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 product and what do I need to know in an emergency?*

1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE

IDENTIFICATION of the SUBSTANCE or PREPARATION:

TRADE NAME:	**TOPOTECAN INJECTION**
CHEMICAL NAME:	Active Ingredient: (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7] indolizino [1,2-b]quinoline-3,14-(4H ,12H)-dione hydrochloride
CHEMICAL CLASS:	Active Ingredient: Semi-Synthetic Derivative of natural alkaloid Camptothecin
THERAPEUTIC CLASS:	Topoisomerase Inhibitor
RELEVANT USE of the SUBSTANCE:	Human Pharmaceutical
USES ADVISED AGAINST:	Other than Relevant Use

COMPANY/UNDERTAKING IDENTIFICATION:

SUPPLIER NAME	Sagent Pharmaceuticals
ADDRESS:	1901 N. Roselle Road Schaumburg, Illinois 60195 Phone: 847-908-1600
Emergency phone number	United States/Canada/Puerto Rico: 1-800/424-9300 (Chemtrec) [24-hrs]
U.S. MANUFACTURER'S NAME:	**TEVA**
ADDRESS:	1090 Horsham Road North Wales, PA 19454
BUSINESS PHONE:	215-591-3000 [08:00 AM --> 05:00 PM]
EUROPEAN CONTACT:	**TEVA/TAPI**
ADDRESS:	Sicor sri-Via Terrazzano 77-20017 Cho (MI), Italy
BUSINESS PHONE:	+39 02 93197 306 [08:00 AM --> 05:00 PM]
EMAIL:	TevaSDSRequest@tevapharm.com
DATE OF PREPARATION:	September 25, 2014
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 all applicable EU Directives through EC 1907: 2006, the European Union CLP EC 1272/2008 and 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 is a clear, light yellow to greenish solution, odorless solution. **Health Hazards:** WARNING! THIS PRODUCT CONTAINS A CYTOTOXIC AGENT. EXPOSURE BY ALL ROUTES OF EXPOSURE MUST BE AVOIDED In the workplace, this product may cause irritation by all routes of exposure. May be harmful if swallowed. In therapeutic use this product can cause bone marrow suppression which can lead to serious infection or death. The most common non-hematologic adverse reactions were nausea, alopecia, vomiting, sepsis or pyrexia/infection with neutropenia, diarrhea, constipation, fatigue, and fever. Can cause fetal harm. Hypersensitivity reactions have been reported from therapeutic use. Suspected of carcinogenic and mutagenic effects, based on animal and microorganism test data. 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 solution is not flammable or combustible. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds, including carbon and nitrogen oxides and hydrogen chloride. **Reactivity Hazards:** This product is not reactive. **Environmental Hazards:** Large quantities released to the aquatic and terrestrial environment may have an adverse effect. No data are available. **Emergency Considerations:** Emergency responders should wear appropriate protection for the situation to which they respond.

3. COMPOSITION and INFORMATION ON INGREDIENTS

NOTE: In formulation, trace amounts of sodium hydroxide and sulfuric acid may be used for pH adjustment. No residue of these materials are left in finished product and so hazards are not addressed in this SDS.

CHEMICAL NAME	CAS #	EINECS #	% w/v	LABEL ELEMENTS EU Classification (67/548/EEC) GHS and EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements
ACTIVE INGREDIENT				
Topotecan Hydrochloride	119413-54-6	Not Listed	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Reproductive Toxicity Cat. 2, Reproductive Toxicity Cat. 3, Germ Cell Mutagenicity Cat. 3, Carcinogenic Cat. 3 Risk Phrase Codes: R61, R62, R68, R40 Hazard Symbols: T GHS and EU 1272/2008 Classification: Reproductive Toxicity Cat. 1B, Germ Cell Mutagenicity Cat. 2, Carcinogenic Cat. 2, Acute Oral Toxicity Cat. 5 Hazard Codes: H360Df, H341, H351, H303 Hazard Symbol/Pictogram: GHS06, GHS08
EXCIPIENTS				
Mannitol	69-65-8	200-711-8	Proprietary	EU (67/548/EEC): No Classification Applicable EU/GHS 1272/2008: No Classification Applicable
Tartaric Acid	87-69-4	201-766-0	Proprietary	EU (67/548/EEC): No Classification Applicable EU/GHS 1272/2008: No Classification Applicable
Water	7732-18-5	231-791-2	Balance	EU (67/548/EEC): No Classification Applicable EU/GHS 1272/2008: No Classification Applicable

See Section 16 for full classification information of this product.

