SAFETY DATA SHEET

Prepared to U.S. OSHA, CMA, ANSI, Canadian WHMIS Standards, European Union CLP EC 1272/2008 and the Global Harmonization Standard

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY UNDERTAKING

PRODUCT IDENTIFIER/TRADE/MATERIAL NAME: CLONIDINE TRANSDERMAL SYSTEM

CHEMICAL NAME: For Active Ingredient: 2, 6-dichloro-N-2-imidazolidinylidenebenzenamin
CHEMICAL FAMILY: For Active Ingredient: Rhodopsin
HOW SUPPLIED: Transdermal patch
OTHER DESIGNATIONS:
FORMULA: Mixture; For Clonidine: $C_9H_9Cl_2N_3$
RELEVANT USE of the SUBSTANCE: Human Pharmaceutical
USES ADVISED AGAINST: Non-Pharmaceutical Use

SUPPLIER OF THE SAFETY DATA SHEET

RESPONSIBLE PARTY U.S.:	**Actavis, Inc.**
U.S. ADDRESS:	400 Interpace Parkway, Morris Corporate Center III Parsippany, NJ 07054, USA
U.S. BUSINESS PHONE/GENERAL SDS INFORMATION:	1-800-272-5525
RESPONSIBLE PARTY EUROPE:	
EUROPEAN ADDRESS:	
EUROPEAN BUSINESS PHONE:	
EMERGENCY PHONE (U.S./NORTH AMERICA):	CHEMTREC: 1-800-424-9300 (24 hours) U.S., Canada, Puerto Rico
EMERGENCY PHONE (OUTSIDE U.S.):	CHEMTREC: +1-703-527-3887 (24 hours) Outside North America
Email:	SDS@Actavis.com

NOTE: ALL United States Occupational Safety and Health Administration Standard (29 CFR 1910.1200), U.S. State equivalent Standards, Canadian WHMIS [Controlled Products Regulations], EU Directives through EC 1907: 2006, and European Union CLP EC 1272/2008, required information is included in appropriate sections based on the U.S. ANSI Z400.1-2010 format. This product has been classified in accordance with the hazard criteria of the countries listed above.

DATE OF PREPARATION: September 22, 2013 **DATE OF REVISION:** New

2. HAZARDS IDENTIFICATION

EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU 67/548/EEC LABELING AND CLASSIFICATION: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

EMERGENCY OVERVIEW:

Product Description: This product is a three-layered laminate patch with polyethylene backing membrane, an adhesive matrix drug reservoir and a peel-off, polyester overlapped release liner.

Health Hazards: The chief health hazard associated with exposure during normal use and handling is the potential for irritation of contaminated skin from prolonged contact. May be absorbed through the skin. In therapeutic use, lightheadedness, dry mouth, hypotension, dizziness and constipation. Limited evidence of harm to fetus during pregnancy, based on animal data. More information on adverse effects from therapeutic use is described in Section 11 (Toxicological Information).

Reactivity Hazards: This product is not reactive.

Flammability Hazards: This product may be combustible and may ignite if involved in a fire and the water evaporates. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including carbon and nitrogen oxides, formaldehyde, hydrogen cyanide, hydrogen fluoride and various hydrocarbons from patch materials).

Environmental Hazards: may cause long-term harm to aquatic organisms. Release to the aquatic and terrestrial environment may have an adverse effect.

Emergency Considerations: Emergency responders should wear appropriate protection for situation to which they respond.

3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	EINECS #	% w/w	LABEL ELEMENTS EU Classification (67/548/EEC) GHS & EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements/Symbol
ACTIVE INGREDIENTS				
Clonidine	4205-90-7	224-119-4	Proprietary	SELF-CLASSIFICATION: EU (67/548/EEC): Classification: Reproductive Toxicity Cat. 3, Toxic Risk Phrases: R63, R25 Symbol: T EU/GHS 1272/2008: Classification: Reproductive Toxicity Cat. 2, Acute Oral Toxicity Cat. 3 Hazard Statement Codes: H361d, H301 Hazard Symbols/Pictograms: GHS06, GHS08
EXCIPIENTS IN DRUG PRODUCT				
Proprietary Synthetic Polymer/Solvent Adhesive Mixture	Mixture	Mixture	Proprietary	EU 67/548 Classification: Not Applicable EU/GHS 1272/2008 Classification: Not Applicable
Sorbitan Monooleate	1338-43-8	215-665-4	Proprietary	EU 67/548 Classification: Not Applicable EU/GHS 1272/2008 Classification: Not Applicable
OTHER EXCIPIENTS FOR PATCH MATERIALS				
Aluminum Foil	7429-90-5	231-072-3	Proprietary	EU 67/548 Classification: Not Applicable EU/GHS 1272/2008 Classification: Not Applicable
Paper Liner	Mixture	Mixture	Proprietary	EU 67/548 Classification: Not Applicable EU/GHS 1272/2008 Classification: Not Applicable
Low Density Polyethylene Backing Film	Mixture	Mixture	Proprietary	EU 67/548 Classification: Not Applicable EU/GHS 1272/2008 Classification: Not Applicable
Polyester Overlapped Release Liner	Mixture	Mixture	Proprietary	EU 67/548 Classification: Not Applicable EU/GHS 1272/2008 Classification: Not Applicable

See Section 16 for full classification information for components.

4. FIRST-AID MEASURES

PROTECTION OF FIRST AID RESPONDERS: First-aid responders should not attempt to treat victims of exposure to this material without adequate personal protective equipment. Rescuers should be taken for medical attention, if necessary.

DESCRIPTION OF FIRST AID MEASURES: Victim(s) must be taken for medical attention. Remove victim(s) to fresh air, as quickly as possible. Only trained personnel should administer supplemental oxygen and/or cardio-pulmonary resuscitation, when necessary. Take copy of SDS to physician or other health professional with victim(s).

