Eli Lilly and Company
Material Safety Data Sheet

MSDS Index

Duloxetine Hydrochloride Capsules

Effective Date: 27-Aug-2005

Section 1 - Chemical Product and Company

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

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

Common Name: Duloxetine Hydrochloride Capsules

Chemical Name: 2-Thiophenepropanamine, N-methyl-gamma-(1-naphthalenyloxy)-, hydrochloride, (gammaS)-
Synonym(s): Duloxetine hydrochloride; Duloxetine; Duloxetine capsule mix; 246916 formulation; 10% W/W duloxetine pellets; Duloxetine hydrochloride capsules, 20 mg; Duloxetine hydrochloride pulvules; Duloxetine hydrochloride pulvules, 30 mg; Duloxetine hydrochloride pulvules, 60 mg; Pulvules duloxetine hydrochloride; Encapsulated Duloxetine, 30 mg; Duloxetine pellets; Duloxetine hydrochloride pulvules, 40 mg; Duloxetine hydrochloride pulvules, 20 mg; Duloxetine hydrochloride pellets; 5% W/W duloxetine pellets; 20% W/W duloxetine pellets
Tradename(s): Yentreve; Cymbalta; AriClaim
Lilly Item Code(s): B02426; B02466; CK1079; CK1084; ND1068; ND1075; ND1078; ND1080; ND1109; PU3235; PU3236; PU3237; PU3240; PU3241; PU3242; PU3243; PU3244; PU3245; QA477P; QD477P; UC5985; UC5986; UC5987; UC9542; UC9543; UC9544; UC9545; UC9564; UC9565; UC9566; UC9567; VF0344

See attached glossary for abbreviations.

Section 2 - Composition / Information on Ingredients

Ingredient	CAS	Concentration %
Duloxetine Hydrochloride	136434-34-9	1.3 - 20
Excipients	NA	80 - 98

Exposure Guidelines:
Duloxetine hydrochloride - LEG 25 micrograms/m3 TWA for 12 hours. LEG 40 micrograms/m3 TWA for 8 hours. Excursion Limit 300 micrograms/m3 for no more than a total of 30 minutes.

Section 3 - Hazards Identification

Appearance: Capsules containing pellets
Physical State: Solid
Odor: Odorless

Emergency Overview

Emergency Overview Effective Date: 17-Aug-2004

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

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

Caution Statement: Intact Duloxetine Hydrochloride Capsules are not considered to be a health hazard. The contents of Duloxetine Hydrochloride Capsules may cause burns or permanent tissue damage to the eyes. Effects of exposure may include dizziness, nausea, drowsiness, fatigue, and liver effects.

Routes of Entry: Inhalation and skin contact.

Effects of Overexposure: Capsules are intended for human consumption under guidance of a physician. Intact capsules are not considered hazardous under normal handling procedures. Adverse events commonly observed during therapeutic administration include nausea, dry mouth, constipation, decreased appetite, fatigue, dizziness, drowsiness, headache, insomnia, and increased sweating.

Duloxetine, the active ingredient, is harmful if swallowed, may cause burns or permanent tissue damage to the eyes, and may be slightly irritating to the skin. In animal studies, the major signs of overdose toxicity would be related to the central nervous (tremors, clonic convulsions, ataxia) and gastrointestinal (emesis, decreased appetite) systems. Liver effects have been reported in long-term animal studies at high doses.

Medical Conditions Aggravated by Exposure: None known.

Carcinogenicity:
Duloxetine 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.

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:
Duloxetine - No specific antidote is known. 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 or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, hemoperfusion, and exchange perfusion are unlikely to be beneficial.

Section 5 - Fire Fighting Measures

Flash Point: No applicable information found
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 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 contents 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 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 contents 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

Boiling Point: Not applicable
Melting Point: No applicable information found
Specific Gravity: 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 fumes when heated to decomposition.

Hazardous Polymerization: Will not occur.

Section 11 - Toxicological Information

Acute Exposure

Data for the active ingredient, duloxetine hydrochloride, are reported.

Oral:
Duloxetine hydrochloride - Rat, median lethal dose 491 mg/kg for males and 279 mg/kg for females, tremors, convulsions.
Dog, 100 mg/kg, no deaths, reduced activity, slow pupillary response, intermittent tremors, rigidity.

Skin:
Duloxetine hydrochloride - Rabbit, 1000 mg/kg, no deaths or toxicity.

Inhalation: No applicable information found.

