SAFETY DATA SHEET

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

PART I *What is the material and what do I need to know in an emergency?*

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE

IDENTIFICATION of the SUBSTANCE or PREPARATION:

TRADE NAME:	**CLARAVIS™ (isotretinoin capsules, USP)**
CHEMICAL NAME:	Active Ingredient: 13-cis-retinoic acid
CHEMICAL CLASS:	Active Ingredient: Retinoid
THERAPEUTIC CLASS:	Immunomodulatory and Anti-inflammatory Agent used Treatment of Severe Acne
RELEVANT USE of the SUBSTANCE:	Human Pharmaceutical
HOW SUPPLIED:	10 mg: NDC:0555-1054-86: 3 in 1 carton, 10 in 1 blister pack; NDC:0555-1054-56: 10 in 1 carton, 10 in 1 blister pack; 20 mg: NDC:0555-1055-86: 3 in 1 carton, 10 in 1 blister pack; NDC:0555-1055-56: 10 in 1 carton, 10 in 1 blister pack; 30 mg: NDC:0555-1056-86: 3 in 1 carton, 10 in 1 blister pack; 40 mg: NDC:0555-1057-86: 3 in 1 carton, 10 in 1 blister pack; NDC:0555-1057-56: 10 in 1 carton, 10 in 1 blister pack

COMPANY/UNDERTAKING IDENTIFICATION:

U.S. SUPPLIER/MANUFACTURER'S NAME:	**TEVA**
ADDRESS:	1090 Horsham Road North Wales, PA 19454
BUSINESS PHONE:	215-591-3000 [08:00 AM --> 05:00 PM]
EUROPEAN. SUPPLIER/MANUFACTURER'S NAME:	**TEVA/TAPI**
ADDRESS:	Sicor sri-Via Terrazzano 77-20017 Cho (MI), Italy
BUSINESS PHONE:	+39 02 93197 306 [08:00 AM --> 05:00 PM]
EMERGENCY PHONE:	United States/Canada/Puerto Rico: 1-800/424-9300 (Chemtrec) [24-hrs] International: 01-703-527-3887 (Chemtrec) [24-hours]
EMAIL:	TevaSDSRequest@tevapharm.com
DATE OF PREPARATION:	July 25, 2013
DATE OF REVISION:	New

ALL WHMIS required information is included in appropriate sections based on the ANSI Z400.1-2010 format. This product has been classified in accordance with the hazard criteria of the CPR and the SDS contains all the information required by the CPR. The product is also classified per the Global Harmonization Standard.

2. HAZARD IDENTIFICATION

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 LABELING/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 consists of a hard gelatin capsules which are light gray (10 mg), brown (20 mg), orange (30 mg) or light-orange (40 mg), filled with pale orange pellets. **Hazards:** In the workplace, dusts from damaged capsules may cause irritation of contaminated skin or eye. No information is available on harmful effects by inhalation. In therapeutic use, reported adverse effects include dry eyes, eye inflammation, decreased night vision and other eye disorders, lip inflammation, dry skin, adverse effects on hearing, blood, and gastrointestinal system. Reports of depression and other psychological effects have occurred, as well as serious adverse skin reactions. Anaphylactic reactions and other allergic reactions have been reported. Exposure during pregnancy will cause harm to fetus. Limited evidence of adverse effects to fertility, based on animal data. Use in persons with incomplete skeletal growth can cause adverse effects on the skeletal system. These effects may be possible as a result of workplace exposure. Refer to Section 11 (Toxicological Information) for additional information on adverse effects. **Flammability Hazards:** This product is combustible and can ignite if highly heated or if exposed to direct flame. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including aluminum, carbon, iron, silicon, sodium, titanium and nitrogen oxides). **Reactivity Hazards:** This product is not reactive. **Environmental Hazards:** The active ingredient, Isotretinoin is toxic to marine organisms; may cause harm to aquatic organisms if accidentally released. All environmental release should be avoided. **Emergency Recommendations:** Emergency responders must wear personal protective equipment suitable for the situation to which they are responding.

3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	EINECS #	% w/v	LABEL ELEMENTS EU Classification (67/548/EEC) GHS & EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements
Isotretinoin 13-cis-retinoic acid	4759-48-2	225-296-0	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Reproductive Toxicity Cat. 2, Reproductive Toxicity Cat. 3, Irritant, Dangerous for the Environment Risk Phrase Codes: R61, R62, R36/37/38, R50/53 Hazard Symbols: T, Xi, N GHS and EU 1272/2008 Classification: Reproductive Toxicity Cat. 1B, Skin Irritation Cat. 2, Eye Irritation Cat. 2B, STOT (Inhalation-Respiratory System) SE Cat. 3, Acute Oral Toxicity Cat. 5, Aquatic Acute Toxicity Cat.1 Hazard Codes: H360Df, H315, H319, H335, H303, H410 Hazard Symbol/Pictogram: GHS07, GHS08, GHS09
EXCIPIENTS				
Aluminum Oxide	1344-28-1	215-691-6	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Black Iron Oxide (10 mg, 20 mg)	1309-33-7	215-166-1	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Butylated Hydroxyanisole	25013-16-5	246-563-8	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Colloidal Silicon Dioxide (40 mg)	112945-52-5	Not Listed	Proprietary	SELF-CLASSIFICATION EU 67/548 Classification: Not Applicable Risk Phrase Codes: Not Applicable Hazard Symbols: Not Applicable GHS and EU 1272/2008 Classification: Acute Oral Toxicity Cat. 5 Hazard Codes: H303 Hazard Symbol/Pictogram: Not Applicable
Cottonseed Oil	8001-29-4	232-280-7	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Edetate Disodium	8013-51-2	As anhydrous: 200-449-4	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
FD&C Yellow # 6 (10 mg, 40 mg)	2783-94-0	220-491-7	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Gelatin	9000-70-8	232-554-6	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Polysorbate 80	9005-65-6	NLP# 500-019-9	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Red Iron Oxide (20 mg, 30 mg)	1332-37-2	215-570-8	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Shellac	9000-59-3	232-549-9	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Sodium Lauryl Sulfate (40 mg)	151-21-3	205-788-1	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Harmful Risk Phrase Codes: R22 Hazard Symbols: Xn GHS & EU 1272/2008 Classification: Acute Oral Toxicity Cat. 4 Hazard Codes: H302 Hazard Symbol/Pictogram: GHS07
Soybean Oil	8001-22-7	232-274-1	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Titanium Dioxide	13463-67-7	236-675-7	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
White Wax (Beeswax)	8006-40-4	Not Listed	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Vitamin E (α-tocopherol)	10191-41-0	233-466-0	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Yellow Iron Oxide (20 mg, 30 mg)	20344-49-4	243-746-4	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.
Edible Ink	Mixture	Mixture	Proprietary	EU 67/548: Classification: Not applicable. GHS & EU 1272/2008: Classification: Not applicable.

See Section 16 for full classification information of product and components.

PART II *What should I do if a hazardous situation occurs?*

4. FIRST-AID MEASURES

DESCRIPTION OF FIRST AID MEASURES: Contaminated individuals must be taken for medical attention if any adverse effects occur. Remove contaminated clothing and shoes. Take a copy of this SDS to health professional with victim. Wash clothing and thoroughly clean shoes before reuse.

SKIN EXPOSURE: If skin contact with the drug product occurs, flush affected area with water. Minimum flushing is for 20 minutes. The contaminated individual must seek medical attention if any adverse effects occur after flushing.

EYE EXPOSURE: If the drug product enters the eyes, open contaminated individual's eyes while under gently running water. Use sufficient force to open eyelids. Have contaminated individual "roll" eyes. Minimum flushing is for 20 minutes. Contaminated individual must seek medical attention if adverse effect occurs or continues after flushing.

INHALATION: If dusts from the drug product are inhaled, remove victim to fresh air. The contaminated individual must seek medical attention if any adverse effects occur.

INGESTION: If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, seek immediate medical attention. If alert, victim should drink up to three glasses of water. Do not induce vomiting. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow. If victim is convulsing, maintain an open airway and obtain emergency medical attention.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: In therapeutic use, pre-existing depression, eye conditions, intracranial hypertension, pancreatitis, abnormal serum triglycerides levels, hearing impairment, clinical hepatitis, inflammatory bowel disease, bone mineral density deficiency may be aggravated. Workplace exposure may also aggravate these conditions. Persons who may have hypersensitivity reactions to tetracyclines 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 immediate medical attention. Tetracycline is not dialyzable to any great extent.

5. FIRE-FIGHTING MEASURES

FLASH POINT: Not available.

AUTOIGNITION TEMPERATURE: Not available.

FLAMMABLE LIMITS (in air by volume, %): Not applicable.

FIRE EXTINGUISHING MEDIA: Unless incompatibilities exist for surrounding materials, carbon dioxide, water spray, 'ABC' type chemical extinguishers, foam, dry chemical and halon extinguishers can be used to fight fires involving this product.

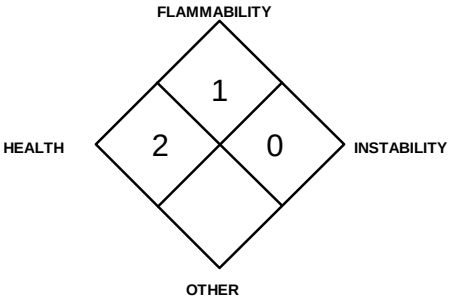
UNSUITABLE FIRE EXTINGUISHING MEDIA: None known.

SPECIAL HAZARDS ARISING FROM THE SUBSTANCE: This product must be substantially pre-heated before ignition can occur. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including aluminum, carbon, iron, silicon, sodium, titanium and nitrogen oxides).

Explosion Sensitivity to Mechanical Impact: Not applicable.

Explosion Sensitivity to Static Discharge: Not sensitive.

NFPA RATING



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

SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS: Structural firefighters must wear Self-Contained Breathing Apparatus and full protective equipment. All personal protective gear and contaminated fire-response equipment should be decontaminated with soapy water and thoroughly rinsed before being returned to service. Move fire-exposed containers if it can be done without risk to firefighters. If possible, prevent runoff water from entering storm drains, bodies of water, or other environmentally sensitive areas.

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES: Spill kits, clearly labeled, should be kept in or near preparation and administrative areas. It is suggested that kits include a respirator, chemical splash goggles, two pairs of gloves, two sheets (12" x 12") of absorbent material, 250-mL and 1-liter spill control pillows, a small scoop to collect glass fragments (if applicable) and two large waste disposal bags. Absorbents should be able to be incinerated. Avoid generating airborne dusts of this material during spill response procedures as described below.