Inhalation: If mists or sprays from this product are inhaled, remove victim to fresh air. If necessary, use artificial respiration to support vital functions. Seek medical attention if adverse effect occurs after removal to fresh air.

Skin Exposure: Basic hygiene should prevent any problems. If the product contaminates the skin, and adverse effect occurs, begin decontamination with running water. Minimum flushing is for 20 minutes. Do not interrupt flushing. Remove exposed or contaminated clothing, taking care not to contaminate eyes. Seek medical attention if adverse effect occurs after flushing.

Eye Exposure: If this product enters the eyes, open victim's eyes while under gently running water. Use sufficient force to open eyelids. Have victim "roll" eyes. Minimum flushing is for 20 minutes. Do not interrupt flushing. Seek immediate medical attention after flushing if adverse effect occurs.

Ingestion Exposure: If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, do not induce vomiting. Rinse mouth with water immediately. Victim should drink large quantities of water. If milk is available, victim should drink it after drinking water. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow.

IMPORTANT SYMPTOMS AND EFFECTS: See Sections 2 (Hazard Identification) and 11 (Toxicological Information).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: When formulated in therapeutic use, pre-existing bradycardia, sick sinus syndrome, cardiac conduction and hypotensive conditions may be aggravated. Workplace exposure may also aggravate these conditions. Persons who may have hypersensitivity reactions to this material or other disorders described in Section 11 (Toxicological Information) may experience aggravation upon exposure.

INDICATION OF IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT IF NEEDED: Treat symptoms and eliminate exposure. Persons developing hypersensitivity reactions should receive medical attention.

5. FIRE-FIGHTING MEASURES

FLASH POINT: Not established.

AUTOIGNITION TEMPERATURE: Not established for product.

FLAMMABLE LIMITS & METHOD OF DETERMINATION (in air by volume, %): Not established.

FIRE EXTINGUISHING MEDIA: In the event of a fire, use suppression methods for surrounding materials, including water spray (for cooling), dry extinguishing media, carbon dioxide, foam.

UNSUITABLE FIRE EXTINGUISHING MEDIA: None known.

5. FIRE-FIGHTING MEASURES

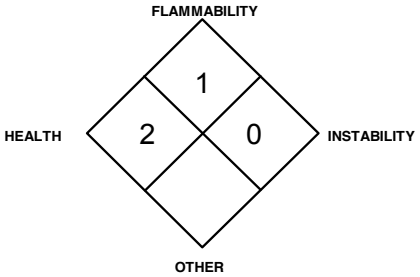
SPECIFIC HAZARDS ARISING FROM THE CHEMICAL: This product may be combustible and ignite if involved in a fire. When involved in a fire, the products of thermal decomposition may include irritating fumes and toxic gases (e.g., carbon and nitrogen oxides, formaldehyde, hydrogen cyanide, hydrogen fluoride and various hydrocarbons from patch materials).

Explosion Sensitivity to Mechanical Impact: Not sensitive.

Explosion Sensitivity to Static Discharge: Not sensitive.

SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS: Incipient fire responders should wear eye protection. Structural firefighters must wear Self-Contained Breathing Apparatus (SCBA) and full protective equipment. If protective equipment is contaminated by this product, it should be thoroughly washed with running water prior to removal of SCBA respiratory protection. Firefighters whose protective equipment becomes contaminated should thoroughly shower with warm, soapy water and should receive medical evaluation if they experience any adverse effects. Firefighters whose protective equipment becomes contaminated should thoroughly shower with warm, soapy water and should receive medical evaluation if they experience any adverse effects.

NFPA RATING



Hazard Scale: **0** = Minimal **1** = Slight **2** = Moderate **3** = Serious **4** = Severe

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS: In the event of a spill, clear the area and protect people. The atmosphere must have levels of components lower than those listed in Section 8, (Exposure Controls and Personal Protective Equipment) if applicable, and have at least 19.5 percent oxygen before personnel can be allowed into the area without Self-Contained Breathing Apparatus (SCBA). Monitor area and confirm levels are bellow exposure limits given in Section 8 (Exposure Controls-Personal Protection), if applicable, before non-response personnel are allowed into the spill area.

PROTECTIVE EQUIPMENT:

All Spills: Wear double latex or nitrile disposable gloves and eye protection.

METHODS FOR CLEANUP AND CONTAINMENT:

All Spills: Sweep-up spilled patches and wipe area with damp sponge or polypad. Decontaminate the area of the spill thoroughly using detergent and water. Place all spill residue in an appropriate container and seal. Do not mix with wastes from other materials. If necessary, discard contaminated response equipment or rinse with soapy water before returning such equipment to service. Dispose of in accordance with applicable international, national, state, and local procedures (see Section 13, Disposal Considerations).

ENVIRONMENTAL PRECAUTIONS: Prevent material from entering sewer or confined spaces, waterways, soil or public waters. Do not flush to sewer. For spills on water, contain, minimize dispersion and collect.

7. HANDLING and USE

PRECAUTIONS FOR SAFE HANDLING: Employees must be trained to properly use this product. Use of this product should be performed in a designated area for working with drugs. As with all chemicals, avoid getting this product ON YOU or IN YOU. Do not eat, drink, smoke, or apply cosmetics while handling this product. Wash hands thoroughly after handling this product or equipment and containers that contain this product. Follow SPECIFIC USE INSTRUCTIONS supplied with this product. Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this compound, and during patient administration. Ensure product is properly labeled.

CONDITIONS FOR SAFE STORAGE: Store this product away from incompatible materials. Store this product in original container. Store product at controlled room temperature (15-30°C [59-86°F]).

PRODUCT PREPARATION INSTRUCTIONS FOR MEDICAL PERSONNEL: Handle this material following standard medical practices and following the recommendations presented on the Package Insert.