Skin Contact:
Duloxetine hydrochloride - Rabbit, slight irritant

Eye Contact:
Duloxetine hydrochloride - Rabbit, corrosive

Chronic Exposure

Data for the active ingredient, duloxetine hydrochloride, are reported.

Target Organ Effects:
Duloxetine hydrochloride - Dilation of the pupil and slow pupillary light response reported in dogs administered 3, 10, and 30 mg/kg orally for 1 year. Slight increase in liver enzymes reported in the mid- and high-dose animals. Liver effects (tissue changes, enzyme induction) reported in rats administered up to 0.08% in diet (47 mg/kg/day) for 6 months.

Reproduction:
Duloxetine - Reproductive performance was not affected in male rats (45 mg/kg/day). In female rats (45 mg/kg/day), reproductive toxicity was demonstrated by a decrease in maternal food consumption and body weight, estrous cycle disruption, depressions in live birth indices and progeny survival, and progeny growth retardation. The no-observed- effect level (NOEL) for maternal toxicity, reproductive toxicity, and developmental toxicity in the female fertility study was 10 mg/kg/day. There was no evidence of teratogenicity in animal studies. Duloxetine and/or its metabolites are excreted into the milk of lactating rats.

Sensitization:
Duloxetine hydrochloride - Guinea pig, negative in active systemic anaphylaxis and passive cutaneous anaphylaxis tests.

Mutagenicity:
Duloxetine - Demonstrated no mutagenic potential in a battery of in vitro and in vivo genotoxicity tests.

Carcinogenicity:
Duloxetine - Administered in the diet to rats and mice for 2 years. In rats, did not cause any increase in incidence of expected or unusual neoplasms or decrease in the latency for any tumor type. In female mice, there was an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation.

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:
Duloxetine
Rainbow trout 96-hour median lethal concentration: 0.4 mg/L
Daphnia magna 48-hour median effective concentration: 2.4 mg/L
Green algae (S. capricornutum) 72-hour median effective concentration: 0.14 mg/L
Green algae (P. subcapitata) 72-hour median effective concentration (biomass): 0.064 mg/L
Activated sludge respiration inhibition 3-hour median effective concentration (1.3 g solids/L): 26.9 mg/L
Activated sludge respiration inhibition 3-hour median effective concentration (1.6 g solids/L): 36.5 mg/L
Daphnia magna 21-day median effective concentration: 0.28 mg/L
Earthworm 14-day median effective concentration: >1000 mg/L

Environmental Fate:
Duloxetine hydrochloride
Log Kow: 0.78, 1.54, 3.35 (pH 4,7,9)
Bioconcentration factor (calculated): 324
pKa: 9.34
Biodegradation half-life in municipal sewage sludge, 24-hour study with 1.3 g solids/L: 8 hours
Municipal sewage sludge Kd: >4500
Sludge biodegredation: 91.3% to 62.1% at 8 hours
Sludge adsorption (Koc): 2893, 3150, 2970, 4296 (at 2500, 1250, 625, 313 mg solids/L)
Photolysis: 100% loss over 1 month (pH 4, 7, 9)
Hydrolysis (35 days at 30 C): 41.7%, 19.7%, 26.0% decline (pH 4, 7, 9)
Hydrolysis half-life (35 days at 30 C): 41.88, 100.62, 72.48 days (pH 4, 7, 9)
Hydrolysis (35 days at 40 C): 70.7%, 44.1%, 57.2% decline (pH 4, 7, 9)
Hydrolysis half-life (35 days at 40 C): 15.73, 31.69, 22.64 days (pH 4, 7, 9)

Environmental Summary:
Duloxetine hydrochloride - Material is highly toxic to green algae and fish, moderately toxic to aquatic invertebrates and slightly toxic to activated sludge microorganisms. Measurable concentrations of material in atmosphere are not expected since it is a non-volatile solid. The solubility in water is high. After 24 hours in activated municipal sludge, the duloxetine concentration declined extensively (biodegradation and adsorption). Material is not expected to bioconcentrate in aquatic organisms.

Lilly Aquatic Exposure Guideline (LAEG):
Duloxetine hydrochloride
LAEG for Drinking Water: 20 micrograms/L
LAEG for Chronic Exposure of Aquatic Organisms: 1.7 micrograms/L
LAEG for Acute Exposure of Aquatic Organisms: 15 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
Duloxetine 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
Xi (Irritant)

Risk Phrases
R 41 - Risk of serious damage to eyes.

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 14.

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)