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. Take a copy of this SDS to health professional with victim.

SKIN OR EYE EXPOSURE: Flush affected area with water for 20 minutes.

INHALATION: Remove victim to fresh air.

INGESTION: CALL PHYSICIAN OR POISON CONTROL CENTER. Give victim up to three glasses of water. Do not induce vomiting.

INJECTION: Flush injection site with water.

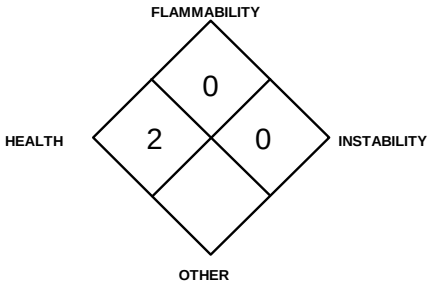
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:
Pre-existing bone marrow disease or insufficiency, interstitial lung disease, blood disorders and those disorders to target organs described in Section 11 may be aggravated upon exposure to this product.

INDICATION OF IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT IF NEEDED: Treat symptoms and eliminate exposure. Persons developing hypersensitivity reactions should receive medical attention. No specific antidote is available.

5. FIRE-FIGHTING MEASURES

FLASH POINT: Not applicable.
AUTOIGNITION TEMPERATURE: Not applicable.
FLAMMABLE LIMITS (in air by volume, %): Not applicable.
FIRE EXTINGUISHING MEDIA: All types acceptable.
UNSUITABLE FIRE EXTINGUISHING MEDIA: None known.
SPECIAL HAZARDS ARISING FROM THE PRODUCT: This solution is not flammable or combustible. When involved in a fire, this product may decompose and produce irritating vapors and toxic compounds (including carbon and nitrogen oxides).
Explosion Sensitivity to Mechanical Impact: Not applicable.
Explosion Sensitivity to Static Discharge: Not applicable.
SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS: Firefighters must wear Self-Contained Breathing Apparatus and full protective equipment. If possible, prevent runoff water from entering storm drains, bodies of water, or other environmentally sensitive areas

NFPA RATING



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

6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES: Spill kits should be kept in or near material handling areas. Avoid generating airborne aerosols of this product during spill response procedures.
PROTECTIVE EQUIPMENT:

Small Spills: Nitrile or other appropriate gloves, labcoat or other protective clothing and eye protection.

Large Spills: Double nitrile or other appropriate gloves, protective clothing (i.e., disposable Tyvek coveralls) and eye/face protection. When there is any danger of airborne aerosols being generated, use a full-face respirator equipped with a High Efficiency Particulate (HEPA) filter or Self-Contained Breathing Apparatus (SCBA).

METHODS FOR CLEAN-UP AND CONTAINMENT:

Small Spills: Clean with wet absorbent pads and dispose of properly. Decontaminate the spill area using a bleach and detergent solution and rinse with clean water.

Large Spills: Restrict access to the spill areas. Clean with wet absorbent pads and dispose of properly. Decontaminate the spill area using a bleach and detergent solution and rinse with clean water. Do not apply chemical in-activators as they may produce hazardous by-products.

All Spills: Place all spill residues in an appropriate, labeled container and seal. 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.

