



Olanzapine Fluoxetine Combination Capsules

Eli Lilly and Company
Material Safety Data Sheet

Effective Date: 12-Jul-2007

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: Olanzapine Fluoxetine Combination Capsules

Chemical Name: 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-
Chemical Name 2: Benzenepropanamine, N-methyl-gamma-[4-(trifluoromethyl)phenoxy]-,
hydrochloride

Synonym(s): 110140/170053 Formulation; LY900000; OFC Capsules; Olanzapine Fluoxetine Capsule Mix

Trademarks(s): Symbyax

Lilly Item Code(s): B02079; B02081; ND1086; ND1087; ND1088; ND1089; PU3230; PU3231; PU3232; PU3233; PU3234; UC9560; UC9561; UC9562; UC9563; ND1085

See attached glossary for abbreviations.

Section 2 - Composition / Information on Ingredients

Ingredient	CAS	Concentration %
Olanzapine	132539-06-1	1 - 6
Fluoxetine Hydrochloride	56296-78-7	12 - 19
Excipients	NA	75 - 87

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

Exposure Guidelines:

Olanzapine - LEG 38 micrograms/m³ TWA for 12 hours, LEG 50 micrograms/m³ TWA for 8 hours, 114 micrograms/m³ TWA for 15 minutes STEG.

Fluoxetine hydrochloride - LEG 30 micrograms/m³ TWA for 12 hours. LEG 50 micrograms/m³ TWA for 8 hours.

Section 3 - Hazards Identification

Appearance: Capsules containing slightly yellow to yellow powder

Physical State: Solid

Odor: Odorless

Emergency Overview



Special
A = Allergen

Emergency Overview Effective Date: 30-Jun-2005

Lilly Laboratory Labeling Codes:

Health 3

Fire 1

Reactivity 0

Special A

Primary Physical and Health Hazards: Not hazardous if intact. Corrosive (eyes). Irritant (skin). Allergen. Nervous System, Liver and Hormonal Effects.

Caution Statement: Intact Olanzapine Fluoxetine Combination Capsules are not considered to be a health hazard. The contents of Olanzapine Fluoxetine Combination Capsules may cause burns or permanent tissue damage to the eyes, may be irritating to the skin, and causes allergic reactions. Effects of exposure may include tremors, drowsiness, liver tissue changes, and increased serum prolactin.

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. However, exposure to the contents of the capsules may produce the following signs and symptoms. Adverse effects associated with therapeutic use of olanzapine/ fluoxetine combination include weakness, swelling of hands and feet, increased appetite, sore throat, sleepiness, trouble concentrating, tremor, and weight gain. Adverse events associated with concurrent overdose of both olanzapine and fluoxetine include sleepiness, impaired consciousness (coma, lethargy), impaired neurologic function (incoordination, confusion, convulsions, slurred speech), and changes in heart rhythm.

Olanzapine - Confirmed cases of allergic contact dermatitis have been reported. Symptoms have included rash with redness, swelling, and scaling of the affected skin areas. Positive reactions have been verified by patch testing with olanzapine (0.1%). Based on the clinical dose, olanzapine is highly potent. May be irritating to the eyes based on animal studies.

Adverse effects associated with therapeutic use of olanzapine include sleepiness, weight gain, mild temporary increase in serum prolactin, dizziness, weakness, restlessness, increased appetite, swelling of hands and feet, decreased blood pressure when standing, dry mouth and constipation. Mild temporary increases in glucose and liver enzyme levels and blood effects have been seen occasionally. Symptoms reported in olanzapine overdose include changes in heart rate and rhythm, slurred speech, reduced level

of consciousness ranging from sedation to coma, convulsion, and muscle rigidity.

Fluoxetine hydrochloride - May cause burns or permanent tissue damage to the eyes. Contact dermatitis (rash) has been reported with occupational exposure. The most common adverse events reported with therapeutic administration include nausea, decreased appetite, anxiety, tremors, drowsiness, and sweating. The most common signs and symptoms associated with non-fatal overdose were seizures, drowsiness, nausea, increased heart rate, and vomiting.

Medical Conditions Aggravated by Exposure:

Olanzapine - Sensitivity to olanzapine.

Fluoxetine hydrochloride - Acute overdose after sustained therapeutic exposure has resulted in seizures. The potential for aggravation of a seizure disorder has not been ruled out.

Carcinogenicity:

Olanzapine - Not listed by IARC, NTP, ACGIH, or OSHA. Olanzapine produced mammary tumors in female rats and female mice. This is consistent with effects of compounds that elevate prolactin levels in rodents. There is no clear understanding of the role of elevated prolactin in human mammary carcinogenesis.

