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Tadalafil Tablets

Effective Date: 07-Mar-2003

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: Tadalafil Tablets

Chemical Name: Pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-

Chemical Name 2: (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione

Synonym(s): 450190 (IC351) tablets; 450190 formulation; 450190, IC351 tablets; IC-351 tablets; IC351 formulation; IC351 tablets; ICOS-351 tablets; Tadalafil Granules 7%

Tradename(s): Cialis

Lilly Item Code(s): B02480; ND1053; ND1054; ND1105; ND1106; QA503V; TA4462; TA4463; TA4464; TA4465; VF0371; VF0372; VF0373

See attached glossary for abbreviations.

Section 2 - Composition / Information on Ingredients

Ingredient	CAS	Concentration %
Tadalafil	171596-29-5	1 - 7
Excipients	NA	93 - 99

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

Exposure Guidelines:

Tadalafil - LEG 13 micrograms/m³ TWA for 12 hours. LEG 20 micrograms/m³ TWA for 8 hours.

Section 3 - Hazards Identification

Appearance: White powder finished as off-white to yellow film-coated tablets

Physical State: Solid

Odor: Odorless

Emergency Overview



Emergency Overview Effective Date: 18-May-2002

Lilly Laboratory Labeling Codes:

Health 0

Fire 1

Reactivity 0

Primary Physical and Health Hazards: Not hazardous if intact.

Caution Statement: Intact Tadalafil Tablets are not considered to be a health hazard.

Routes of Entry: Inhalation and skin contact.

Effects of Overexposure: Tablets are intended for human consumption under guidance of a physician. Intact coated tablets are not considered hazardous under normal handling procedures. The active ingredient, Tadalafil, is considered highly potent based on clinical trial data. Based on animal studies with Tadalafil, chronic overexposure by ingestion may cause testicular tissue changes and decreased sperm production. However, two six-month human clinical studies reported no changes in sperm parameters. The most common adverse effects related to drug treatment were headache, lower back pain, and vasodilation (flushing), which can result in transient decreases in blood pressure.

Medical Conditions Aggravated by Exposure:

Tadalafil - Individuals on nitrate or alpha blocker therapy.

Carcinogenicity:

Tadalafil - Not listed by IARC, NTP, ACGIH, or OSHA. Not carcinogenic to rats or mice when administered for 24 months.

Section 4 - First Aid Measures

Eyes: Flush eyes with plenty of water. Get medical attention.

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.

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: 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.

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 powder may occur.

Respiratory Protection: Use an approved respirator.

Eye Protection: Safety glasses.

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: 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: No applicable information found

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:

Tadalafil - Rat, 2000 mg/kg, no deaths or toxicity.

Skin:

Tadalafil - Rabbit, 1000 mg/kg, no deaths, soft stools.

Inhalation: No applicable information found.

Skin Contact:

Tadalafil - Rabbit, slight irritant

Eye Contact:

Tadalafil - Rabbit, slight irritant

Chronic Exposure

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

Target Organ Effects:

Tadalafil - Repeated oral doses of tadalafil for more than six months resulted in decreased testicular weight in dogs. The decreased testes weights (reported at doses of 25 mg/kg/day and above in the 12-month study) correlated with degeneration and atrophy of the seminiferous epithelium. Decreased sperm in the epididymes was also reported with aspermia in the most severely affected dogs. No effects on semen parameters reported in humans after six-months of daily dosing (10 or 20 mg/day). When administered orally for 5 or 28 days at 5 mg/kg/day, blood pressure was reduced in rats. No significant findings were reported in rats or mice administered up to 800 mg/kg by oral gavage for up to 3 months.

Reproduction:

Tadalafil - There was no impairment of fertility in male and female rats. In beagle dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day and above, there were alterations to the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. These findings were not observed in rats or mice. Furthermore, in men taking tadalafil 10 or 20 mg/daily for 6 months, there were no clinically relevant effects on sperm concentration, count, motility, or morphology. Additionally, there were no significant effects of serum levels of testosterone, luteinizing hormone, or follicle stimulating hormone. There was no evidence of teratogenicity, embryotoxicity or fetotoxicity in rats or mice that received up to 1000 mg/kg/day. In a rat pre- and postnatal development study, the observed no effect dose was 30 mg/kg/day.

Sensitization: No applicable information found.

Mutagenicity:

Tadalafil - Not mutagenic or genotoxic in in vitro bacterial and mammalian cell assays, and in vitro human lymphocytes, and in vivo rat micronucleus assays.

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:

Tadalafil

Rainbow trout 96-hour median lethal concentration: >2.1 mg/L

Daphnia magna 48-hour median effective concentration: >2 mg/L

Activated sludge 3-hour median effective respiration inhibition: >1000 mg/L

Green algae (*S. capricornutum*) 72-hour median effective concentration: >1.95 mg/L

Environmental Fate:

Tadalafil

Log Kow: 2.32 (pH 7.5)

Bioconcentration factor: 24

24-Hour municipal sewage sludge Kd (g total suspended solids/L): 180

24-Hour biodegradation in municipal sewage sludge (g total suspended solids/L): none

Environmental Summary:

Tadalafil - Material was not toxic to aquatic organisms at highest concentration tested and is expected to be practically non-toxic to aquatic organisms due to low solubility. Material is not expected to bioaccumulate in aquatic organisms. Material is not expected to be degraded by microorganisms in the soil and water. Material is practically insoluble in water and is not expected to leach significantly from soil into groundwater. Measurable concentrations in the atmosphere are not expected since it is a non-volatile solid.

Lilly Aquatic Exposure Guideline (LAEG):

Tadalafil

LAEG for Drinking Water: 2.5 micrograms/L

LAEG for Chronic Exposure of Aquatic Organisms: 200 micrograms/L

LAEG for Acute Exposure of Aquatic Organisms: 1000 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

Tadalafil

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

Not assigned an overall EC classification.

Section 16 - Other Information

MSDS Sections Revised: Section 3.

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)