PROTECTIVE EQUIPMENT:

Small Spills/Spills in Hoods: Personnel wearing nitrile or other appropriate gloves, labcoat or other protective clothing and eye protection should immediately clean incidental spills (e.g. a single container).

Large Spills: For large spills (e.g., a pallet of containers), proper protective equipment, including double nitrile or appropriate gloves, and protective clothing (i.e., disposable Tyvek coveralls). When there is any danger of airborne dusts being generated, use a full-face respirator equipped with a High Efficiency Particulate (HEPA) filter. Self-Contained Breathing Apparatus (SCBA) can be used instead of an air-purifying respirator.

METHODS FOR CLEAN-UP AND CONTAINMENT:

Cleanup of Small Spills: Pick-up or wipe-up spilled capsules with damp absorbent sheets to prevent generation of dusts. Decontaminate the spill area (three times) using a bleach and detergent solution and then rinse with clean water.

6. ACCIDENTAL RELEASE MEASURES (Continued)

METHODS FOR CLEAN-UP AND CONTAINMENT (continued):

Large Spills: Restrict access to the spill areas. Gently wet down area and carefully sweep up spilled product, avoiding the generation of airborne dusts. The dispersion of particles into surrounding air and the possibility of inhalation is a serious matter and should be treated as such. Do not apply chemical in-activators as they may produce hazardous by-products. Thoroughly clean all contaminated surfaces three times using a bleach and detergent solution and then rinse with clean water.

All Spills: Use procedures described above and then place all spill residues in an appropriate, labeled container and seal. Move to a secure area. Dispose of in accordance with Federal, State, and local hazardous waste disposal regulations (see Section 13, Disposal Considerations). For spills on water, contain, minimize dispersion and collect. Dispose of recovered material and report spill per regulatory requirements.

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.

REFERENCE TO OTHER SECTIONS: Review Sections 2, 8, 11 and 12 before proceeding with cleanup. See Section 13, Disposal Considerations for more information.

PART III *How can I prevent hazardous situations from occurring?*

7. HANDLING and STORAGE

PRECAUTIONS FOR SAFE HANDLING: All employees who handle this product should be thoroughly trained to handle it safely. As with all chemicals, avoid getting this product ON YOU or IN YOU. Do not eat or drink while handling this product. After handling this product, wash face and hands thoroughly prior to eating, drinking, smoking or applying cosmetics. Ensure this product is used with adequate ventilation. Appropriate personal protective equipment must be worn (see Section 8, Exposure Controls - Personal Protection). Open containers slowly on a stable surface in areas that have been designated for use of this product. Minimize all exposures to this product. Avoid generation of dusts. Areas in which this product is used should be wiped down, so that this dusts from product do not accumulate.

CONDITIONS FOR SAFE STORAGE: Containers of this product must be properly labeled. Store containers in a cool, dry location, away from direct sunlight and sources of intense heat. Recommended Storage Temperature: 20-25°C (68-77°F). Store away from incompatible materials (see Section 10, Stability and Reactivity). Product should be stored in secondary containers. Keep containers tightly closed when not in use. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged. Have appropriate extinguishing equipment in the storage area (e.g., sprinkler system, portable fire extinguishers). Empty containers may contain residual product; therefore, empty containers should be handled with care and disposed of properly.

SPECIFIC END USE(S): This product is a human pharmaceutical.

PROTECTIVE PRACTICES DURING MAINTENANCE OF CONTAMINATED EQUIPMENT: When cleaning non-disposable equipment, wear nitrile or other appropriate gloves (double gloving is recommended), goggles, and lab coat. Prevent dispersion of particulates by wetting or dampening surfaces prior to clean up of equipment. If applicable, wash equipment using a bleach and detergent solution and then rinse with clean water

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

EXPOSURE LIMITS/CONTROL PARAMETERS:

VENTILATION AND ENGINEERING CONTROLS: General: Use with adequate ventilation. Follow standard operating procedures and requirements for handling this product. Ensure eyewash stations and deluge showers are available and accessible in areas where this product is used. Wear appropriate personal protect equipment consistent with the recommendations of this SDS. Prevent accumulation of product on work surfaces by routinely cleaning areas appropriately.

WORKPLACE EXPOSURE LIMITS/CONTROL PARAMETERS:

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELs		NIOSH	OTHER
		TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	IDLH mg/m^3	mg/m^3
Isotretinoin	4759-48-2	NE	NE	NE	NE	NE	NE	NE	**Teva OEL TWA = 4 µg/m^3** (established 7Mar2012)
Aluminum Oxide	1344-28-1	NE	NE	15 (total dust), 5 (resp. fract.)	NE	NE	NE	NE	DFG MAKs: TWA = 4 (inhalable fraction), 1.5 (respirable fraction) DFG MAK Pregnancy Risk Classification: D Carcinogen: MAK-2 (fibrous dust)
Black Iron Oxide Red Iron Oxide Yellow Iron Oxide Exposure limits given are for CAS# 1309-37-1 (Fe2O3)	1309-33-7 1332-37-2 20344-49-4	5 (resp. fract.)	NE	10 (fume)	NE	5 (dusts & fume, as Fe)	NE	2500 (dust & fume, as Fe)	Carcinogen: IARC-3, MAK-3B, TLV-A4
Colloidal Silicon Dioxide	112926-00-8	NE	NE	20 mppcf or	80 mg/m^3 % SO_2	6 See NIOSH Pocket Guide App. C	NE	3000	Carcinogen: IARC-3, TLV-A3

NE = Not Established See Section 16 for Definitions of Other Terms Used

8. EXPOSURE CONTROLS - PERSONAL PROTECTION (Continued)

EXPOSURE LIMITS/CONTROL PARAMETERS (continued):

WORKPLACE EXPOSURE LIMITS/CONTROL PARAMETERS (continued):

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELs		NIOSH	OTHER
		TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	TWA mg/m^3	STEL mg/m^3	IDLH mg/m^3	mg/m^3
Edetate Disodium	8013-51-2	NE	NE	NE	NE	NE	NE	NE	NE
FD&C Yellow # 6	2783-94-0	NE	NE	NE	NE	NE	NE	NE	Carcinogen: IARC-3
Gelatin	9000-70-8	NE	NE	NE	NE	NE	NE	NE	NE
Hydrogenated Vegetable Oil Exposure limits are for vegetable oil mist	67701-26-2	NE	NE	15 (total dust), 5 (respirable fraction)	NE	10 (total dust), 5 (respirable fraction)	NE	NE	NE
Polysorbate 80	9005-65-6	NE	NE	NE	NE	NE	NE	NE	NE
Shellac	9000-59-3	NE	NE	NE	NE	NE	NE	NE	NE
Sodium Lauryl Sulfate	151-21-3	NE	NE	NE	NE	NE	NE	NE	NE
Soybean Oil	8001-22-7	NE	NE	NE	NE	NE	NE	NE	NE
Titanium Dioxide	13463-67-7	10	NE	15 (total dust) 10 (vacated 1989 PEL)	NE	See NIOSH Pocket Guide Appendix A		Ca, 5000	Carcinogen: IARC-2B, MAK-3A, NIOSH-Ca, TLV-A4; NIC: TLV-A3
White Wax (Beeswax)	8006-40-4	NE	NE	NE	NE	NE		NE	NE
Vitamin E (α-Tocopherol)	10191-41-0	NE	NE	NE	NE	NE		NE	NE

NE = Not Established NIC = Notice of Intended Change See Section 16 for Definitions of Other Terms Used

INTERNATIONAL OCCUPATIONAL EXPOSURE LIMITS: Exposure limits available for some excipient components are given below.

ALUMINUM OXIDE:
Australia: TWA = 10 mg/m^3, JAN 1993
Austria: TRK = 0.25 fibers/cc, JAN 2006
Belgium: TWA = 10 mg(Al)/m^3, MAR 2002
Denmark: TWA = 10 mg/m^3, OCT 2002
France: VME = 10 mg/m^3, FEB2006
Germany: MAK = 1.5 mg/m^3 (respirable, fume), 2005
Hungary: TWA = 6 mg/m^3 (resp), SEP 2000
Japan: OEL = 0.5 mg/m^3 (respirable), 2 mg/m^3 (total), APR 2007
Korea: TWA = 10 mg/m^3, 2006
Mexico: TWA = 10 mg(Al2O3)/m^3 (inhalable), 2004
The Netherlands: MAC-TGG = 10 mg/m^3, 2003
New Zealand: TWA = 10 mg/m^3 (inspirable dust), JAN 2002
Norway: TWA = 2 mg(Al)/m^3, JAN 1999
Poland: MAC(TWA) = 2 mg/m^3, MAC(STEL) = 16 mg/m^3, JAN 1999
Russia: TWA = 6 mg/m^3, JUN 2003
Sweden: TWA = 5 mg/m^3 (total dust); TWA = 2 mg/m^3 (resp. dust), JUN2005
Switzerland: MAK-W = 3 mg/m^3, DEC 2006
Switzerland: MAK-W = 3 mg/m^3; KZG-W = 24 mg/m^3, fume, DEC 2006
United Kingdom: TWA = 10 mg/m^3 (inhalable), 2005
United Kingdom: TWA = 4 mg/m^3 (respirable), 2005
In Argentina, Bulgaria, Colombia, Jordan, Singapore, Vietnam check ACGIH TLV

GELATIN:
Russia: STEL = 10 mg/m^3, JUN 2003

IRON OXIDES:
ARAB Republic of Egypt: TWA = 3 ppm (5 mg/m^3) (fume), JAN 1993
Australia: TWA = 0.1 mg(Fe)/m^3, JUL 2008
Australia: TWA = 5 mg(Fe)/m^3 (fume), JUL 2008
Belgium: TWA = 2 ppm (5 mg(Fe)/m^3) (fume), MAR2002
Denmark: TWA = 3.5 mg(Fe)/m^3, OCT 2002
Finland: TWA = 5 mg(Fe)/m^3, fume, SEP 2009
France: VME = 5 mg(Fe)/m^3 (fume), FEB 2006
Germany: MAK = 1.5 mg(Fe)/m^3 (respirable), 2005
Hungary: TWA = 6 mg/m^3 (resp), SEP2000
Japan: OEL = 1 mg/m^3 (respirable), 4 mg/m^3 (total), APR 2007
Korea: TWA = 10 mg/m^3, 2006
Korea: TWA = 5 mg/m^3, 2006
Mexico: TWA = 10 mg/m^3; STEL = 20 mg/m^3, 2004
The Netherlands: MAC-TGG = 5 mg(Fe)/m^3, 2003
The Netherlands: MAC-TGG = 10 mg/m^3, 2003
New Zealand: TWA = 5 mg(Fe)/m^3 (dust and fume), JAN 2002
New Zealand: TWA = 10 mg/m^3 (inspirable dust), JAN 2002
Norway: TWA = 3 mg/m^3, JAN 1999
The Philippines: TWA = 10 mg/m^3 (fume), JAN 1993
Poland: MAC(TWA) fume = 5 mg/m^3, MAC(STEL) = 10 mg/m^3, JAN 1999
Russia: TWA = 6 mg/m^3, JUN 2003
Sweden: TWA = 3.5 mg(Fe)/m^3 (resp. dust), JUN 2005
Switzerland: MAK-W = 3 mg/m^3, DEC 2006
Thailand: TWA = 10 mg/m^3 (fume), JAN1993
Turkey: TWA = 10 mg/m^3 (fume), JAN 1993