SPECIFIC END USE(S): This product human pharmaceutical. Follow all industry standards for use of this product.

CONDITIONS FOR SAFE STORAGE: Containers of this product must be properly labeled. Store at 20-25°C (68-77°F) and away from moisture, humidity and light. Material should be stored in secondary containers or in a diked area, as appropriate. Store away from incompatible materials (see Section 10, Stability and Reactivity). Store containers in a cool, dry location, away from direct sunlight, sources of intense heat or other sources of ignition or where freezing is possible. Material should be stored in secondary containers or in a diked area, as appropriate. Store containers away from incompatible chemicals (see Section 10, Stability and Reactivity). Post warning and “NO SMOKING” signs in storage and use areas, as appropriate. Have appropriate extinguishing equipment in the storage area (i.e., sprinkler system, portable fire extinguishers). Inspect all incoming containers before storage to ensure containers are properly labeled and not damaged. Empty containers may contain residual product; therefore, empty containers should be handled with care.

SPECIFIC END USE(S): This product is a human pharmaceutical. Follow all industry standards for use of this product.

PROTECTIVE PRACTICES DURING MAINTENANCE OF CONTAMINATED EQUIPMENT: When cleaning non-disposable equipment, wear latex or butyl rubber (double gloving is recommended), goggles, and lab coat. Wash equipment with soap and water. Wipe equipment down with damp sponge or polypad.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

EXPOSURE LIMITS/CONTROL PARAMETERS:

Ventilation and Engineering Controls: Use with adequate ventilation. Follow standard medical product handling procedures. During decontamination of work surfaces, workers should wear the same equipment recommended in Section 6 (Accidental Release Measures) of this SDS.

Occupational/Workplace Exposure Limits/Guidelines:

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELs		NIOSH	OTHER
		TWA ppm	STEL ppm	TWA ppm	STEL ppm	TWA ppm	STEL ppm	IDLH ppm	ppm
Clonidine	4205-90-7	NE	NE	NE	NE	NE	NE	NE	Actavis WEL: 0.2 µg/m^3
Aluminum Foil Exposure limits are for aluminum metal	7429-90-5	1 (resp. fract.)	NE	15 (total dust), 5 (resp. fract.)	NE	10 (total dust), 5 (resp. fract.)	NE	NE	DFG MAKs: 4 (inhalable fraction); 1.5 (respirable fraction) DFG MAK Pregnancy Risk Classification: D Carcinogen: TLV-A4
Low-Density Polyethylene Film		NE	NE	NE	NE	NE	NE	NE	NE
Paper Liner		NE	NE	NE	NE	NE	NE	NE	NE
Proprietary Acrylic Resin		NE	NE	NE	NE	NE	NE	NE	NE
Sorbitan Monooleate	1338-43-8	NE	NE	NE	NE	NE	NE	NE	NE

NE = Not Established

International Occupational Exposure Limits: Currently there are no additional international exposure limits in force for components. Limits are added and change and should be checked.

PERSONAL PROTECTIVE EQUIPMENT: Use of personal protective equipment must be in compliance with U.S. OSHA 29 CFR Subpart I (beginning at 1910.132), Canadian CSA Standards Z94.4-02 and Z94.3-02, EU EN 529:2005, CEN/TR 15419:2006, and CR 13464:1999. Please reference applicable regulations and standards for relevant details.

Respiratory Protection: A respirator is not required for routine conditions of use with adequate engineering controls. A full-face Air-Purifying Respirator with high-efficiency particulate filter or a Supplied-Air Respirator must be worn during operations where engineering controls are not sufficient, large spill cleanup, or when processing generates airborne aerosols. If respiratory protection is needed, use only respiratory protection authorized under appropriate regional regulations.

Eye Protection: During operations in which mists or sprays may be generated, splash goggles or safety glasses should be considered.

Hand Protection: During manufacture or other similar industrial operations, wear the appropriate hand protection for the process. Use double gloves for spill response, as stated in Section 6 (Accidental Release Measures) of this SDS.

Body Protection: Use appropriate protective clothing for the task (e.g., lab coat, etc.)

9. PHYSICAL and CHEMICAL PROPERTIES

The following information is available for the product.

FORM: Gel.
COLOR: Clear, colorless.
MOLECULAR WEIGHT: Mixture.
MOLECULAR FORMULA: Mixture.
ODOR: Faint odor.
ODOR THRESHOLD: Not applicable.
BOILING POINT: Not established.
FREEZING/MELTING POINT Not established.
EVAPORATION RATE (nBuAc = 1): Not established.
SOLUBILITY IN WATER: Partially soluble.
VAPOR PRESSURE (air = 1): Not available.
SPECIFIC GRAVITY (water = 1): Not available.
pH: Not established.
VAPOR DENSITY: Not available.
COEFFICIENT WATER/OIL DISTRIBUTION: Not established. **VISCOSITY:** Not available.
HOW TO DETECT THIS SUBSTANCE (identification/warning properties): The gelled appearance of this product may act as a distinguishing characteristic.

The following information is available for the active ingredient.

FORM: Crystalline solid.
COLOR: White to off-white.
MOLECULAR WEIGHT: 230.10
MOLECULAR FORMULA: $C_9H_9Cl_2N_3$
ODOR: Odorless.
ODOR THRESHOLD: Not applicable.
BOILING POINT @ 760 mmHg: 319.3°C (595.94°F)
MELTING POINT: 130°C (266°F)
VAPOR PRESSURE (air = 1) @ 25°C: 0.000342 mmHg
SPECIFIC GRAVITY (water = 1): 1.5 g/cm^3
EVAPORATION RATE (nBuAc = 1): Not applicable.
SOLUBILITY IN WATER: Soluble to 100 mM.
OTHER SOLUBILITIES: 75 in DMSO.
pH: Not applicable
COEFFICIENT WATER/OIL DISTRIBUTION: Log Kow= 1.57; Log p = 1.41 (predicted)
FLASH POINT: 146.9°C (296°F)

10. STABILITY and REACTIVITY

CHEMICAL STABILITY: This product is stable.