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

7. HANDLING and STORAGE

NOTE: Consistent with the OSHA Bloodborne Pathogen regulation (29 CFR 1910.1030), observe Universal Precautions while using this product. Place used or product-contaminated hypodermic needles and syringes in a rigid “Sharps” container. Dispose of materials in accordance with regulations.
PRECAUTIONS FOR SAFE HANDLING: THIS PRODUCT CONTAINS A CYTOTOXIC AGENT. ALL WORK PRACTICES MUST BE DESIGNED TO REDUCE HUMAN EXPOSURE TO THE LOWEST LEVEL. All employees who handle this material should be thoroughly trained to handle it safely. Do not eat or drink while handling this material. Ensure this material is used with adequate ventilation. Appropriate personal protective equipment must be worn (see Section 8, Exposure Controls - Personal Protection). Good hygiene practices must be in place for workers handling this material, including change facilities and a work place clothing program.
CONDITIONS FOR SAFE STORAGE: Containers of this material must be properly labeled. Recommended Storage Temperature: 2-8°C (35-46°F). Empty containers may contain residual material; therefore, empty containers should be handled with care and disposed of properly.
SPECIFIC END USE(S): This is a human pharmaceutical.
PROTECTIVE PRACTICES DURING MAINTENANCE OF CONTAMINATED EQUIPMENT: When cleaning non-disposable equipment, wear appropriate personal protective equipment.

8. EXPOSURE CONTROLS - PERSONAL PROTECTION

EXPOSURE LIMITS/CONTROL PARAMETERS:

VENTILATION AND ENGINEERING CONTROLS: 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.

WORKPLACE EXPOSURE LIMITS/CONTROL PARAMETERS: There are no occupational exposure limits for this product. This is a cytotoxic agent. All work place practices must be designed to reduce human exposure. Information on exposure limits for the active ingredient can be obtained from Teva.

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: None needed for normal handling of this product. For large spill response or tasks involving generation of aerosols, use the appropriate Self-Contained Breathing Apparatus (SCBA) pressure-demand or other positive-pressure mode.

EYE PROTECTION: Wear splash goggles or safety glasses as appropriate for the task.

HAND PROTECTION: Wear nitrile or other appropriate gloves to avoid contact and/or absorption of the product. Use double gloves for spill response.

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

9. PHYSICAL and CHEMICAL PROPERTIES

The following information is available for the product:

FORM: Liquid.

COLOR: Clear, light yellow to greenish.

pH: 2.0-2.5 (adjusted with trace sulfuric acid or sodium hydroxide, as appropriate and if necessary)

HOW TO DETECT THIS SUBSTANCE (identification properties): The appearance may be a distinguishing characteristic to identify this product in event of a spill.

The following information is available for the active ingredient:

FORM: Powdered solid.

COLOR: Light yellow to greenish.

MOLECULAR WEIGHT: 457.91

MOLECULAR FORMULA: $C_{23}H_{23}N_3O_5 \bullet HCl$

ODOR: Odorless.

ODOR THRESHOLD: Odorless.

BOILING POINT @ 760 mmHg: 782.9°C (1441.2°F) [predict.]

MELTING POINT: ~ 213-218°C (~ 415.4-424.4°F)

VAPOR PRESSURE (air = 1) @ 25°C: 8.13E-26 mmHg [predict.]

SPECIFIC GRAVITY (water = 1): Not available.

EVAPORATION RATE (nBuAc = 1): Not applicable.

pH (1% solution): 2.5-3.5

DECOMPOSITION TEMPERATURE: > 199.8°C (> 392°F)

FLASH POINT: 427.3°C (810.14°F) [predict.]

SOLUBILITY IN WATER: Soluble in water (1mg/mL).

OTHER SOLUBILITIES: Soluble in methanol.

COEFFICIENT WATER/OIL DISTRIBUTION: 1.08 [predict.]

10. STABILITY and REACTIVITY

CHEMICAL STABILITY: Normally stable.

DECOMPOSITION PRODUCTS: *Combustion:* Products of thermal decomposition may include carbon and nitrogen oxides. *Hydrolysis:* None known.

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE: Strong acids and bases. Avoid materials that are incompatible with water.

POSSIBILITY OF HAZARDOUS REACTION/POLYMERIZATION: None known.

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

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

11. TOXICOLOGICAL INFORMATION

SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE: This product is a cytotoxic and anti-neoplastic agent that may cause significant health effects from workplace exposure. The main expected routes of occupational exposure to this product are via inhalation of aerosols, eye and skin contact. Exposure may cause allergic reaction. Exposure may cause effects described under 'Other Potential Health Effects'.

