hour median effective concentration (growth rate): 0.73 mg/L
Green algae (*P. subcapitata*) 72-hour no observable effect concentration: 0.26 mg/L
Activated sludge respiration inhibition - 3-hour median effective concentration (1.6 g solids/L): 73.1 mg/L
Fathead minnow early life stage toxicity test: no observable effect concentration: 32 microgram/L
C. riparius 28-day (sediment) chronic no observable effect concentration: >77 mg/kg

Environmental Fate:
Atomoxetine hydrochloride (concentrations below as atomoxetine free base)
Log Kow: 0.104, 0.676, 2.81 (pH 4, 7, 9)
pKa: 9.23
Sludge adsorption (Koc, after 4 hours, normalized to % organic carbon): 452 to 794

Sludge adsorption (Kd, after 4 hours): 211 to 370
Sludge biodegradation (96-hour batch method, aerobic, 2.5g/L activated sludge solids)
Half-life of atomoxetine: 136 hours
1.92% CO_2 evolution
23% transformation
Degradation in aquatic sediment (100 days, static, aerobic)
0.3% to 0.9% CO_2 evolution
Half-life from overlying water: <3 days
Half-life from water/sediment system: 301 to 630 days
Hydrolysis: < 10% over 5 days at 50C
Photolysis: not expected

Environmental Summary:
Atomoxetine hydrochloride - Material is highly toxic to green algae, moderately toxic to aquatic invertebrates and fish, and is practically non-toxic to activated sludge microorganisms. Measurable concentrations in the atmosphere are not expected since it is a non-volatile solid. The solubility of the material in water is high. The atomoxetine concentration in activated municipal sludge declined due to sorption and biodegradation. Material will not bioconcentrate in aquatic organisms.

Lilly Aquatic Exposure Guideline (LAEG):
Atomoxetine hydrochloride (concentrations below as atomoxetine free base)
LAEG for Drinking Water: 12.5 micrograms/L
LAEG for Chronic Exposure of Aquatic Organisms: 14 micrograms/L
LAEG for Acute Exposure of Aquatic Organisms: 120 micrograms/L

Section 13 - Disposal Considerations

Waste Disposal: Dispose of any cleanup materials and waste residue according to all applicable laws and regulations.

Section 14 - Transport Information

Regulatory Organizations:

DOT: Not Regulated

ICAO/IATA: Not Regulated

IMO: Not Regulated

Section 15 - Regulatory Information

Below is selected regulatory information chosen primarily for possible Eli Lilly and Company usage. This section is not a complete analysis or reference to all applicable regulatory information. Please consider all applicable laws and regulations for your country/state.

U.S. Regulations

Atomoxetine hydrochloride
TSCA - No
CERCLA - Not on this list
SARA 302 - Not on this list
SARA 313 - Not on this list
OSHA Substance Specific - No

EU Regulations

EC Classification
Xn (Harmful)
Xi (Irritant)
N (Dangerous for the Environment)

Risk Phrases
R 22 - Harmful if swallowed.
R 41 - Risk of serious damage to eyes.
R 50 - Very toxic to aquatic organisms.

Safety Phrases
S 26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S 36/37/39 - Wear suitable protective clothing, gloves and eye/face protection.
S 45 - In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

Section 16 - Other Information

MSDS Sections Revised: Section 12.

As of the date of issuance, we are providing available information relevant to the handling of this material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. THIS MATERIAL SAFETY DATA SHEET SHALL NOT BE DEEMED TO CREATE ANY WARRANTY OF ANY KIND (INCLUDING WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE). In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

For additional information contact:
Eli Lilly and Company
Hazard Communication
317-277-6029

GLOSSARY:

ACGIH = American Conference of Governmental Industrial Hygienists
AIHA = American Industrial Hygiene Association
BEI = Biological Exposure Index
CAS Number = Chemical Abstract Service Registry Number
CERCLA = Comprehensive Environmental Response Compensation and Liability Act (of 1980)

CHAN = Chemical Hazard Alert Notice
CHEMTREC = Chemical Transportation Emergency Center
DOT = Department of Transportation
EC = European Community
EINECS = European Inventory of Existing Chemical Substances
ELINCS = European List of New Chemical Substances
EPA = Environmental Protection Agency
HEPA = High Efficiency Particulate Air (Filter)
IARC = International Agency for Research on Cancer
ICAO/IATA = International Civil Aviation Organization/International Air Transport Association
IEG = Lilly Interim Exposure Guideline
IMO = International Maritime Organization
Kow = Octanol/Water Partition Coefficient
LEG = Lilly Exposure Guideline
LEL = Lower Explosive Limit
MSDS = Material Safety Data Sheet
MSHA = Mine Safety and Health Administration
NA = Not Applicable, except in Section 14 where NA = North America
NADA = New Animal Drug Application
NAIF = No Applicable Information Found
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
NOS = Not Otherwise Specified
NTP = National Toxicology Program
OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit (OSHA)
RCRA = Resource Conservation and Recovery Act
RQ = Reportable Quantity
RTECS = Registry of Toxic Effects of Chemical Substances
SARA = Superfund Amendments and Reauthorization Act
STEG = Lilly Short Term Exposure Guideline
STEL = Short Term Exposure Limit
TLV = Threshold Limit Value (ACGIH)
TPQ = Threshold Planning Quantity
TSCA = Toxic Substances Control Act
TWA = Time Weighted Average/8 Hours Unless Otherwise Noted
UEL = Upper Explosive Limit
UN = United Nations
WEEL = Workplace Environmental Exposure Level (AIHA)