DECOMPOSITION PRODUCTS: *Combustion:* If exposed to extremely high temperatures, the products of thermal decomposition may include irritating fumes and toxic gases (e.g., carbon and nitrogen oxides, formaldehyde, hydrogen cyanide, hydrogen fluoride and various hydrocarbons from patch materials). *Hydrolysis:* None known.

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE: This product is generally compatible with other common materials in a medical facility.

POSSIBILITY OF HAZARDOUS REACTIONS OR POLYMERIZATION: Will not occur.

CONDITIONS TO AVOID: Avoid heat, light, and contact with incompatible chemicals.

11. TOXICOLOGICAL INFORMATION

SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE: The health hazard information provided below is pertinent to medical employees using this product in an occupational setting. The following paragraphs describe the symptoms of exposure by route of exposure.

Inhalation: Not a likely route of exposure.

CONTACT WITH SKIN or Eyes: Brief skin contact is not expected to cause acute symptoms. Prolonged or repeated skin contact may cause dermatitis (dry, red skin), irritation and symptoms as described under 'Other Health Effects'. Contact of this product with the eyes may cause moderate to severe irritation, redness, and tearing.

Skin Absorption: This product is designed to be absorbed through the skin. Symptoms may include those described under described under 'Other Health Effects'.

Ingestion: Not a likely route of exposure. If accidentally ingested due to poor hygiene practices, no acute effects are anticipated. The active ingredient is toxic by ingestion. Chronic exposure by this route may cause symptoms as described under 'Other Health Effects'.

Injection: Not a likely route of exposure.

OTHER POTENTIAL HEALTH EFFECTS-Therapeutic Doses: In therapeutic use, lightheadedness, dry mouth, hypotension, dizziness and constipation. Limited evidence of harm to fetus during pregnancy, based on animal data. These effects may be possible as a result of workplace exposure. The actual risk in the workplace is not known. Additional adverse effects from therapeutic doses have included those described below. These effects may not necessarily be relevant to occupational exposure, but are presented to provide the most detailed information available for potential exposure to this product. Other effects reported from oral administration of Clonidine are not given in this SDS, refer to the API SDS for Clonidine for more information.

HAZARDOUS MATERIAL IDENTIFICATION SYSTEM

HEALTH HAZARD	(BLUE)	2*
FLAMMABILITY HAZARD	(RED)	1
PHYSICAL HAZARD	(YELLOW)	0

PROTECTIVE EQUIPMENT

EYES	RESPIRATORY	HANDS	BODY
	SEE SECTION 8		SEE SECTION 8

For Routine Industrial Use and Handling Applications

Hazard Scale: **0** = Minimal **1** = Slight **2** = Moderate **3** = Serious **4** = Severe * = Chronic hazard

- **Body as a Whole:** Fatigue Fever, malaise, weakness, pallor, and withdrawal syndrome.
- **Cardiovascular:** Congestive heart failure, cerebrovascular accident, electrocardiographic abnormalities (i.e., bradycardia, sick sinus syndrome disturbances and arrhythmias), chest pain; orthostatic symptoms, fainting; increases in blood pressure, sinus bradycardia and atrioventricular (AV) block with and without the use of concomitant digitalis, Raynaud's phenomenon, abnormal rapid or slow heart beat, and palpitations.
- **Central and Peripheral Nervous System/Psychiatric:** Delirium, mental depression, hallucinations (including visual and auditory), localized numbness, vivid dreams or nightmares, restlessness, anxiety, agitation, irritability, other behavioral changes, and drowsiness.
- **Dermatological:** Swelling under the skin, localized or generalized rash, hives, itching, contact dermatitis, hair loss; and localized hypo or hyper pigmentation.
- **Eyes:** Blurred vision, burning of the eyes and dryness of the eyes.
- **Gastrointestinal System:** Anorexia and vomiting.
- **Genitourinary/Reproductive System:** Difficult urination, potential fetal harm, loss of libido; and decreased sexual activity, breast enlargement.
- **Metabolic:** Weight gain.
- **Musculoskeletal System:** Leg cramps and muscle or joint pain.

HEALTH EFFECTS OR RISKS FROM EXPOSURE: An Explanation in Lay Terms. Exposure to this product may cause the following health effects:

Acute: The primary health effects that may be experienced by medical personnel exposed to this product is mild irritation of contaminated skin. In the event of exposures to therapeutic doses of this product, effects described in "Other Potential Health Effects" may result.

Chronic: Repeated skin contact may cause dermatitis (dry, red skin) or other effects described under 'Other Potential Health Effects'.

TARGET ORGANS: Acute: Workplace Exposure: Skin. Therapeutic Doses: Skin. Chronic: Workplace Exposure: Skin. Therapeutic Doses: Skin, harm to fetus and other organs described under 'Other Health Effects'.

IRRITANCY OF PRODUCT: This product may irritate contaminated tissue, especially if contact is prolonged.

SENSITIZATION OF PRODUCT: In therapeutic use, hives, rash, and swelling of the skin when ingested have been reported, but Clonidine is not known to cause these effects by skin contact.

TOXICITY DATA: This SDS presents only toxicity data currently available for the active component. Additional data are available for the active ingredient and data are available for the excipient components, but are not presented in this SDS. Contact Watson Pharmaceuticals for more information.