IRON OXIDES (continued):
United Kingdom: TWA = 4 mg/m^3 (respirable), 2005
United Kingdom: TWA = 10 mg/m^3 (inhalable), 2005
United Kingdom: TWA = 5 mg(Fe)/m^3;STEL = 10 mg(Fe)/m^3, 2005
In Argentina, Bulgaria, Colombia, Jordan, Singapore, Vietnam check ACGIH TLV

TITANIUM DIOXIDE:
ARAB Republic of Egypt: TWA = 15 mg/m^3, JAN 1993
Belgium: TWA = 10 mg/m^3, MAR 2002
Denmark: TWA = 6 mg(Ti)/m^3, OCT 2002
France: VME = 10 mg/m^3, FEB 2006
Germany: MAK = 1.5 mg/m^3 (respirable), 2005
Japan: OEL = 1 mg/m^3 (respirable), 4 mg/m^3 (total), APR 2007
Korea: TWA = 10 mg/m^3, 2006
Mexico: TWA = 10 mg(Ti)/m^3; STEL = 20 mg(Ti)/m^3, 2004
The Netherlands: MAC-TGG = 10 mg/m^3, 2003
New Zealand: TWA = 10 mg/m^3 (inspirable dust), JAN 2002
Norway: TWA = 5 mg/m^3, JAN 1999
Poland: MAC(TWA) = 10 mg(Ti)/m^3, MAC(STEL) = 30 mg(Ti)/m^3, JAN 1999
Russia: TWA = 10 mg/m^3, JUN 2003
Sweden: TWA = 5 mg/m^3 (total dust), JUN 2005
Switzerland: MAK-W = 3 mg/m^3, DEC 2006
Turkey: TWA = 15 mg/m^3, JAN 1993
United Kingdom: TWA = 10 mg/m^3 (inhalable), 2005
United Kingdom: TWA = TWA 4 mg/m^3 (respirable), 2005
In Argentina, Bulgaria, Colombia, Jordan, Singapore, Vietnam check ACGIH TLV

PROTECTIVE EQUIPMENT: *The following information on appropriate Personal Protective Equipment is provided to assist employers in complying with OSHA regulations found in 29 CFR Subpart I (beginning at 1910.132, including U.S. Federal OSHA Respiratory Protection (29 CFR 1910.134), OSHA Eye Protection 29 CFR 1910.133, OSHA Hand Protection 29 CFR 1910.138, OSHA Foot Protection 29 CFR 1910.136 and OSHA Body Protection 29 CFR1910.132), equivalent standards of Canada (including CSA Respiratory Standard Z94.4-02, Z94.3-M1982,* Industrial Eye and Face Protectors *and CSA Standard Z195-02,* Protective Footwear*), or standards of EU member states (including EN 529:2005 for respiratory PPE, CEN/TR 15419:2006 for hand protection, and CR 13464:1999 for face/eye protection). Please reference applicable regulations and standards for relevant details.*

RESPIRATORY PROTECTION: Maintain airborne contaminant concentrations below exposure limits listed above, if applicable. For materials without listed exposure limits, minimize respiratory exposure. If necessary, use only respiratory protection authorized under appropriate regulations. Oxygen levels below 19.5% are considered IDLH by U.S. OSHA. In such atmospheres, use of a full-facepiece pressure/demand SCBA or a full facepiece, supplied air respirator with auxiliary self-contained air supply is required under U.S. OSHA's Respiratory Protection Standard (1910.134-1998).

EYE PROTECTION: Wear splash goggles or safety glasses as appropriate for the task. If necessary, refer to appropriate regulations.

HAND PROTECTION: Wash hands and wrists before putting on and after removing gloves. During manufacture or other similar industrial operations, wear the appropriate hand protection for the process. When used in medical administration of the product, double glove with nitrile or other appropriate gloves to avoid contact and/or absorption of the product.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION (Continued)

PROTECTIVE EQUIPMENT (continued):

HAND PROTECTION (continued): Use double gloves for spill response, as stated in Section 6 (Accidental Release Measures) of this SDS. Because all gloves are to some extent permeable and their permeability increases with time, they should be changed regularly (hourly is preferable) or immediately if torn or punctured. If necessary refer to appropriate regulations.

SKIN PROTECTION: Use appropriate protective clothing for the task (e.g., lab coat, etc.). If necessary, refer to the U.S. OSHA Technical Manual (Section VII: Personal Protective Equipment) or other appropriate regulations.

9. PHYSICAL and CHEMICAL PROPERTIES

The following information is for the product as a whole.

PHYSICAL FORM: Capsules, filled with pale orange spheres.
COLOR: As described in Section 2.
ODOR: Practically odorless.
ODOR THRESHOLD: Not applicable.
MOLECULAR WEIGHT: Mixture.
MOLECULAR FORMULA: Mixture.
HOW TO DETECT THIS SUBSTANCE (identification/warning properties): The appearance may be a distinguishing characteristic of this product in event of accidental release.

The following information is available for the active ingredient, Isotretinoin:

FORM: Crystalline powder.
COLOR: Yellow to orange.
MOLECULAR WEIGHT: 300.44
MOLECULAR FORMULA: $C_{20}H_{28}O_2$
MELTING POINT: 174-175°C (347°F)
BOILING POINT @ 760 mmHg: 462.8°C (865°F) [predict.]
ODOR: Mild odor.
ODOR THRESHOLD: Not available.
FLASH POINT: 350.6°C (663.1°F) [predict.]
DECOMPOSITION TEMPERATURE: > 60°C (> 140°F)
SPECIFIC GRAVITY: 1.011 g/cm^3 [predict.]
BULK DENSITY @ 20°C: ~480 kg/cm^3
VAPOR PRESSURE @ 25°C: 0 mmHg
pH: Not available.
SOLUBILITY IN WATER @ 25°C: Insoluble.
OTHER SOLUBILITIES: Soluble in organic solvents.
COEFFICIENT OF OIL/WATER DISTRIBUTION (PARTITION COEFFICIENT): 6.3; Log Kow: 7.85 (predict.)

10. STABILITY and REACTIVITY

CHEMICAL STABILITY: Stable under normal conditions.

DECOMPOSITION PRODUCTS: *Combustion:* Products of thermal decomposition may include aluminum, carbon, iron, silicon, sodium, titanium and nitrogen oxides. *Hydrolysis:* None known.

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE: Incompatible with strong oxidizing agents, alkalies and acids.

POSSIBILITY OF HAZARDOUS REACTION/POLYMERIZATION: Will not occur.

CONDITIONS TO AVOID: Exposure to or contact with extreme temperatures, incompatible chemicals.

PART IV *Is there any other useful information about this material?*

11. TOXICOLOGICAL INFORMATION

SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE: The main route of occupational exposure to this product is via inhalation of dusts and skin contact. The anticipated symptoms of exposure, by route of exposure are described further in this section.

INHALATION: Inhalation of dusts generated by damaged tablets of this product may cause irritation. Symptoms of such exposure may include sneezing, coughing, sore throat, itching and nasal congestion. In addition, inhalation may result in adverse effects as described under 'Other Potential Health Effects'.

CONTACT WITH SKIN or EYES: Symptoms of skin contact may include itching and redness and swelling. Eye irritation due to dust is expected to be mechanical in nature and may cause redness and watering of the eyes. Other potential health effects are unknown.

SKIN ABSORPTION: The active ingredient, Isotretinoin, is known to be absorbed via intact skin. Care must be taken to avoid all contact with this material for pregnant women due to potential harm to fetus.

INGESTION: Ingestion of this product is not anticipated to be a significant route of occupational exposure. Accidental ingestion of this product (i.e., through poor hygiene practices) may irritate the mouth, throat, and other tissues of the gastrointestinal system. Other effects may occur as described under 'Other Potential Health Effects'.

OTHER POTENTIAL HEALTH EFFECTS: In therapeutic use, reported adverse effects include dry eyes, eye inflammation, decreased night vision and other eye disorders, lip inflammation, dry skin, adverse effects on hearing, blood, and gastrointestinal system. Reports of depression and other psychological effects have occurred, as well as serious adverse skin reactions. Exposure during pregnancy will cause harm to fetus. Limited evidence of adverse effects to fertility, based on animal data. Use in persons with incomplete skeletal growth can cause adverse effects on the skeletal system. These effects may be possible as a result of workplace exposure. The actual risk in the workplace is not known.

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

11. TOXICOLOGICAL INFORMATION (Continued)

OTHER POTENTIAL HEALTH EFFECTS (continued): Body systems adversely affected during therapeutic use are provided below. More details are given in the Teva Active Ingredient SDS for Isotretinoin.

- Body as a Whole
- Cardiovascular System
- Endocrine/Metabolic System
- Eyes
- Gastrointestinal System
- Hematologic System
- Musculoskeletal System
- Neurological System
- Psychiatric Disorders.
- Reproductive System
- Respiratory System
- Skin and Appendages
- Urinary System

HEALTH EFFECTS OR RISKS FROM EXPOSURE:

Acute: Dusts from product may cause irritation if inhaled and in contact with skin or eyes. Accidental ingestion may be harmful. Acute exposure may cause effects described in "Other Potential Health Effects".

Chronic: May cause fetal harm. Chronic exposure may also lead to symptoms described under 'Other Potential Health Effects'. No other chronic effects have been reported from workplace exposure.

TARGET ORGANS: It is anticipated that for Occupational Exposure the target organs are: Acute: Skin, eyes, respiratory system. Chronic: Skin, fetus. In therapeutic use this material may have an impact on the body systems described under 'Other Potential Health Effects'.