Fluoxetine hydrochloride - Not listed by IARC, NTP, ACGIH, or OSHA. The dietary administration to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day produced no evidence of carcinogenicity.

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:

Olanzapine fluoxetine combination - In managing overdose, consider the possibility of multiple drug involvement. Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension.

Olanzapine - There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%. Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of

hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension.

Fluoxetine hydrochloride - Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. No specific antidote is known. Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. In limited human overdose experience, seizures have been reported. Appropriate seizure precautions are advised for any patient regularly taking fluoxetine who has been exposed to an acute overdose. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

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 capsule contents or tablet powder may occur.

Spills: Wear protective equipment, including eye protection, to avoid exposure (see Section 8 for specific handling precautions). 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.

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.

Section 9 - Physical and Chemical Properties

Appearance: Capsules containing slightly yellow to yellow powder

Odor: Odorless

Boiling Point: No applicable information found

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

No data available for mixture or formulation. Data for ingredient(s) or related material(s) are presented.

Oral:

Olanzapine - Rat, median lethal dose 177 mg/kg, reduced activity, lethargy, coma, tremors, convulsions, drooping eyelids, salivation.

Monkey, 100 mg/kg, no deaths, sedation, prostration, reduced activity, anorexia.

Fluoxetine hydrochloride - Rat, median lethal dose 451 mg/kg, reduced activity, tremors, convulsions, increased irritability, labored breathing, increased urine output.

Mouse, median lethal dose 248 mg/kg, increased irritability, tremors.
Monkey, 50 mg/kg, no deaths, vomiting.

Skin:

Olanzapine - Rabbit, 200 mg/kg, no deaths or toxicity.
Fluoxetine hydrochloride - Rabbit, 500 mg/kg, no deaths or toxicity.

Inhalation:

Olanzapine - Rat, 880 mg/m³ for 4 hours, no deaths, reduced activity, lethargy, labored breathing, prostration.

Skin Contact:

Olanzapine - Rabbit, nonirritant
Fluoxetine hydrochloride - Rabbit, nonirritant

Eye Contact:

Olanzapine - Rabbit, irritant
Fluoxetine hydrochloride - Rabbit, corrosive

Chronic Exposure

Target Organ Effects:

Olanzapine fluoxetine combination - No new or unexpected toxicity resulting from co-administration of olanzapine and fluoxetine were reported in rats or dogs dosed orally for 3 months. In animals, exposure to olanzapine caused nervous system effects (sedation), increased heart rate, and decreased circulating blood cell counts. Liver effects such as reversible increases in serum enzymes and tissue changes were observed following exposure to fluoxetine.

Other Effects:

Fluoxetine hydrochloride - In a juvenile toxicology study in rats, where the exposure period corresponds to human childhood and adolescence, administration of 30 mg/kg resulted in skeletal muscle necrosis. Other findings in rats included necrosis of the testis and immaturity and inactivity of the female reproductive tract. Following an approximate 11-week recovery period, sperm assessments indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation indicated that testicular degeneration was irreversible. Delays in sexual maturation occurred with administration of 10 or 30 mg/kg. The significance of these findings in humans is unknown. Femur lengths at 30 mg/kg increased to a lesser extent compared with control rats.

Reproduction:

Olanzapine fluoxetine combination - No unexpected toxicity resulting from co-administration of olanzapine and fluoxetine was observed in embryo-fetal developmental studies with rabbits and rats. A Pre- and Postnatal development study in rats reported an elevation of offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low dose combination and were attributed to lack of postpartum maternal care. In animals, exposure to olanzapine resulted in decreased mating activity (due to sedation), decreased fertility, abnormal reproductive cycles, reproductive tissue changes (linked to elevations of prolactin levels), and embryo and fetal toxicity at maternally toxic doses. Slight reductions in neonatal survival have been reported along with maternal toxicity in animals exposed to fluoxetine.

Fluoxetine hydrochloride - Two fertility studies conducted in adult rats indicated no adverse effects on fertility. In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 7.5 mg/kg/day during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats. The no effect dose for rat pup mortality was 5 mg/kg/day.

Data on a large number of exposed pregnancies in humans indicate no appearance of adverse effects on pregnancy or on the overall health of the fetus/newborn child. However, a few epidemiological studies have noted that some women treated with fluoxetine and other SSRIs late in the third trimester have had newborns with increased complications that could be consistent with drug discontinuation syndrome (e.g. transient jitteriness, difficulty feeding, tachypnea and irritability) and required prolonged hospitalizations.

Sensitization:

Olanzapine - Guinea pig, subcutaneous, intravenous, dermal - negative systemic response.

Mutagenicity:

Olanzapine - Not mutagenic in bacterial or mammalian cells.