CLONIDINE:

TDLo (Oral-Human) 4.3 µg/kg: Behavioral: analgesia; Cardiac: change in rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Oral-Human) 1.97 mg/kg: Behavioral: somnolence (general depressed activity), analgesia; Cardiac: change in rate

TDLo (Oral-Human) 1.97 mg/kg: Vascular: BP lowering not characterized in autonomic section

TDLo (Oral-Human) 5 µg/kg: Blood: changes in serum composition (e.g. TP, bilirubin, cholesterol); Endocrine: changes in growth hormone

CLONIDINE (continued):

TDLo (Oral-Human) 2.14 µg/kg: Behavioral: somnolence (general depressed activity), changes in psychophysiological tests

TDLo (Oral-Human) 20 µg/kg/4 weeks-intermittent: Gastrointestinal: changes in structure or function of salivary glands

TDLo (Oral-Woman) 3 µg/kg: Behavioral: changes in psychophysiological tests

TDLo (Oral-Woman) 225 µg/kg: Behavioral: sleep; Cardiac: pulse rate; Vascular: BP elevation not characterized in autonomic section

CLONIDINE (continued):

TDLo (Oral-Woman) 400 µg/kg: Behavioral: muscle contraction or spasticity; Cardiac: EKG changes not diagnostic of specified effects; Nutritional and Gross Metabolic: body temperature decrease

TDLo (Oral-Woman) 30 µg/kg: Behavioral: general anesthetic; Cardiac: pulse rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Oral-Man) 2.86 µg/kg: Vascular: BP lowering not characterized in autonomic section; Gastrointestinal: changes in structure or function of salivary glands; Behavioral: changes in psychophysiological tests

TOXICITY DATA (continued):

CLONIDINE (continued):

TDLo (Oral-Man) 2.14 µg/kg: Behavioral: changes in psychophysiological tests

TDLo (Oral-Man) 0.015 mg/kg: Behavioral: coma; Vascular: BP lowering not characterized in autonomic section; Lungs, Thorax, or Respiration: respiratory depression

TDLo (Oral-Man) 583 µg/kg/15 weeks-intermittent: Kidney/Ureter/Bladder: proteinuria; Endocrine: hyperglycemia

TDLo (Oral-Man) 2857 ng/kg: Vascular: BP lowering not characterized in autonomic section

TDLo (Oral-Man) 43 µg/kg/10 hours-intermittent: Behavioral: somnolence (general depressed activity); Behavioral: antipsychotic; Cardiac: pulse rate

TDLo (Oral-Man) 114.3 µg/kg: Behavioral: somnolence (general depressed activity); Cardiac: change in rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Oral-Man) 5 µg/kg/9 weeks-intermittent: Behavioral: altered sleep time (including change in righting reflex)

TDLo (Oral-Child) 0.015 mg/kg: Behavioral: coma; Vascular: BP lowering not characterized in autonomic section; Lungs, Thorax, or Respiration: respiratory depression

TDLo (Oral-Child) 60 µg/kg: Peripheral Nerve and Sensation: sensory change involving peripheral nerve; Vascular: BP lowering not characterized in autonomic section; Lungs, Thorax, or Respiration: respiratory depression

TDLo (Eye-Human) 0.0021 mg/kg/1 hour: Sense Organs and Special Senses (Eye): effect, not otherwise specified; Vascular: measurement of regional blood flow

TDLo (Intravenous-Human) 1 µg/kg: Cardiac: change in rate; Biochemical: Neurotransmitters or modulators (putative): catecholamine levels in sympathetic nerves

TDLo (Intravenous-Human) 2.43 µg/kg/1 hour: Autonomic Nervous System: central sympatholytic; Vascular: BP lowering not characterized in autonomic section

TDLo (Intraspinal-Human) 2.1 mg/kg: Behavioral: analgesia; Cardiac: change in rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Unreported-Woman) 376 µg/kg/4 days-intermittent: Cardiac: cardiomyopathy including infarction, EKG changes not diagnostic of specified effects, pulse rate

TDLo (Unreported-Child) 5 µg/kg: Cardiac: cardiomyopathy including infarction, EKG changes not diagnostic of specified effects, pulse rate

Standard Draize Test (Skin-Rabbit) 500 mg: Mild

LD_{50} (Oral-Rat) 67,300 µg/kg

LD_{50} (Oral-Mouse) 108 mg/kg: Behavioral: tremor, ataxia; Skin and Appendages: hair

LD_{50} (Oral-Mouse) 135 mg/kg

LD_{50} (Skin-Rabbit) > 70 mg/kg: Sense Organs and Special Senses (Olfaction): effect, not otherwise specified; Sense Organs and Special Senses (Eye): chromodacryorrhea

LD_{50} (Intraperitoneal-Rat) 88,400 µg/kg: Sense Organs and Special Senses (Eye): chromodacryorrhea; Behavioral: tremor, ataxia

LD_{50} (Subcutaneous-Rat) 108 mg/kg: Behavioral: somnolence (general depressed activity), ataxia; Skin and Appendages: hair

LD_{50} (Subcutaneous-Mouse) 364 mg/kg: Behavioral: tremor, ataxia; Skin and Appendages: hair

LD_{50} (Intravenous-Mouse) 180 mg/kg

LD_{50} (Intraperitoneal-Mammal-Species Unspecified) 102 mg/kg

LD (Skin-Dog) > 20 mg/kg: Sense Organs and Special Senses (Eye): ptosis; Behavioral: somnolence (general depressed activity); Blood: changes in leukocyte (WBC) count

CLONIDINE (continued):

LDLo (Subcutaneous-Dog) 15 mg/kg: Behavioral: convulsions or effect on seizure threshold; Lungs, Thorax, or Respiration: dyspnea, cyanosis

TDLo (Oral-Rat) 10 µg/kg: Cardiac: change in rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Oral-Rat) 2100 µg/kg/7 days-intermittent: Sense Organs and Special Senses (Eye): lacrymation, effect, not otherwise specified