TOXICITY DATA: The following toxicity data are currently available for the active ingredient. In addition, data are available for excipients, but are not provided in this SDS. Contact Teva for more information.

ISOTRETINOIN:

TDLo (Oral-Human) 469.3 mg/kg/3 years-intermittent: Behavioral: headache
TDLo (Oral-Human) 112 mg/kg/16 weeks-intermittent: Musculoskeletal: joints; Skin and Appendages: dermatitis, other (after systemic exposure); Biochemical: Metabolism (Intermediary): lipids including transport
TDLo (Oral-Human) 637 mg/kg/218 weeks-intermittent: Musculoskeletal: other changes
TDLo (Oral-Human) 153.3 mg/kg/3 years-intermittent: Musculoskeletal: other changes
TDLo (Oral-Human) 14 mg/kg/4 weeks-intermittent: Lungs, Thorax, or Respiration: other changes
TDLo (Oral-Human) 90 mg/kg/90 days-intermittent: Behavioral: rigidity (including catalepsy), headache, convulsions or effect on seizure threshold
TDLo (Oral-Human) 6.86 mg/kg/12 weeks-intermittent: Skin and Appendages: nails
TDLo (Oral-Human) 90 mg/kg/24 weeks-intermittent: Gastrointestinal: changes in structure or function of salivary glands; Biochemical: Metabolism (Intermediary): effect on inflammation or mediation of inflammation
TDLo (Oral-Child) 30 mg/kg/21 weeks: Musculoskeletal: other changes Skin and Appendages: dermatitis, irritative (after systemic exposure); Skin and Appendages: nails
TDLo (Oral-Child) 360 mg/kg/26 weeks-intermittent: Skin and Appendages: sweating
TDLo (Oral-Woman) 56 mg/kg/8 weeks-intermittent: Skin and Appendages: dermatitis, irritative (after systemic exposure)
TDLo (Oral-Woman) 105 mg/kg/105 days-intermittent: Blood: hemorrhage, changes in platelet count; Biochemical: Enzyme inhibition, induction, or change in blood or tissue levels: transaminases
TDLo (Oral-Woman) 105 mg/kg/15 weeks-intermittent: Blood: hemorrhage, thrombocytopenia; Biochemical: Enzyme inhibition, induction, or change in blood or tissue levels: other transferases
TDLo (Oral-Woman) 2400 µg/kg: female 22-24 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System, eye/ear, craniofacial (including nose and tongue)
TDLo (Oral-Woman) 74 mg/kg: female 1-62 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System, craniofacial (including nose and tongue), urogenital system
TDLo (Oral-Woman) 157 mg/kg: female 2 week(s) pre-mating 1-12 week(s) after conception: Reproductive: Specific Developmental Abnormalities: cardiovascular (circulatory) system, blood and lymphatic systems (including spleen and marrow), respiratory system
TDLo (Oral-Woman) 7200 µg/kg: female 26-34 day(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear, cardiovascular (circulatory) system, hepatobiliary system
TDLo (Oral-Woman) 4800 µg/kg: female 26-28 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System, eye/ear, cardiovascular (circulatory) system
TDLo (Oral-Woman) 84 mg/kg: female 1-15 week(s) after conception: Reproductive: Specific Developmental Abnormalities: skin and skin appendages; Effects on Newborn: other postnatal measures or effects
TDLo (Oral-Woman) 24 mg/kg: female 1-4 week(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear, craniofacial (including nose and tongue); Effects on Newborn: Apgar score (human only)
TDLo (Oral-Woman) 7 mg/kg: female 14-27 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System, Specific Developmental Abnormalities: craniofacial (including nose and tongue)
TDLo (Oral-Man) 24 mg/kg/4 weeks-intermittent: Gastrointestinal: hypermotility, diarrhea, other changes
TDLo (Oral-Man) 37 mg/kg/5 weeks-intermittent: Skin and Appendages: dermatitis, irritative (after systemic exposure); Immunological Including Allergic: decreased immune response
TDLo (Oral-Man) 10 mg/kg/10 days-intermittent: Behavioral: stiffness
TDLo (Oral-Man) 7 mg/kg: female 7 day(s) pre-mating: Reproductive: Paternal Effects: other effects on male
TDLo (Unreported-Man) 21 mg/kg/3 weeks-intermittent: Skin and Appendages: dermatitis, other (after systemic exposure)
LD_{50} (Oral-Rat) > 4000 mg/kg
LD_{50} (Oral-Mouse) 3389 mg/kg
LD_{50} (Oral-Rabbit) 1960 mg/kg
LD_{50} (Intraperitoneal-Rat) 901 mg/kg
LD_{50} (Intraperitoneal-Mouse) 138 mg/kg
ICLo (*In vitro*-Rat Embryo) 1 mg/L/48 hours: Reproductive: Effects on Embryo or Fetus: extra-embryonic structures (e.g., placenta, umbilical cord), fetotoxicity (except death, e.g., stunted fetus); Specific Developmental Abnormalities: Central Nervous System

ISOTRETINOIN (continued):

TDLo (Oral-Rat) 5 mg/kg: Behavioral: alteration of operant conditioning
TDLo (Oral-Rat) 240 mg/kg/6 days-intermittent: Blood: changes in serum composition (e.g. TP, bilirubin, cholesterol)
TDLo (Oral-Rat) 1260 mg/kg/12 weeks-intermittent: Blood: pigmented or nucleated red blood cells; Biochemical: Enzyme inhibition, induction, or change in blood or tissue levels: phosphatases; Metabolism (Intermediary): Plasma proteins not involving coagulation
TDLo (Oral-Rat) 8400 mg/kg/21 days-intermittent: Blood: pigmented or nucleated red blood cells; Musculoskeletal: other changes; Related to Chronic Data: death
TDLo (Oral-Rat) 105 mg/kg/7 days-intermittent: Blood: changes in serum composition (e.g. TP, bilirubin, cholesterol); Biochemical: Metabolism (Intermediary): lipids including transport, Plasma proteins not involving coagulation
TDLo (Oral-Rat) 105 mg/kg/7 days-intermittent: Endocrine: hypoglycemia; Biochemical: Metabolism (Intermediary): lipids including transport, Metabolism (Intermediary): Plasma proteins not involving coagulation
TDLo (Oral-Rat) 4 mg/kg/10 days-intermittent: Liver: other changes; Blood: changes in spleen; Biochemical: Metabolism (Intermediary): other proteins
TDLo (Oral-Rat) 4 mg/kg/10 days-intermittent: Endocrine: other changes; Nutritional and Gross Metabolic: weight loss or decreased weight gain; Biochemical: Metabolism (Intermediary): effect on inflammation or mediation of inflammation
TDLo (Oral-Rat) 330 mg/kg/44 days-intermittent: Behavioral: alteration of classical conditioning
TDLo (Oral-Rat) 1260 mg/kg/42 days-intermittent: Behavioral: alteration of classical conditioning
TDLo (Oral-Rat) 100 mg/kg: female 10-11 day(s) after conception: Reproductive: Fertility: post-implantation mortality (e.g. dead and/or resorbed implants per total number of implants); Specific Developmental Abnormalities: craniofacial (including nose and tongue), musculoskeletal system
TDLo (Oral-Mouse) 200 mg/kg: female 12 day(s) after conception: Reproductive: Specific Developmental Abnormalities: craniofacial (including nose and tongue)
TDLo (Oral-Mouse) 200 mg/kg: female 11 day(s) after conception: Reproductive: Specific Developmental Abnormalities: musculoskeletal system
TDLo (Oral-Mouse) 200 mg/kg: female 7 day(s) after conception: Reproductive: Fertility: post-implantation mortality (e.g. dead and/or resorbed implants per total number of implants); Specific Developmental Abnormalities: eye/ear
TDLo (Oral-Mouse) 200 mg/kg: female 8 day(s) after conception: Reproductive: Fertility: litter size (e.g. # fetuses per litter; measured before birth); Specific Developmental Abnormalities: Central Nervous System, eye/ear
TDLo (Oral-Rabbit) 60 mg/kg: female 8-11 day(s) after conception: Reproductive: Fertility: pre-implantation mortality (e.g. reduction in number of implants per female; total number of implants per corpora lutea); Effects on Embryo or Fetus: other effects to embryo
TDLo (Oral-Dog) 15,840 mg/kg/55 weeks-intermittent: Sense Organs and Special Senses (Eye): lacrymation; Nutritional and Gross Metabolic: weight loss or decreased weight gain; Related to Chronic Data: death
TDLo (Oral-Monkey) 50 mg/kg: female 10-27 day(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear, endocrine system
TDLo (Oral-Monkey) 35 mg/kg: female 16-27 day(s) after conception: Reproductive: Specific Developmental Abnormalities: craniofacial (including nose and tongue)
TDLo (Oral-Monkey) 47,500 µg/kg: female 10-24 day(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear, craniofacial (including nose and tongue)
TDLo (Oral-Monkey) 35 mg/kg: female 16-27 day(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear
TDLo (Oral-Monkey) 70 mg/kg: female 12-25 day(s) after conception: Reproductive: Effects on Embryo or Fetus: other effects to embryo
TDLo (Oral-Monkey) 60 mg/kg: female 16-27 day(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear, craniofacial (including nose and tongue), musculoskeletal system
TDLo (Oral-Monkey) 60 mg/kg: female 16-27 day(s) after conception: Reproductive: Specific Developmental Abnormalities: cardiovascular (circulatory) system, endocrine system
TDLo (Oral-Monkey) 45 mg/kg: female 12-27 day(s) after conception: Reproductive: Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus)
TDLo (Oral-Hamster) 25 mg/kg: female 8 day(s) after conception: Reproductive: Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus); Specific Developmental Abnormalities: Central Nervous System, craniofacial (including nose and tongue)
TDLo (Oral-Hamster) 25 mg/kg: female 8 day(s) after conception: Reproductive: Specific Developmental Abnormalities: musculoskeletal system, gastrointestinal system

TOXICITY DATA (continued):

ISOTRETINOIN (continued):

TDLo (Oral-Hamster) 50 mg/kg: female 8 day(s) after conception: Reproductive: Specific Developmental Abnormalities: eye/ear

TDLo (Intraperitoneal-Rat) 2100 mg/kg/21 days-intermittent: Blood: changes in erythrocyte (RBC) count; Musculoskeletal: other changes; Related to Chronic Data: death