INHALATION: Aerosols may irritate the nose and upper respiratory system. Symptoms may include sneezing, coughing, and nasal congestion.

CONTACT WITH SKIN or EYES: Mild irritation possible. Symptoms may include itching and redness and swelling.

SKIN ABSORPTION: No data on potential absorption of this product through intact skin. All possible contact must be avoided.

INGESTION: May irritate the mouth, throat, and gastrointestinal system.

INJECTION: May cause pain and irritation in addition to the wound.

OTHER POTENTIAL HEALTH EFFECTS: In therapeutic use, this product may cause bone marrow suppression which can lead to serious infection or death. The most common non-hematologic adverse reactions were nausea, hair loss, vomiting, infection or fever/infection with neutropenia, diarrhea, constipation, fatigue, and fever. Inadvertent extravasation with Topotecan has been observed. Most reactions have been mild but severe cases have been reported. Can cause fetal harm. Hypersensitivity reactions have been reported from therapeutic use. These effects may be possible as a result of workplace exposure. The actual risk in the workplace is not known. Body systems adversely affected during therapeutic use are provided below. More details can be obtained from Teva.

HAZARDOUS MATERIAL IDENTIFICATION SYSTEM

HEALTH HAZARD	(BLUE)	2*
FLAMMABILITY HAZARD	(RED)	0
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

- Blood System
- Body as a Whole
- Digestive System
- Metabolic System
- Nervous System
- Reproductive System
- Respiratory System
- Skin

HEALTH EFFECTS OR RISKS FROM EXPOSURE:

Acute: This product may be harmful by ingestion, skin contact and inhalation. Eye contact may cause redness, pain, and watering. This product contains a compound that can cause severe allergic reaction in susceptible individuals.

Chronic: Dermatitis (inflammation and redness of the skin) may occur after chronic, low-level skin contact. May cause fetal harm. Limited evidence of carcinogenic and mutagenic effects. May cause adverse effects on fertility. Chronic exposure may also lead to symptoms described under 'Other Potential Health Effects'. No other chronic effects have been reported from workplace exposure.

11. TOXICOLOGICAL INFORMATION (Continued)

TARGET ORGANS: It is anticipated that for Occupational Exposure the target organs are:

Acute: Skin, eyes, respiratory system.

Chronic: Skin.

TOXICITY DATA: Details for the active ingredient can be obtained from Teva.

CARCINOGENICPOTENTIAL OF COMPONENTS: No studies have been reported. No components are found on the following lists: U.S. EPA, U.S. NTP, U.S. OSHA, U.S. NIOSH, GERMAN MAK, IARC, or ACGIH.

IRRITANCY OF PRODUCT: May cause respiratory, skin or eye irritation.

SENSITIZATION TO THE PRODUCT: This product has been reported to cause hypersensitivity reactions during therapeutic use (by injection) in sensitive individuals, including serious anaphylaxis reactions. Reactions can include angioedema, severe dermatitis, severe itching.

REPRODUCTIVE TOXICITY INFORMATION: There are no adequate and well-controlled studies of Topotecan Hydrochloride in pregnant women; however, Topotecan Hydrochloride can 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 D** (refer to Definition of Terms for full category definitions).

Mutagenicity: Topotecan is known to be genotoxic to mammalian cells.

Embryotoxicity/Teratogenicity: Topotecan caused embryolethality, fetotoxicity, and teratogenicity in animal models.

Reproductive Toxicity: Adverse effects on reproductivity in animal studies. It is not known whether the drug is excreted in human 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.

MOBILITY: This product has not been tested.

PERSISTENCE AND BIODEGRADABILITY: This product has not been tested.

BIO-ACCUMULATION POTENTIAL: This product has not been tested.

ECOTOXICITY: This product may be harmful to contaminated plant and animal life, especially in large quantities. All releases to terrestrial, atmospheric and aquatic environments should be avoided. No data are currently available for this product.

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

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

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

13. DISPOSAL CONSIDERATIONS

WASTE TREATMENT/DISPOSAL METHODS: Waste disposal must be in accordance with appropriate Federal, State, and local regulations. 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 and/or regulated medical waste requirements. It is the responsibility of the generator to determine at the time of disposal whether the product meets the criteria of a hazardous waste or regulated medical 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.