TDLo (Oral-Rat) 0.2 mg/kg/2 days-intermittent: Vascular: BP lowering not characterized in autonomic section; Blood: changes in serum composition (e.g. TP, bilirubin, cholesterol)

TDLo (Oral-Rat) 0.2 mg/kg/2 days-intermittent: Vascular: BP lowering not characterized in autonomic section; Kidney/Ureter/Bladder: urine volume decreased; Nutritional and Gross Metabolic: changes in sodium

TDLo (Oral-Rat) 2100 mg/kg: female 1-21 day(s) after conception: Reproductive: Effects on Newborn: other postnatal measures or effects

TDLo (Oral-Mouse) 20 mg/kg: female 11 day(s) after conception: Reproductive: Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus)

TDLo (Oral-Mouse) 10 mg/kg: female 11 day(s) after conception: Reproductive: Specific Developmental Abnormalities: craniofacial (including nose and tongue)

TDLo (Oral-Monkey) 0.28 mg/kg/7 days-continuous: Behavioral: changes in psychophysiological tests

TDLo (Subcutaneous-Rat) 0.03 mg/kg: Endocrine: effect on menstrual cycle

TDLo (Subcutaneous-Rat) 1 mg/kg: Reproductive: Fertility: mating performance (e.g. # sperm positive females per # females mated; # copulations per # estrus cycles)

TDLo (Subcutaneous-Rat) 6.9 µg/kg: Gastrointestinal: other changes

TDLo (Subcutaneous-Rat) 43.7 µg/kg: Gastrointestinal: decreased motility or constipation

TDLo (Subcutaneous-Rat) 9100 µg/kg/13 weeks-intermittent: Blood: pigmented or nucleated red blood cells, other changes, changes in erythrocyte (RBC) count

TDLo (Subcutaneous-Rat) 0.24 mg/kg/8 days-intermittent: Reproductive: Maternal Effects: uterus, cervix, vagina

TDLo (Subcutaneous-Rat) 2080 µg/kg: female 8-20 day(s) after conception: Reproductive: Effects on Newborn: growth statistics (e.g.%, reduced weight gain)

TDLo (Subcutaneous-Mouse) 0.25 mg/kg: Behavioral: stiffness

TDLo (Subcutaneous-Mouse) 15 µg/kg: Behavioral: analgesia

TDLo (Subcutaneous-Dog) 10 µg/kg: Gastrointestinal: decreased motility or constipation

TDLo (Intracerebral-Rat) 20 µg/kg: Behavioral: analgesia

TDLo (Intracerebral-Rat) 23,931 ng/kg: Gastrointestinal: decreased motility or constipation

TDLo (Skin-Rat) 2275 mg/kg/13 weeks-intermittent: Sense Organs and Special Senses (Eye): corneal damage; Kidney/Ureter/Bladder: other changes in urine composition; Related to Chronic Data: changes in prostate weight

TDLo (Skin-Dog) 900 mg/kg/90 days-intermittent: Endocrine: hyperglycemia; Blood: normocytic anemia, changes in platelet count

TDLo (Intravenous-Rat) 1 µg/kg: Reproductive: Paternal Effects: testes, epididymis, sperm duct; Vascular: BP lowering not characterized in autonomic section

TDLo (Intravenous-Rat) 948 µg/kg: Vascular: BP lowering not characterized in autonomic section

TDLo (Intravenous-Rat) 10 µg/kg: Reproductive: Paternal Effects: testes, epididymis, sperm duct

TDLo (Intravenous-Rat) 10 µg/kg: Brain and Coverings: other degenerative changes

TDLo (Intravenous-Rat) 5 µg/kg: Brain and Coverings: recordings from specific areas of CNS

CLONIDINE (continued):

TDLo (Intravenous-Rat) 10 µg/kg: Cardiac: change in rate; Vascular: BP elevation not characterized in autonomic section, BP lowering not characterized in autonomic section

TDLo (Intravenous-Rat) 172.6 µg/kg: Gastrointestinal: decreased motility or constipation. other changes

TDLo (Intravenous-Rat) 25 µg/kg/1 minute: Kidney/Ureter/Bladder: urine volume increased, other changes in urine composition

TDLo (Intravenous-Rat) 1 µg/kg: male 1 day(s) pre-mating: Reproductive: Paternal Effects: testes, epididymis, sperm duct

TDLo (Intravenous-Rabbit) 20 µg/kg: Cardiac: change in rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Intravenous-Guinea Pig) 3 mg/kg: Cardiac: EKG changes not diagnostic of specified effects

TDLo (Intraspinal-Rat) 2.73 µg/kg: Behavioral: analgesia

TDLo (Intraspinal-Mouse) 48.8 ng/kg: Behavioral: analgesia

TDLo (Intraperitoneal-Rat) 0.004 mg/kg: Behavioral: analgesia

TDLo (Intraperitoneal-Rat) 0.1 mg/kg: Brain and Coverings: recordings from specific areas of CNS

TDLo (Intraperitoneal-Rat) 50 µg/kg: Biochemical: Metabolism (Intermediary): other proteins

TDLo (Intraperitoneal-Rat) 0.1 mg/kg: Behavioral: alteration of classical conditioning

TDLo (Intraperitoneal-Rat) 7 mg/kg/2 weeks-intermittent: Cardiac: change in rate

TDLo (Intraperitoneal-Rat) 3200 mg/kg/8 days-intermittent: Behavioral: alteration of classical conditioning

TDLo (Intraperitoneal-Rat) 700 µg/kg/1 week-intermittent: Vascular: BP lowering not characterized in autonomic section

TDLo (Intraperitoneal-Rat) 2800 µg/kg/4 weeks-intermittent: Biochemical: Neurotransmitters or modulators (putative): catecholamine levels in sympathetic nerves