TDLo (Intraperitoneal-Rat) 80 mg/kg: female 8 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System, body wall, cardiovascular (circulatory) system

TDLo (Intraperitoneal-Mouse) 18 mg/kg/18 days-intermittent: Tumorigenic: active as anti-cancer agent

ISOTRETINOIN (continued):

TDLo (Intraperitoneal-Mouse) 200 mg/kg/10 days-intermittent: Tumorigenic: protects against induction of experimental tumors

TDLo (Unreported-Mouse) 150 mg/kg: female 9-11 day(s) after conception: Reproductive: Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus); Specific Developmental Abnormalities: musculoskeletal system

TDLo (Unreported-Mouse) 300 mg/kg: female 9-11 day(s) after conception: Reproductive: Effects on Embryo or Fetus: extra-embryonic structures (e.g., placenta, umbilical cord)

TDLo (Unreported-Mouse) 150 mg/kg: female 10-12 day(s) after conception: Reproductive: Specific Developmental Abnormalities: hepatobiliary system

Mutation Test Systems-Not Otherwise Specified (Human Embryo) 25 µmol/L

Sister Chromatid Exchange (Human Lymphocyte) 50 µmol/L

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

In male and female Fischer 344 rats given oral Isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma (adrenal gland tumors) relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The excipient components are listed by agencies tracking the carcinogenic potential of chemical compounds, as follows:

COLLOIDAL SILICON DIOXIDE: ACGIH TLV-A3 (Confirmed Animal Carcinogen with Unknown Relevance to Humans); IARC-3 (Unclassifiable as to Carcinogenicity in Humans)

FD&C YELLOW # 6: IARC-3 (Unclassifiable as to Carcinogenicity in Humans)

IRON OXIDES (based on CAS# 1309-37-1): ACGIH TLV-A4 (Not Classifiable as a Human Carcinogen); IARC-3 (Unclassifiable as to Carcinogenicity in Humans); MAK-3B [respirable fraction] (Substances for Which in vitro tests or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories.)

TITANIUM DIOXIDE: ACGIH TLV-A4 (Not Classifiable as a Human Carcinogen); IARC-2B (Possibly Carcinogenic to Humans); MAK-3A (Substances Which Cause Concern that They Could Be Carcinogenic for Man But Cannot Be Assessed Conclusively Because of Lack of Data. Substances for which the criteria for classification in Category 4 or 5 are fulfilled, but for which the database is insufficient for the establishment of a MAK value.); NIOSH-Ca (Potential Occupational Carcinogen with No Further Categorization); Notice of Intended Change: ACGIH TLV-A3 (Confirmed Animal Carcinogen with Unknown Relevance to Humans)

No other component 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.

IRRITANCY OF PRODUCT: Inhalation of dusts from this product may be irritating to the respiratory system. Dusts will also be irritating to the eyes.

SENSITIZATION TO THE MATERIAL: Anaphylactic reactions and other allergic reactions have been reported. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extra-cutaneous involvement (including renal) have been reported.

REPRODUCTIVE TOXICITY INFORMATION: There are no adequate and well-controlled studies of Isotretinoin in pregnant women; however, Isotretinoin is a known human teratogen and exposure may cause fetal harm when administered to a pregnant woman. In the workplace, the risk to the fetus should be communicated and the appropriate action should be taken to prevent exposure in accordance with company policy and regulatory requirements. This product is rated by the FDA for therapeutic risk as Pregnancy Risk Category X (refer to Definition of Terms for full category definitions).

Mutagenicity: The Ames test was conducted with Isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 x background) was noted in S. typhimurium TA100 when the assay was conducted with metabolic activation. No dose-response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, S. cerevisiae D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

Embryotoxicity/Teratogenicity:

Human Information: Isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Isotretinoin in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected. Birth defects which have been documented following Isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

Animal Information: Pregnant Golden Syrian hamsters were given a single intubation dose of 0 or 50 mg/kg of Isotretinoin dissolved in Tween 20, on day 8 of pregnancy. The pregnant hamsters were killed at 4, 8, 12, 24, 48, or 72 hr after intubation. Three treated and 3 control litters were studied at each time interval. Embryos and fetuses were prepared for scanning electron microscopic observations and examined. At 4 hr after exposure to Isotretinoin, there was no difference in development between treated and control embryos. Within 8 hr of Isotretinoin treatment, the maxillary and mandibular processes of the treated embryos failed to show the clear swelling of those of controls. Some treated embryos showed complete failure of neural fold apposition and fusion or failure of neural tube closure in the midbrain and hindbrain regions, while controls showed normal closures. The terminal microstomia was not associated with excessive merging or overgrowth of the first arch components. Hypoplasia of the first arch can account for retinoid-induced macrostomia and microstomia.

11. TOXICOLOGICAL INFORMATION (Continued)

REPRODUCTIVE TOXICITY INFORMATION (continued):

Reproductive Toxicity: In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of Isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area). In dogs, testicular atrophy was noted after treatment with oral Isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral Isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Isotretinoin therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose. The drug readily crosses the placenta in animals. It is not known if Isotretinoin is distributed into milk. Because of the potential for serious adverse reactions in nursing infants, nursing mothers should be advised of these effects and the appropriate action should be taken to prevent exposure.

BIOLOGICAL EXPOSURE INDICES: Currently, there are no Biological Exposure Indices (BEIs) determined for the components of this product.

12. ECOLOGICAL INFORMATION

ALL WORK PRACTICES MUST BE AIMED AT ELIMINATING ENVIRONMENTAL CONTAMINATION.

Estimated values for the active ingredient are available from the U.S. Environmental Protection Agency's EPISuite™; however, this information is not provided in this SDS. Contact Teva for more information.

MOBILITY: This product has not been tested for mobility in soils.

PERSISTENCE AND BIODEGRADABILITY: This product has not been tested for persistence and biodegradability.

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

ECOTOXICITY: This product may be harmful or fatal to contaminated plant and animal-life (especially if large quantities are released). This product has not been tested for aquatic toxicity. The active ingredient is acutely toxic to marine organisms. The following toxicity data are available for the active ingredient of this product.

LC_{50} (zebra fish) 96 hours = 0.2 mg/L

EC_{50} (Daphnia magna) 48 hours = 0.1275 mg/L

OTHER ADVERSE EFFECTS: The components of this product are not listed as having ozone depletion potential.

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. This product, if unaltered by use, may be disposed of by treatment at a permitted facility or as advised by your local hazardous waste regulatory authority. All protective clothing, gloves, and disposable materials used in the preparation or handling of this drug should be disposed of in accordance with established hazardous waste disposal procedures. It is the responsibility of the generator to determine at the time of disposal whether the product meets the criteria of a hazardous waste per regulations of the area in which the waste is generated and/or disposed. Incineration is recommended for the product and disposable equipment. Shipment of wastes must be done with appropriately permitted and registered transporters. Reusable equipment should be cleaned with soap and water and thoroughly rinsed.

DISPOSAL CONTAINERS: Waste materials must be placed in and shipped in appropriate 5-gallon or 55-gallon poly or metal waste pails or drums. Permeable cardboard containers are not appropriate and should not be used. Ensure that any required marking or labeling of the containers be done to all applicable regulations.

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

U.S. EPA WASTE NUMBER: Not applicable.

EWC WASTE CODE: 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: 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 material does not meet the criteria of classification of Dangerous Goods, per regulations of Transport Canada.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): This product does not meet the criteria as Dangerous Goods, per rules of IATA.

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

EUROPEAN AGREEMENT CONCERNING THE INTERNATIONAL CARRIAGE OF DANGEROUS GOODS BY ROAD (ADR): This product does not meet the criteria as Dangerous Goods of the United Nations Economic Commission for Europe.

TRANSPORT IN BULK ACCORDING TO THE IBC CODE: Not applicable.

14. TRANSPORTATION INFORMATION (Continued)

ENVIRONMENTAL HAZARDS: This product does not meet the criteria of environmentally hazardous according to the criteria of the UN Model Regulations (as reflected in the IMDG Code, ADR, RID, and ADN); the Isotretinoin component is not specifically listed in Annex III under MARPOL 73/78, however, it meet the criteria of a marine pollutant.

15. REGULATORY INFORMATION

ADDITIONAL U.S. REGULATIONS:

U.S. SARA REPORTING REQUIREMENTS: The components of this product are not 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: There are no specific Threshold Planning Quantities for components of this product. The default Federal SDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) may apply, per 40 CFR 370.20.

U.S. SARA HAZARD CATEGORIES (SECTION 311/312, 40 CFR 370-21): ACUTE: Yes; CHRONIC: No; FIRE: No; REACTIVE: No; SUDDEN RELEASE: No

U.S. CERCLA REPORTABLE QUANTITY (RQ): Not applicable.

U.S. TSCA INVENTORY STATUS: This product is regulated under Food and Drug Administration standards; this product is not subject to requirements under TSCA

OTHER U.S. FEDERAL REGULATIONS: Under the Hazard Communication Standard (HCS), Section (b)(5)(ii) drugs are subject to labeling requirements by the FDA under the Federal Food, Drug and Cosmetic Act and are exempt from labeling provisions of the HCS; this section of the HCS exempts only labeling requirements and not requirements for a Safety Data Sheet for drugs.

CALIFORNIA SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT (PROPOSITION 65): The active ingredient of this product, Isotretinoin is on the California Proposition 65 lists. WARNING! This product contains a compound known to the State of California to cause developmental harm.

ADDITIONAL CANADIAN REGULATIONS:

CANADIAN DSL/NDSL STATUS: This product is regulated by the Therapeutic Products Programme (TPP) of Health Canada; it is exempt from the requirements of CEPA.

OTHER CANADIAN REGULATIONS: Not applicable.

CANADIAN ENVIRONMENTAL PROTECTION ACT (CEPA) PRIORITY SUBSTANCES LISTS: The components of this product are not on the CEPA Priority Substances Lists.

CANADIAN WHMIS CLASSIFICATION and SYMBOLS: 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.