Fluoxetine hydrochloride - No genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

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:

Olanzapine

Rainbow trout 96-hour median lethal concentration: 1.74 mg/L

Daphnia magna 48-hour median effective concentration: 8.0 mg/L

Green algae (*S. capricornutum*) median effective concentration: >14.1 mg/L (average specific growth rate)

Microorganisms:

fungus (*Chaetomium globosum*): MIC = 400 mg/L

mold (*Aspergillus flavus*): MIC = 1000 mg/L

soil bacteria (*Comamonas acidovorans*): MIC > 1000 mg/L

N-fixing bacteria (*Azotobacter chroococcum*): MIC > 1000 mg/L

blue-green algae (*Nostoc* sp.): MIC = 255 mg/L

Fluoxetine hydrochloride

Rainbow trout 96-hour median lethal concentration: 1.57 mg/L

Daphnia magna 48-hour median effective concentration: 0.94 mg/L

Green algae (*S. capricornutum*) median effective concentration: 30.5 micrograms/L (average specific growth rate)

Microorganisms:

fungus (*Chaetomium globosum*): MIC = 64 mg/L
mold (*Aspergillus flavus*): MIC = 64 mg/L
soil bacteria (*Pseudomonas acidovorans*): MIC = 1000 mg/L
N-fixing bacteria (*Azotobacter chroococcum*): MIC = 64 mg/L
blue-green algae (*Nostoc sp.*): MIC = 250 mg/L

Environmental Fate:

Olanzapine

Dissociation constants (pKa): 7.37, 4.69

Log Kow: 0.3, 1.7, 2.1 (pH 5, 7, 9)

Log Koc: 0.04, 1.48, 1.94 (pH 5, 7, 9)

Bioconcentration Factor: 11 (pH 7)

Solubility (g/L): 87.4, 0.1926, 0.0165 (pH 5, 7, 9)

Light absorption (nm): none between 290 and 800

Hydrolysis half-life (days): 65.30, 75.97, 77.93 (pH 5, 7, 9)

Hydrolysis rate (1/day): 0.0106, 0.00912, 0.00889 (pH 5, 7, 9)

Aerobic biodegradation half-life (days): 7.4

Fluoxetine hydrochloride

Dissociation constant (pKa): 8.7

Log Kow: 1.0, 1.8, 2.6 (pH 5, 7, 9)

Solubility (g/L): 15.0, 6.84, 5.47 (pH 5, 7, 9)

Light absorption (nm): none between 290 and 800

Hydrolysis rate (1/day): 0, 0, 0 (pH 5, 7, 9)

Aerobic biodegradation half-life (days): not measurable

Environmental Summary:

Olanzapine - Moderately toxic to fish and invertebrates. No more than slightly toxic to green algae. Practically non-toxic to microorganisms. No volatility expected. Low potential to bioconcentrate in aquatic organisms. Persistence in the environment not expected due to biodegradation and hydrolysis.

Fluoxetine hydrochloride - Moderately toxic to fish and highly toxic to invertebrates and green algae. No volatility expected. Low potential to bioaccumulate in aquatic organisms. Can be considered persistent due to low rates of biodegradation and hydrolysis.

Lilly Aquatic Exposure Guideline (LAEG):

Olanzapine

LAEG for Drinking Water: 2.5 micrograms/L

LAEG for Chronic Exposure of Aquatic Organisms: 7.4 micrograms/L

LAEG for Acute Exposure of Aquatic Organisms: 67 micrograms/L

Fluoxetine hydrochloride

LAEG for Drinking Water: 11.2 micrograms/L

LAEG for Chronic Exposure of Aquatic Organisms: 1.2 micrograms/L

LAEG for Acute Exposure of Aquatic Organisms: 30.5 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: Not Regulated

IMO: Not Regulated

Additional Information: This material is considered to be an Environmentally Hazardous Substance according to the criteria set forth in the European Agreement Concerning the International Carriage of Dangerous Goods by Road (ADR) and is regulated as a Hazard Class 9 (UN3077 or UN3082) when shipping under ADR.

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

Olanzapine

TSCA - No

CERCLA - Not on this list

SARA 302 - Not on this list

SARA 313 - Not on this list

OSHA Substance Specific - No

Fluoxetine 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)

N (Dangerous for the Environment)

Risk Phrases

R 38 - Irritating to skin.

R 41 - Risk of serious damage to eyes.

R 43 - May cause sensitization by skin contact.

R 51/53 - Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

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).

S 61 - Avoid release to the environment. Refer to special instructions/Safety data sheets.

Section 16 - Other Information

MSDS Sections Revised: Section 1.

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

317-651-9533

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)