TDLo (Intraperitoneal-Rat) 1400 µg/kg/2 weeks-intermittent: Cardiac: change in rate; Vascular: BP lowering not characterized in autonomic section

TDLo (Intraperitoneal-Rat) 2800 µg/kg/4 weeks-intermittent: Biochemical: Neurotransmitters or modulators (putative): catecholamine: levels in sympathetic nerves, catecholamine levels in CNS, dopamine at other sites

TDLo (Intraperitoneal-Mouse) 1 mg/kg: Gastrointestinal: decreased motility or constipation

TDLo (Intraperitoneal-Mouse) 0.1 mg/kg: Biochemical: Metabolism (Intermediary): effect on inflammation or mediation of inflammation

TDLo (Intraperitoneal-Mouse) 0.1 mg/kg: Behavioral: changes in motor activity (specific assay)

TDLo (Intraperitoneal-Mouse) 0.03 mg/kg: Behavioral: changes in psychophysiological tests

TDLo (Intraperitoneal-Mouse) 0.1 mg/kg: Behavioral: analgesia

TDLo (Intramuscular-Monkey) 0.01 mg/kg: Vascular: BP lowering not characterized in autonomic section

TDLo (Intramuscular-Monkey) 0.116 µg/kg: Behavioral: alteration of operant conditioning

TDLo (Unreported-Rat) 0.4 mg/kg: Behavioral: alteration of classical conditioning

TDLo (Unreported-Rat) 2 mg/kg: female 20 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System; Effects on Newborn: other neonatal measures or effects

TDLo (Unreported-Rat) 60 mg/kg/30 days-intermittent: Reproductive: Maternal Effects: ovaries, fallopian tubes

TDLo (Unreported-Mouse) 10 µg/kg: Cardiac: change in rate

CARCINOGENIC POTENTIAL OF COMPONENTS: The following information is available for the active ingredient.

Chronic dietary administration of Clonidine was not carcinogenic to rats (132 weeks) or mice (78 weeks) dosed, respectively, at up to 46 to 70 times the maximum recommended daily human dose as mg/kg (9 or 6 times the MRDHD on a mg/m^2 basis).

The remaining components of this product are not found on the following lists: U.S. EPA, U.S. NTP, U.S. OSHA, U.S. NIOSH, GERMAN MAK, IARC, or ACGIH and therefore are neither considered to be nor suspected to be cancer-causing agents by these agencies.

REPRODUCTIVE TOXICITY INFORMATION: There are no adequate and well-controlled studies of Clonidine when in pregnant women. This compound in formulated pharmaceutical products is rated as Pregnancy Category C (RISK CANNOT BE RULED OUT. Adequate, well controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is given during pregnancy; but the potential benefits may outweigh the potential risk).

11. TOXICOLOGICAL INFORMATION (Continued)

REPRODUCTIVE TOXICITY INFORMATION (continued):

Mutagenicity: There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Embryotoxicity/Teratogenicity: Oral administration of Clonidine to pregnant rabbits during embryo/fetal organogenesis, at doses up to 80 mcg/kg/day (human equivalent dose 26 mcg/kg/day), produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (HED 2.4 mcg/kg/day) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or higher dose levels (up to 150 mcg/kg/day (HED 24 mcg/kg/day)) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both mice and rats at 500 or more mcg/kg/day (HED 80 mcg/kg/day for rats and 40 mcg/kg/day for mice) when the animals were treated on gestation days 1-14.

Reproductive Toxicity: Fertility of male and female rats was unaffected by Clonidine doses as high as 150 mcg/kg (approximately 3 times the MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 mcg/kg (10 to 40 times the oral MRDHD on a mg/kg basis; 2 to 8 times the MRDHD on a mg/m^2 basis). Clonidine is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing mothers should be advised of these effects and the appropriate action should be taken to prevent exposure.

ACGIH BIOLOGICAL EXPOSURE INDICES (BEIs): Currently, ACGIH Biological Exposure Indices (BEIs) have not been determined for the components of this product.

12. ECOLOGICAL INFORMATION

ALL WORK PRACTICES MUST BE AIMED AT ELIMINATING ENVIRONMENTAL CONTAMINATION.

MOBILITY: This product has not been tested for mobility in soil; it is expected to be somewhat mobile due to its composition.

PERSISTENCE AND BIODEGRADABILITY: This product has not been tested for persistence or biodegradability. It is expected that the components will slowly degrade in the environment and form a variety of organic and inorganic materials; however, no specific information is known.

BIO-ACCUMULATION POTENTIAL: This product has not been tested for bio-accumulation potential.

ECOTOXICITY: This product may be harmful to contaminated plant and animal life, especially in large quantities. Female hormones are increasingly detected in the environment and are linked to feminization males in some animal species. All releases to terrestrial, atmospheric and aquatic environments should be avoided.

OTHER ADVERSE EFFECTS: This product does not contain any component with known ozone depletion potential.

RESULTS OF PBT AND vPvB ASSESSMENT: No Data Available. PBT and vPvB assessments are part of the chemical safety report required for some substances in European Union Regulation (EC) 1907/2006, Article 14.

ENVIRONMENTAL EXPOSURE CONTROLS: Controls should be engineered to prevent release to the environment, including procedures to prevent spills, atmospheric release and release to waterways.

13. DISPOSAL CONSIDERATIONS

WASTE TREATMENT/DISPOSAL METHODS: Waste disposal must be in accordance with appropriate Federal, State, and local regulations. Waste containers should be handled with uncontaminated gloves. Reusable equipment should be decontaminated using 0.05M Boric acid solution adjusted to pH 9 with 10 N sodium hydroxide followed by a detergent wash and then clean water rinse or by using a bleach solution (triple wash) and a detergent solution followed by clean water rinse.

PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING: Wear proper protective equipment when handling waste materials.

U.S. EPA WASTE NUMBER: Not applicable.