ADDITIONAL EUROPEAN REGULATIONS:

SAFETY, HEALTH, AND ENVIRONMENTAL REGULATIONS/LEGISLATION SPECIFIC FOR THE PRODUCT: Formulated, finished medicinal products for human use, are 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 (Z129.1, Provided to Summarize Occupational Hazard Information): **DANGER!** CONTAINS KNOWN HUMAN TERATOGEN. ALL CONTACT SHOULD BE AVOIDED FOR WOMEN WHO ARE PREGNANT. MAY CAUSE RESPIRATORY SYSTEM, EYE, AND SKIN IRRITATION. MAY BE HARMFUL IF ACCIDENTALLY SWALLOWED. MAY CAUSE ADVERSE EYE, EAR, NERVOUS OR GASTROINTESTINAL SYSTEM EFFECTS. LIMITED EVIDENCE OF ADVERSE EFFECTS ON FERTILITY, BASED ON ANIMAL DATA. COMBUSTIBLE IF EXPOSED TO HIGH TEMPERATURES. CONTAINS COMPOUND THAT CAN CAUSE HARM TO AQUATIC ORGANISMS. Do not take internally without prescription. Avoid contact with skin, eyes, and clothing. Keep container closed. Use gloves, safety glasses, and appropriate respiratory and body protection. **FIRST-AID:** If exposed, seek immediate medical attention. If swallowed, do not induce vomiting. If alert, give victim up to three glasses of water. Never give anything by mouth to an unconscious person. In case of contact, immediately flush skin with copious amounts of warm water for 20 minutes. Remove contaminated clothing and shoes. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. **IN CASE OF FIRE:** Use water fog, dry chemical or CO_2, or alcohol foam. **IN CASE OF SPILL:** Refer to Safety Data Sheet for complete spill response procedures. Spill response should be performed by persons properly trained to do so. Decontaminate area with bleach and detergent solution and triple rinse area. Place spill debris in a suitable container. Refer to SDS 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.

67/548/EEC EU LABELING/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:

Isotretinoin: This is a self-classification:

Classification: Reproductive Toxicity Category 1B, Skin Irritation Category 2, Eye Irritation Category 2B, Specific Target Organ Toxicity (Inhalation-Respiratory System) Single Exposure Category 3, Acute Oral Toxicity Category 5, Aquatic Acute Toxicity Category 1

Hazard Statements: H360Df: May damage the unborn child. Suspected of damaging fertility. H315: Causes skin irritation. H319: Causes serious eye irritation. H335: May cause respiratory irritation. H303: May be harmful if swallowed. H410: Very toxic to aquatic life with long-lasting effects.

16. OTHER INFORMATION (Continued)

CLASSIFICATION FOR COMPONENTS (continued):

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

Colloidal Silicon Dioxide: This is a self-classification.

Classification: Acute Oral Toxicity Category 5

Hazard Statement Codes: H303: May be harmful if swallowed.

Sodium Lauryl Sulfate: This is a self-classification.

Classification: Acute Oral Toxicity Category 4

Hazard Statements: H302: Harmful if swallowed.

All Other Components: No classification has been published or is applicable.

FULL TEXT EU 67/548/EEC:

Isotretinoin: This is a self-classification:

Classification: Reproductive Toxicity Category 2, Reproductive Toxicity Category 3, Irritant, Dangerous for the Environment

Hazard Statements: R61: May cause harm to the unborn child. R62: Possible risk of impaired fertility. R36/37/38: Irritating to eyes, respiratory system and skin. R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Sodium Lauryl Sulfate: This is a self-classification.

Classification: Harmful, Irritant

Risk Phrases: R22: Harmful if swallowed. R36: Irritating to eyes.

All Other Components: No classification has been published or is applicable.

REVISION DETAILS: New.

REFERENCES AND DATA SOURCES: Contact the supplier for information.

METHODS OF EVALUATING INFORMATION FOR THE PURPOSE OF CLASSIFICATION: The criteria of CLP 1272: 2008/2011 and 67/548/EEC were used to classify this material.

PREPARED BY: CHEMICAL SAFETY ASSOCIATES, Inc. • PO Box 1961, Hilo, HI 96721-1961 • (800) 441-3365

DATE OF PRINTING: July 29, 2013

REVISION HISTORY: New.

DEFINITIONS OF TERMS

For information on medical terms used in this SDS consult an on-line database such as Medline Plus: http://www.nlm.nih.gov/medlineplus/druginformation.html.
A large number of abbreviations and acronyms appear on a SDS. Some of these, which are commonly used, include the following:

EXPOSURE LIMITS IN AIR:

CAS #: This is the Chemical Abstract Service Number that uniquely identifies each constituent.
CEILING LEVEL: The concentration that shall not be exceeded during any part of the working exposure.
ACGIH - American Conference of Governmental Industrial Hygienists, a professional association which establishes exposure limits. **TLV -** Threshold Limit Value - an airborne concentration of a substance which represents conditions under which it is generally believed that nearly all workers may be repeatedly exposed without adverse effect. The duration must be considered, including the 8-hour Time Weighted Average **(TWA)**, the 15-minute Short Term Exposure Limit, and the instantaneous Ceiling Level **(C)**. Skin absorption effects must also be considered.
DFG MAK Germ Cell Mutagen Categories: 1: Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed humans. **2:** Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed mammals. **3A:** Substances which have been shown to induce genetic damage in germ cells of human of animals, or which produce mutagenic effects in somatic cells of mammals *in vivo* and have been shown to reach the germ cells in an active form. **3B:** Substances which are suspected of being germ cell mutagens because of their genotoxic effects in mammalian somatic cell *in vivo*; in exceptional cases, substances for which there are no *in vivo* data, but which are clearly mutagenic *in vitro* and structurally related to known in vivo mutagens. **4:** Not applicable (Category 4 carcinogenic substances are those with non-genotoxic mechanisms of action. By definition, germ cell mutagens are genotoxic. Therefore, a Category 4 for germ cell mutagens cannot apply. At some time in the future, it is conceivable that a Category 4 could be established for genotoxic substances with primary targets other than DNA [e.g. purely aneugenic substances] if research results make this seem sensible.) **5:** Germ cell mutagens, the potency of which is considered to be so low that, provided the MAK value is observed, their contribution to genetic risk for humans is expected not to be significant.
DFG MAK Pregnancy Risk Group Classification: Group A: A risk of damage to the developing embryo or fetus has been unequivocally demonstrated. Exposure of pregnant women can lead to damage of the developing organism, even when MAK and BAT (Biological Tolerance Value for Working Materials) values are observed. **Group B:** Currently available information indicates a risk of damage to the developing embryo or fetus must be considered to be probable. Damage to the developing organism cannot be excluded when pregnant women are exposed, even when MAK and BAT values are observed. **Group C:** There is no reason to fear a risk of damage to the developing embryo or fetus when MAK and BAT values are observed. **Group D:** Classification in one of the groups A-C is not yet possible because, although the data available may indicate a trend, they are not sufficient for final evaluation.
IDLH-Immediately Dangerous to Life and Health: This level represents a concentration from which one can escape within 30-minutes without suffering escape-preventing or permanent injury.
LOQ: Limit of Quantitation.
MAK: Federal Republic of Germany Maximum Concentration Values in the workplace.
NE: Not Established. When no exposure guidelines are established, an entry of NE is made for reference.
NIC: Notice of Intended Change.
NIOSH CEILING: The exposure that shall not be exceeded during any part of the workday. If instantaneous monitoring is not feasible, the ceiling shall be assumed as a 15-minute TWA exposure (unless otherwise specified) that shall not be exceeded at any time during a workday.
NIOSH RELs: NIOSH's Recommended Exposure Limits.
PEL-Permissible Exposure Limit: OSHA's Permissible Exposure Limits. This exposure value means exactly the same as a TLV, except that it is enforceable by OSHA. The OSHA Permissible Exposure Limits are based in the 1989 PELs and the June, 1993 Air Contaminants Rule (Federal Register: 58: 35338-35351 and 58: 40191). Both the current PELs and the vacated PELs are indicated. The phrase, "Vacated 1989 PEL," is placed next to the PEL that was vacated by Court Order.
SKIN: Used when a there is a danger of cutaneous absorption.
STEL-Short Term Exposure Limit: Short Term Exposure Limit, usually a 15-minute time-weighted average (TWA) exposure that should not be exceeded at any time during a workday, even if the 8-hr TWA is within the TLV-TWA, PEL-TWA or REL-TWA.
TLV-Threshold Limit Value: An airborne concentration of a substance that represents conditions under which it is generally believed that nearly all workers may be repeatedly exposed without adverse effect. The duration must be considered, including the 8-hour.
TWA-Time Weighted Average: Time Weighted Average exposure concentration for a conventional 8-hr (TLV, PEL) or up to a 10-hr (REL) workday and a 40-hr workweek.

HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS:

This rating system was developed by the National Paint and Coating Association and has been adopted by industry to identify the degree of chemical hazards.
HEALTH HAZARD: 0 (Minimal Hazard: No significant health risk, irritation of skin or eyes not anticipated. *Skin Irritation*: Essentially non-irritating. PII or Draize = "0". *Eye Irritation*: Essentially non-irritating, or minimal effects which clear in < 24 hours [e.g. mechanical irritation]. Draize = "0". *Oral Toxicity LD_{50} Rat*: < 5000 mg/kg. *Dermal Toxicity LD_{50}Rat or Rabbit*: < 2000 mg/kg. *Inhalation Toxicity 4-hrs LC_{50} Rat*: < 20 mg/L.); **1** (Slight Hazard: Minor reversible Injury may occur; slightly or mildly irritating. *Skin Irritation*: Slightly or mildly irritating. *Eye Irritation*: Slightly or mildly irritating. *Oral Toxicity LD_{50} Rat*: > 500-5000 mg/kg. *Dermal Toxicity LD_{50}Rat or Rabbit*: > 1000-2000 mg/kg. *Inhalation Toxicity LC_{50}* 4-hrs *Rat*: > 2-20 mg/L); **2** (Moderate Hazard: Temporary or transitory injury may occur. *Skin Irritation*: Moderately irritating; primary irritant; sensitizer. PII or Draize > 0, < 5. *Eye Irritation*: Moderately to severely irritating and/or corrosive; reversible corneal opacity; corneal involvement or irritation clearing in 8-21 days. Draize > 0, ≤ 25. *Oral Toxicity LD_{50} Rat*: > 50-500 mg/kg. *Dermal Toxicity LD_{50}Rat or Rabbit*: > 200-1000 mg/kg. *Inhalation Toxicity LC_{50} 4-hrs Rat*: > 0.5-2 mg/L.); **3** (Serious Hazard: Major injury likely unless prompt action is taken and medical treatment is given; high level of toxicity; corrosive. *Skin Irritation*: Severely irritating and/or corrosive; may destroy dermal tissue, cause skin burns, dermal necrosis. PII or Draize > 5-8 with destruction of tissue. *Eye Irritation*: Corrosive, irreversible destruction of ocular tissue; corneal involvement or irritation persisting for more than 21 days. Draize > 80 with effects irreversible in 21 days. *Oral Toxicity LD_{50} Rat*: > 1-50 mg/kg. *Dermal Toxicity LD_{50}Rat or Rabbit*: > 20-200 mg/kg. *Inhalation Toxicity LC_{50} 4-hrs Rat*: > 0.05-0.5 mg/L.); **4** (Severe Hazard: Life-threatening; major or permanent damage may result from single or repeated exposure. *Skin Irritation*: Not appropriate. Do not rate as a "4", based on skin irritation alone. *Eye Irritation*: Not appropriate. Do not rate as a "4", based on eye irritation alone. *Oral Toxicity LD_{50} Rat*: ≤ 1 mg/kg. *Dermal Toxicity LD_{50}Rat or Rabbit*: ≤ 20 mg/kg. *Inhalation Toxicity LC_{50} 4-hrs Rat*: ≤ 0.05 mg/L).
FLAMMABILITY HAZARD: 0 (Minimal Hazard-Materials that will not burn in air when exposure to a temperature of 815.5°C [1500°F] for a period of 5 minutes.); **1** (Slight Hazard-Materials that must be pre-heated before ignition can occur. Material require considerable pre-heating, under all ambient temperature conditions before ignition and combustion can occur, Including:

HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS (continued):

FLAMMABILITY HAZARD (continued): 1 (continued): Materials that will burn in air when exposed to a temperature of 815.5°C (1500°F) for a period of 5 minutes or less; Liquids, solids and semisolids having a flash point at or above 93.3°C [200°F] (e.g. OSHA Class IIIB, or; Most ordinary combustible materials [e.g. wood, paper, etc.]; **2** (Moderate Hazard-Materials that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur. Materials in this degree would not, under normal conditions, form hazardous atmospheres in air, but under high ambient temperatures or moderate heating may release vapor in sufficient quantities to produce hazardous atmospheres in air, Including: Liquids having a flash-point at or above 37.8°C [100°F]; Solid materials in the form of course dusts that may burn rapidly but that generally do not form explosive atmospheres; Solid materials in a fibrous or shredded form that may burn rapidly and create flash fire hazards (e.g. cotton, sisal, hemp; Solids and semisolids that readily give off flammable vapors.); **3** (Serious Hazard-Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials in this degree produce hazardous atmospheres with air under almost all ambient temperatures, or, unaffected by ambient temperature, are readily ignited under almost all conditions, including: Liquids having a flash point below 22.8°C [73°F] and having a boiling point at or above 38°C [100°F] and below 37.8°C [100°F] [e.g. OSHA Class IB and IC]; Materials that on account of their physical form or environmental conditions can form explosive mixtures with air and are readily dispersed in air [e.g., dusts of combustible solids, mists or droplets of flammable liquids]; Materials that burn extremely rapidly, usually by reason of self-contained oxygen [e.g. dry nitrocellulose and many organic peroxides]); **4** (Severe Hazard-Materials that will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air, and which will burn readily, including: Flammable gases; Flammable cryogenic materials; Any liquid or gaseous material that is liquid while under pressure and has a flash point below 22.8°C [73°F] and a boiling point below 37.8°C [100°F] [e.g. OSHA Class IA; Material that ignite spontaneously when exposed to air at a temperature of 54.4°C [130°F] or below [e.g. pyrophoric]).
PHYSICAL HAZARD: 0 (*Water Reactivity*: Materials that do not react with water. *Organic Peroxides*: Materials that are normally stable, even under fire conditions and will not react with water. *Explosives*: Substances that are Non-Explosive. Unstable *Compressed Gases*: No Rating. *Pyrophorics*: No Rating. *Oxidizers*: No "0" rating allowed. *Unstable Reactives*: Substances that will not polymerize, decompose, condense or self-react.); **1** (*Water Reactivity*: Materials that change or decompose upon exposure to moisture. *Organic Peroxides*: Materials that are normally stable, but can become unstable at high temperatures and pressures. These materials may react with water, but will not release energy. *Explosives*: Division 1.5 & 1.6 substances that are very insensitive explosives or that do not have a mass explosion hazard. *Compressed Gases*: Pressure below OSHA definition. *Pyrophorics*: No Rating. *Oxidizers*: Packaging Group III; Solids: any material that in either concentration tested, exhibits a mean burning time less than or equal to the mean burning time of a 3:7 potassium bromate/cellulose mixture and the criteria for Packing Group I and II are not met. Liquids: any material that exhibits a mean pressure rise time less than or equal to the pressure rise time of a 1:1 nitric acid (65%)/cellulose mixture and the criteria for Packing Group I and II are not met. *Unstable Reactives*: Substances that may decompose, condense or self-react, but only under conditions of high temperature and/or pressure and have little or no potential to cause significant heat generation or explosive hazard. Substances that readily undergo hazardous polymerization in the absence of inhibitors.); **2** *Water Reactivity*: Materials that may react violently with water. *Organic Peroxides*: Materials that, in themselves, are normally unstable and will readily undergo violent chemical change, but will not detonate. These materials may also react violently with water. *Explosives*: Division 1.4 – Explosive substances where the explosive effect are largely confined to the package and no projection of fragments of appreciable size or range are expected. An external fire must not cause virtually instantaneous explosion of almost the entire contents of the package. *Compressed Gases*: Pressurized and meet OSHA definition but < 514.7 psi absolute at 21.1°C (70°F) [500 psig]. *Pyrophorics*: No Rating. *Oxidizers*: Packing Group II Solids: any material that, either in concentration tested, exhibits a mean burning time of less than or equal to the mean burning time of a 2:3 potassium bromate/cellulose mixture and the criteria for Packing Group I are not met. Liquids: any material that exhibits a mean pressure rise time less than or equal to the pressure rise of a 1:1 aqueous sodium chlorate solution (40%)/cellulose mixture and the criteria for Packing Group I are not met. *Unstable Reactives*: Substances that may polymerize, decompose, condense, or self-react at ambient temperature and/or pressure, but have a low potential for significant heat generation or explosion. Substances that readily form peroxides upon exposure to air or oxygen at room temperature); **3** (*Water Reactivity*: Materials that may form explosive reactions with water. *Organic Peroxides*: Materials that are capable of detonation or explosive reaction, but require a strong initiating source, or must be heated under confinement before initiation; or materials that react explosively with water. *Explosives*: Division 1.2 – Explosive substances that have a fire hazard and either a minor blast hazard or a minor projection hazard or both, but do not have a mass explosion hazard. *Compressed Gases*: Pressure ≥ 514.7 psi absolute at 21.1°C (70°F) [500 psig]. *Pyrophorics*: No Rating. *Oxidizers*: Packing Group I Solids: any material that, in either concentration tested, exhibits a mean burning time less than the mean burning time of a 3.:2 potassium bromate/cellulose mixture. Liquids: Any material that spontaneously ignites when mixed with cellulose in a 1:1 ratio, or which exhibits a mean pressure rise time less than the pressure rise time of a 1:1 perchloric acid (50%)/cellulose mixture. *Unstable Reactives*: Substances that may polymerize, decompose, condense or self-react at ambient temperature and/or pressure and have a moderate potential to cause significant heat generation or explosion.); **4** (*Water Reactivity*: Materials that react explosively with water without requiring heat or confinement. *Organic Peroxides*: Materials that are readily capable of detonation or explosive decomposition at normal temperature and pressures. *Explosives*: Division 1.1 & 1.2-explosive substances that have a mass explosion hazard or have a projection hazard. A mass explosion is one that affects almost the entire load instantaneously. *Compressed Gases*: No Rating. *Pyrophorics*: Add to the definition of Flammability "4". *Oxidizers*: No "4" rating. *Unstable Reactives*: Substances that may polymerize, decompose, condense or self-react at ambient temperature and/or pressure and have a high potential to cause significant heat generation or explosion).

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS:

HEALTH HAZARD: **0** Materials that, under emergency conditions, would offer no hazard beyond that of ordinary combustible materials. Gases and vapors with an LC_{50} for acute inhalation toxicity greater than 10,000 ppm. Dusts and mists with an LC_{50} for acute inhalation toxicity greater than 200 mg/L. Materials with an LD_{50} for acute dermal toxicity greater than 2000 mg/kg. Materials with an LD_{50} for acute oral toxicity greater than 2000 mg/kg. Materials essentially non-irritating to the respiratory tract, eyes, and skin. **1** Materials that, under emergency conditions, can cause significant irritation. Gases and vapors with an LC_{50} for acute inhalation toxicity greater than 5,000 ppm but less than or equal to 10,000 ppm. Dusts and mists with an LC_{50} for acute inhalation toxicity greater than 10 mg/L but less than or equal to 200 mg/L. Materials with an LD_{50} for acute dermal toxicity greater than 1000 mg/kg but less than or equal to 2000 mg/kg. Materials that slightly to moderately irritate the respiratory tract, eyes and skin. Materials with an LD_{50} for acute oral toxicity greater than 500 mg/kg but less than or equal to 2000 mg/kg.