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.

EUROPEAN EWC WASTE CODE: Wastes from natal care, diagnosis, treatment, or prevention of disease in humans: cytotoxic and cytostatic medicines, 18-01-08

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 product 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.
ENVIRONMENTAL HAZARDS: The active ingredient meets the criteria of environmentally hazardous according to the criteria of the UN Model Regulations (as reflected in the IMDG Code, ADR, RID, and ADN)
5

15. REGULATORY INFORMATION

ADDITIONAL U.S. REGULATIONS:
U.S. SARA REPORTING REQUIREMENTS: This product is 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 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 (FDA) standards; this product is not subject to requirements under TSCA.
OTHER U.S. FEDERAL REGULATIONS: This product is regulated under FDA regulations.
STATE REGULATIONS: Regulated Medical Waste.
CALIFORNIA SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT (PROPOSITION 65): The Topotecan Hydrochloride component is listed on the California Proposition 65 Lists as a Quinoline and its strong acid salts. WARNING! This product contains a compound known to the State of California to cause cancer.
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.
CANADIAN ENVIRONMENTAL PROTECTION ACT (CEPA) PRIORITY SUBSTANCES LISTS: Components are not on the CEPA substances lists.
OTHER CANADIAN REGULATIONS: Requirements under the Canadian Heath Canada, Laboratory Biosafety Guidelines may be applicable.
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 CYTOTOXIC AGENT. ALL EXPOSURE MUST BE MINIMIZED. MAY BE HARMFUL IF SWALLOWED, BASED ON ANIMAL DATA. MAY CAUSE RESPIRATORY SYSTEM, EYE, AND SKIN IRRITATION. CAN CAUSE HARM TO FETUS DURING PREGNANCY, BASED ON ANIMAL DATA. LIMITED EVIDENCE OF CARCINOGENIC AND MUTAGENIC EFFECTS, BASED ON ANIMAL DATA. ACCIDENTAL INJECTION MAY CAUSE SEVERE ALLERGIC REACTIONS.

Do not taste or swallow. 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; give victim up to three glasses of water. In case of contact, immediately flush skin with copious amounts of warm water for 20 minutes. If inhaled, remove to fresh air. If not breathing, give artificial respiration or oxygen if necessary.

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.

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:

Topotecan Hydrochloride: This is a self-classification:

Classification: Reproductive Toxicity Category 1B, Germ Cell Mutagenicity Category 2, Carcinogenic Category 2, Acute Oral Toxicity Category 5

Hazard Statements: H360Df: May damage the unborn child. Suspected of damaging fertility. H341: Suspected of causing genetic effects. H351: Suspected of causing cancer. H303: May be harmful if swallowed.

All Other Components:

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

FULL TEXT EU 67/548/EEC:

Topotecan Hydrochloride: This is a self-classification:

Classification: Reproductive Toxicity Category 2, Reproductive Toxicity Category 3, Germ Cell Mutagenic Category 3, Carcinogenic Category 3

Hazard Statements: R61: May cause harm to the unborn child. R62: Possible risk of impaired fertility. R40: Limited evidence of a carcinogenic effect. R68: Possible risk of irreversible effects.

All Other Components:

An official classification for these substances has not been published in Commission Directives 93/72/EEC, 94/69 EC, 96/54/EC or subsequent directives and is not applicable for self-classification.

REFERENCES AND DATA SOURCES: Contact the supplier for information.

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

PREPARED BY: Teva Pharmaceuticals, Inc., EHS Department (215) 591-3000

DATE OF PRINTING: September 29, 2014

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:

CAS #: This is the Chemical Abstract Service Number that uniquely identifies each constituent.

EXPOSURE LIMITS IN AIR:

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.

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: 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.];

HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS (continued):

FLAMMABILITY HAZARD (continued): 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 and 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 and 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. **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.

DEFINITIONS OF TERMS (Continued)

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

HEALTH HAZARD (continued): **2 (continued):** 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. **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.

NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

INSTABILITY HAZARD: **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 and 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.