EUROPEAN WASTE CODES: Wastes from Human or Animal Health Care or Related Research: 18 01 08: Medicines Other Than Those Mentioned in 18 01 07.

14. TRANSPORTATION INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION REGULATIONS: This product is NOT classified as dangerous goods, per U.S. DOT regulations, under 49 CFR 172.101.

TRANSPORT CANADA TRANSPORTATION OF DANGEROUS GOODS REGULATIONS: This product is NOT classified as Dangerous Goods, per regulations of Transport Canada.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): This product is NOT classified as Dangerous Goods, by rules of IATA.

INTERNATIONAL MARITIME ORGANIZATION (IMO) DESIGNATION: This product is NOT classified as Dangerous Goods by the International Maritime Organization.

UNITED NATIONS ECONOMIC COMMISSION FOR EUROPE (UNECE): This product is NOT classified by the United Nations Economic Commission for Europe to be dangerous goods. Refer to current regulations for all additional provisions other information not given here.

TRANSPORT IN BULK ACCORDING TO THE IBC CODE: See the information under the UN ADR and IMO, in this section.

ENVIRONMENTAL HAZARDS: This product is neither environmentally hazardous according to the criteria of the UN Model Regulations (as reflected in the IMDG Code, ADR, RID, and ADN); components are not marine pollutant according to the IMDG Code and is not listed in Annex III under MARPOL 73/78.

15. REGULATORY INFORMATION

ADDITIONAL UNITED STATES REGULATIONS:

U.S. SARA Reporting Requirements: No components of this product are subject to the reporting requirements of Sections 302, 304, and 313 of Title III of the Superfund Amendments and Reauthorization Act.

U.S. SARA Threshold Planning Quantity (TPQ): There are no specific Threshold Planning Quantities for any component of this product. The default Federal SDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) therefore applies, per 40 CFR 370.20.

U.S. CERCLA Reportable Quantities (RQ): Not applicable.

U.S. TSCA Inventory Status: This product is regulated under Food and Drug Administration standards; it is not subject to requirements under TSCA.

California Safe Drinking Water and Toxic Enforcement Act (Proposition 65): No component is listed on the California Proposition 65 Lists.

Other U.S. Federal Regulations: Not applicable.

ADDITIONAL CANADIAN REGULATIONS:

Canadian DSL Inventory Status: This product regulated by the Therapeutic Products Programme (TPP) of Health Canada and so it excepted from requirements of the DSL/NDSL Inventory.

Canadian Environmental Protection Act (CEPA) Priorities Substances Lists: The components of this product are not on the CEPA Priorities Substances Lists.

Canadian WHMIS Classification and Symbol: The WHMIS Requirements of the Hazardous Products Act does not apply in respect of the advertising, sale or importation of any cosmetic, device, drug or food within the meaning of the Food and Drugs Act.

Other Canadian Regulations: Requirements under the Canadian Heath Canada, Laboratory Biosafety Guidelines may be applicable.

ADDITIONAL EUROPEAN UNION REGULATIONS:

Safety, Health, and Environmental Regulations/Legislation Specific for the Product: When formulated in a finished medicinal compound for human use, this material is subject to Directive 2001/83/EC and subsequent amendments to the directive.

Chemical Safety Assessment: No Data Available. The chemical safety assessment is required for some substances according to European Union Regulation (EC) 1907/2006, Article 14.

16. OTHER INFORMATION

ANSI LABELING (Based on 129.1, Provided to Summarize Occupational Exposure Hazards): WARNING! PROLONGED CONTACT MAY CAUSE SKIN IRRITATION. MAY CAUSE HARM TO THE FETUS DURING PREGNANCY, BASED ON ANIMAL DATA. COMBUSTIBLE IF EXPOSED TO HIGH TEMPERATURES. Keep away from heat, sparks, and flame. Avoid contact with skin, eyes, and clothing. Avoid breathing vapors. Keep container tightly closed. Use only with adequate ventilation. Wash thoroughly after handling. Wear gloves, goggles, and appropriate body protection during handling or administration. FIRST-AID: In case of contact, flush skin or eyes with plenty of water. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. If swallowed, do NOT induce vomiting. If vomiting occurs, have person lean forward. Call physician or poison control center immediately. Never give anything by mouth to an unconscious person. IN CASE OF FIRE: Use water fog, dry chemical, CO_2, or "alcohol" foam. IN CASE OF SPILL: Wipe up spilled product. Place residue in appropriate container and seal. Dispose of according to applicable regulations. Consult Safety Data Sheet for additional information.

GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION: According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

EU 67/548/EEC LABELING AND CLASSIFICATION: According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

CLASSIFICATION FOR COMPONENTS:

FULL TEXT GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008:

Clonidine: This is a self-classification.

Classification: Reproductive Toxicity Category 2, Acute Oral Toxicity Category 3

Hazard Statement Codes: H361d: Suspected of damaging the unborn child. H301: Toxic if swallowed.

All Other Components: An official classification for these substances has not been published in the CLP 1272: 2008 and a self-classification is not applicable.

67/548/EEC:

Clonidine: This is a self-classification.

Classification: Reproductive Toxicity Category 3, Toxic

Risk Phrases: R63: Possible risk of harm to the unborn child. R25: Toxic if swallowed.

All Other Components: An official classification for these substances has not been published in Commission Directives and a self-classification is not applicable.

REFERENCES AND DATA SOURCES: Contact the supplier for information.

METHODS OF EVALUATING INFORMATION FOR THE PURPOSE OF CLASSIFICATION: Bridging principles were used to classify this product.

REVISION DETAILS: New.

PREPARED BY: CHEMICAL SAFETY ASSOCIATES, Inc. • PO Box 1961, Hilo, HI 96721 • 800/441-3365 • 808/969-4846
DATE OF PRINTING: September 24, 2013