DEFINITIONS OF TERMS (Continued)

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

HEALTH HAZARD (continued): **2** Materials that, under emergency conditions, can cause temporary incapacitation or residual injury. Gases with an LC_{50} for acute inhalation toxicity greater than 3,000 ppm but less than or equal to 5,000 ppm. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC_{50} for acute inhalation toxicity, if its LC_{50} is less than or equal to 5000 ppm and that does not meet the criteria for either degree of hazard 3 or degree of hazard 4. Dusts and mists with an LC_{50} for acute inhalation toxicity greater than 2 mg/L but less than or equal to 10 mg/L. Materials with an LD_{50} for acute dermal toxicity greater than 200 mg/kg but less than or equal to 1000 mg/kg. Compressed liquefied gases with boiling points between -30°C (-22°F) and -55°C (-66.5°F) that cause severe tissue damage, depending on duration of exposure. Materials that are respiratory irritants. Materials that cause severe, but reversible irritation to the eyes or are lachrymators. Materials that are primary skin irritants or sensitizers. Materials whose LD_{50} for acute oral toxicity is greater than 50 mg/kg but less than or equal to 500 mg/kg. Dusts and mists with an LC_{50} for acute inhalation toxicity greater than 10 mg/L but less than or equal to 200 mg/L. Materials with an LD_{50} for acute dermal toxicity greater than 1000 mg/kg but less than or equal to 2000 mg/kg. Materials that slightly to moderately irritate the respiratory tract, eyes and skin. Materials with an LD_{50} for acute oral toxicity greater than 500 mg/kg but less than or equal to 2000 mg/kg. **3** (materials that, under emergency conditions, can cause serious or permanent injury): Gases and vapors whose LC_{50} for acute inhalation toxicity is greater than 1,000 ppm but less than or equal to 3,000 ppm. Dusts and mists whose LC_{50} for acute inhalation toxicity is greater than 0.5 mg/L but less than or equal to 2 mg/L. Materials whose LD_{50} for acute dermal toxicity is greater than 40 mg/kg but less than or equal to 200 mg/kg. Materials whose LD_{50} for acute oral toxicity is greater than 5 mg/kg but less than or equal to 50 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC_{50} for acute inhalation toxicity, if its LC_{50} is less than or equal to 3000 ppm and that does not meet the criteria for degree of hazard 4. Compressed liquefied gases with boiling points between -30°C (-22°F) and -55°C (-66.5°F) that cause frostbite and irreversible tissue damage. Materials that are respiratory irritants. Cryogenic gases that cause frostbite and irreversible tissue damage. Materials that are corrosive to the respiratory tract. Materials that are corrosive to the eyes or cause irreversible corneal opacity. Materials that are corrosive to the skin. **4** (materials that, under emergency conditions, can be lethal): Gases and vapors whose LC_{50} for acute inhalation toxicity less than or equal to 1,000 ppm. Dusts and mists whose LC_{50} for acute inhalation toxicity is less than or equal to 0.5 mg/L. Materials whose LD_{50} for acute dermal toxicity is less than or equal to 40 mg/kg. Materials whose LD_{50} for acute oral toxicity is less than or equal to 5 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC_{50} for acute inhalation toxicity, if its LC_{50} is less than or equal to 1000 ppm.

FLAMMABILITY HAZARD: **0** Materials that will not burn under typical fire conditions, including intrinsically noncombustible materials such as concrete, stone, and sand: Materials that will not burn in air when exposed to a temperature of 816°C (1500°F) for a period of 5 minutes in according with Annex D. **1** Materials that must be preheated before ignition can occur. Materials in this degree require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur: Materials that will burn in air when exposed to a temperature of 816°C (1500°F) for a period of 5 minutes in accordance with Annex D. Liquids, solids and semisolids having a flash point at or above 93.4°C (200°F) (i.e. Class IIIB liquids). Liquids with a flash point greater than 35°C (95°F) that do not sustain combustion when tested using the *Method of Testing for Sustained Combustibility*, per 49 CFR 173, Appendix H or the UN *Recommendation on the Transport of Dangerous Goods, Model Regulations* (current edition) and the related *Manual of Tests and Criteria* (current edition). Liquids with a flash point greater than 35°C (95°F) in a water-miscible solution or dispersion with a water non-combustible liquid/solid content of more than 85 percent by weight. Liquids that have no fire point when tested by ASTM D 92 Standard Test Method for Flash and Fire Points by Cleveland Open Cup, up to a boiling point of the liquid or up to a temperature at which the sample being tested shows an obvious physical change. Combustible pellets with a representative diameter of greater than 2 mm (10 mesh). Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed up flash point of the solvent. Most ordinary combustible materials. **2** Materials that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur. Materials in this degree would not under normal conditions form hazardous atmospheres with air, but under high ambient temperatures or under moderate heating could release vapor in sufficient quantities to produce hazardous atmospheres with air: Liquids having a flash point at or above 37.8°C (100°F) and below 93.4°C (200°F) (i.e. Class II and Class IIIA liquids.) Solid materials in the form of powders or coarse dusts of representative diameter between 420 microns (40 mesh) and 2 mm (10 mesh) that burn rapidly but that generally do not form explosive mixtures in air. Solid materials in fibrous or shredded form that burn rapidly and create flash fire hazards, such as cotton, sisal and hemp. Solids and semisolids that readily give off flammable vapors. Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent. **3** Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials in this degree produce hazardous atmospheres with air under almost all ambient temperatures or, though unaffected by ambient temperatures, are readily ignited under almost all conditions: Liquids having a flash point below 22.8°C (73°F) and having a boiling point at or above 37.8°C (100°F) and those liquids having a flash point at or above 22.8°C (73°F) and below 37.8°C (73°F) and below 37.8°C (100°F) (i.e. Class IB and IC liquids). Materials that, on account of their physical form or environmental conditions, can form explosive mixtures with air and are readily dispersed in air. Flammable or combustible dusts with a representative diameter less than 420 microns (40 mesh). Materials that burn with extreme rapidity, usually by reason of self-contained oxygen (e.g. dry nitrocellulose and many organic peroxides). Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent. **4** Materials that will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air and will burn readily: Flammable gases. Flammable cryogenic materials. Any liquid or gaseous materials that is liquid while under pressure and has a flash point below 22.8°C (73°F) and a boiling point below 37.8°C (100°F) (i.e. Class IA liquids). Materials that ignite when exposed to air, Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent.

INSTABILITY HAZARD: **0** Materials that in themselves are normally stable, even under fire conditions: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) below 0.01 W/mL. Materials that do not exhibit an exotherm at temperatures less than or equal to 500°C (932°F) when tested by differential scanning calorimetry. **1** Materials that in themselves are normally stable, but that can become unstable at elevated temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 0.01 W/mL and below 10 W/mL.

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

INSTABILITY HAZARD (continued): **2** Materials that readily undergo violent chemical change at elevated temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 10 W/mL and below 100W/mL. **3** Materials that in themselves are capable of detonation or explosive decomposition or explosive reaction, but that require a strong initiating source or that must be heated under confinement before initiation: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 100 W/mL and below 1000 W/mL. Materials that are sensitive to thermal or mechanical shock at elevated temperatures and pressures. **4** Materials that in themselves are readily capable of detonation or explosive decomposition or explosive reaction at normal temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) of 1000 W/mL or greater. Materials that are sensitive to localized thermal or mechanical shock at normal temperatures and pressures.

FLAMMABILITY LIMITS IN AIR:

Much of the information related to fire and explosion is derived from the **N**ational **F**ire **P**rotection **A**ssociation (**NFPA**). Flash Point - Minimum temperature at which a liquid gives off sufficient vapors to form an ignitable mixture with air. Autoignition Temperature: The minimum temperature required to initiate combustion in air with no other source of ignition. LEL - the lowest percent of vapor in air, by volume, that will explode or ignite in the presence of an ignition source. UEL - the highest percent of vapor in air, by volume, that will explode or ignite in the presence of an ignition source.

TOXICOLOGICAL INFORMATION:

Human and Animal Toxicology: Possible health hazards as derived from human data, animal studies, or from the results of studies with similar compounds are presented. Definitions of some terms used in this section are: **LD_{50}** - Lethal Dose (solids & liquids) which kills 50% of the exposed animals; **LC_{50}** - Lethal Concentration (gases) which kills 50% of the exposed animals; **ppm** concentration expressed in parts of material per million parts of air or water; **mg/m^3** concentration expressed in weight of substance per volume of air; **mg/kg** quantity of material, by weight, administered to a test subject, based on their body weight in kg. Other measures of toxicity include **TDLo**, the lowest dose to cause a symptom and **TCLo** the lowest concentration to cause a symptom; **TDo**, **LDLo**, and **LDo**, or **TC**, **TCo**, **LCLo**, and **LCo**, the lowest dose (or concentration) to cause lethal or toxic effects. **Cancer Information:** The sources are: **IARC** - the International Agency for Research on Cancer; **NTP** - the National Toxicology Program, **RTECS** - the Registry of Toxic Effects of Chemical Substances, **OSHA** and **CAL/OSHA**. IARC and NTP rate chemicals on a scale of decreasing potential to cause human cancer with rankings from 1 to 4. Subrankings (2A, 2B, etc.) are also used. **Other Information: BEI** - ACGIH Biological Exposure Indices, represent the levels of determinants which are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the TLV.

REPRODUCTIVE TOXICITY INFORMATION:

A mutagen is a chemical which causes permanent changes to genetic material (DNA) such that the changes will propagate through generational lines. An embryotoxin is a chemical which causes damage to a developing embryo (i.e. within the first eight weeks of pregnancy in humans), but the damage does not propagate across generational lines. A teratogen is a chemical which causes damage to a developing fetus, but the damage does not propagate across generational lines. A reproductive toxin is any substance which interferes in any way with the reproductive process.

United States FDA Pharmaceutical Pregnancy Categories: Pregnancy Category A: Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). **Pregnancy Category B:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. **Pregnancy Category C:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Pregnancy Category D:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Pregnancy Category X:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. **Pregnancy Category N:** FDA has not classified this drug.

ECOLOGICAL INFORMATION:

EC is the effect concentration in water. **BCF** = Bioconcentration Factor, which is used to determine if a substance will concentrate in lifeforms which consume contaminated plant or animal matter. **TL_m** = median threshold limit; Coefficient of Oil/Water Distribution is represented by **log K_{ow}** or **log K_{oc}** and is used to assess a substance's behavior in the environment.

REGULATORY INFORMATION:

U.S. and CANADA:

ACGIH: American Conference of Governmental Industrial Hygienists, a professional association which establishes exposure limits.

This section explains the impact of various laws and regulations on the material. **EPA** is the U.S. Environmental Protection Agency. **NIOSH** is the National Institute of Occupational Safety and Health, which is the research arm of the U.S. **O**ccupational **S**afety and **H**ealth **A**dministration (**OSHA**). **WHMIS** is the Canadian Workplace Hazardous Materials Information System. **DOT** and **TC** are the U.S. Department of Transportation and the Transport Canada, respectively. Superfund Amendments and Reauthorization Act **(SARA)**; the Canadian Domestic/Non-Domestic Substances List **(DSL/NDSL)**; the U.S. Toxic Substance Control Act **(TSCA)**; Marine Pollutant status according to the **DOT**; the Comprehensive Environmental Response, Compensation, and Liability Act **(CERCLA or Superfund)**; and various state regulations. This section also includes information on the precautionary warnings which appear on the material's package label. **OSHA** - U.S. Occupational Safety and Health Administration.

EUROPEAN and INTERNATIONAL:

The DFG: This is the Federal Republic of Germany's Occupation Health Agency, similar to the U.S. OSHA. **EU** is the European Community (formerly known as the **EEC,** European Economic Community). **EINECS:** This is the European Inventory of Now-Existing Chemical Substances. The **ARD** is the European Agreement Concerning the International Carriage of Dangerous Goods by Road and the **RID** are the International Regulations Concerning the Carriage of Dangerous Goods by Rail. **AICS** is the Australian Inventory of Chemical Substances.