

CONTROL OF SUBSTANCES HAZARDOUS TO HEALTH (COSHH) SHEET

SECTION 1 – IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

PRODUCT NAME:

Doxorubicin 2 mg/mL Concentrate for Solution for Infusion, 5 mL, 25 mL and 100 mL

PRODUCT USE:

Medical Treatment; Anticancer Agent

MANUFACTURER:

Intas Pharmaceuticals Ltd.

Plot No. 457, 458

Village-Matoda,

Bavla Road, Ta. Sanand,

Dist. Ahmedabad-382 210,

Gujarat, India

MARKETING AUTHORISATION HOLDER:

Accord Healthcare Limited

Sage House

319, Pinner Road

North Harrow

Middlesex, HA1 4HF

United Kingdom

RECOMMENDED INTERNATIONAL NONPROPRIETARY NAME:

Doxorubicin Hydrochloride

CHEMICAL NAME:

(8S,10S)-10-[(3-Amino-2,3,6-trideoxy- α -L-/yxo-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

5,12-Naphthacenedione,10- [(3-amino-2,3,6-trideoxy- α -L-/yxo-hexopyranosyl)oxy]-7,8,9,10- tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-,hydrochloride (8S-cis)

(8S,10S)-10-[3-Amino-2,3,6 trideoxy- α -L-/yxo-hexopyranosyl)-oxy-8-glycoloyl]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride

(8S-cis)-10-[(3-Amino-2,3,6-trideoxy- α -L-/yxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione Hydrochloride

(SP-4-2)-Diammine [cyclobutane - 1,1-dicarboxylato (2-)-O, O'] platin.

cis-Diammine(1, 1-cyclobutanedicarboxylato) platinum.

CHEMICAL FORMULA:

$C_{27}H_{29}NO_{11} \cdot HCl$

CHEMICAL FAMILY:

Cytotoxic Anthracycline Antibiotic

DOXORUBICIN HYDROCHLORIDE INJECTION

HOW SUPPLIED:

- For 5 ml,

Concentrate for solution for infusion is filled in 5 ml Type - I clear tubular glass vial closed with teflon rubber stopper and aluminium flip off pink seal.

- For 25 ml,

Concentrate for solution for infusion is filled in 30 ml Type - I clear molded glass vial closed with teflon rubber stopper and aluminium flip off pink seal.

- For 100 ml,

Concentrate for solution for infusion is filled in 100 ml Type - I clear glass vial closed with teflon rubber stopper and aluminium flip off pink seal.

PACK SIZES:

- 1 × 5 ml vial
- 1 × 25 ml vial
- 1 × 100 ml vial

Not all pack sizes may be marketed.

DATE OF PREPARATION:

October 16, 2009

SECTION 2 – HAZARDS IDENTIFICATION**EMERGENCY OVERVIEW:**

Material is clear red solution. Probable cancer hazard. May cause damage to the heart, bone marrow and reproductive system. Harmful to the fetus. May cause allergic reactions. Avoid exposure during pregnancy and while breastfeeding. Avoid breathing vapor. Avoid contact with eyes, skin and clothing. Do not taste or swallow. Wash thoroughly after handling.

**SYMPTOMS OF OVEREXPOSURE BY ROUTE OF EXPOSURE:**

This material is intended for intravenous use only.

INHALATION:

Inhalation of significant amounts of the product is not anticipated to occur because of the small size of individual containers.

CONTACT WITH SKIN OR EYES:

Contact causes irritation. Effects may include stinging, watering, and redness of the eyes and redness and a burning sensation on the skin. High concentrations of Doxorubicin hydrochloride are irritating to tissues and may lead to local ulceration and necrosis. May cause allergic skin reactions.

INGESTION:

Ingestion is not an anticipated route of occupational exposure. However, the active ingredient, Doxorubicin hydrochloride, is highly toxic. Symptoms similar to those identified under injection may occur.

INJECTION:

Local redness and pain are the primary symptoms of accidental injection in an occupational setting. Medical personnel are not anticipated to experience over-exposures to the therapeutic doses of this product. However, effects including burning sensation, alopecia, nausea, vomiting, anorexia, stomatitis and dose-limiting cardiac effects (e.g., increased heart rate, arrhythmia, congestive heart failure) may occur. See package insert for adverse reactions associated with therapeutic doses of this product.

HEALTH EFFECTS OR RISKS FROM EXPOSURE (AN EXPLANATION IN LAY TERMS):**Acute:**

- The primary health effects anticipated in an occupational setting include irritation of eyes and skin as well as redness and local swelling after accidental injection. In case of over-exposure by injection, burning sensation, infection, hair loss, nausea, vomiting, anorexia, mouth sores and cardiac effects (e.g., increased heart rate, arrhythmia, congestive heart failure) may occur. Death can occur in the event of a massive accidental overdose.

Chronic:

- Potential hazard to the fetus (see Section 11).

Target Organs:

- Potential hazard to the heart, bone marrow and reproductive systems (see Section 11).

Pre-Existing Medical Conditions:

- Conditions aggravated by exposure may include skin, respiratory heart, bone marrow and reproductive disorders. Cardiac toxicity is more common in patients who have received prior anthracyclines or who have pre-existing cardiac disease.

SECTION 3 – COMPOSITION/DATA ON COMPONENTS

Chemical Name	CAS #	Wt %	EXPOSURE LIMIT IN AIR				
			ACGIH		OSHA		Other
			TLV	CEIL	PEL	CEIL	0.4µg/m ³ (*)
Doxorubicin Hydrochloride (exposure limit for Platinum, soluble salts as Platinum)	41575-94-4	0.2	NE	NE	NE	NE	NE
Sodium chloride	7647-14-5	0.9	NE	NE	NE	NE	NE
Hydrochloric acid 37%	7647-01-0	q.s.	NE	NE	NE	NE	NE
Water (for injection)	7732-18-5	q.s.	NE	NE	NE	NE	NE

NE - Not Established C - Ceiling Limit

NOTE:

All WHMIS required information is included. It is located in appropriate sections based on the ANSI Z400.1 format

CHEMTREC NUMBER:

Use only in the event of a chemical emergency involving a spill, leak, fire, exposure or accident involving this drug.

SECTION 4 – EMERGENCY AND FIRST AID MEASURES**SKIN EXPOSURE:**

Remove contaminated shoes and clothing and cleanse affected area(s) thoroughly by washing with mild soap and water. If irritation or redness develops and persists, seek medical attention.

EYE EXPOSURE:

If irritation or redness develops, move victim away from exposure and into fresh air. Flush eyes with clean water and seek medical attention. For direct contact, hold eyelids apart and flush the affected eye(s) with clean water for at least 15 minutes. Seek medical attention.

INHALATION:

If respiratory symptoms develop, move victim away from source of exposure and into fresh air. If symptoms persist, seek medical attention. If victim is not breathing, clear airway and immediately begin artificial respiration. If breathing difficulties develop, oxygen should be administered by qualified personnel. Seek immediate medical attention.

INGESTION:

If swallowed, seek emergency medical attention. If victim is drowsy or unconscious and vomiting, place on the left side with the head down and DO NOT give anything by mouth. If not vomiting and professional advice is not available, DO NOT induce vomiting. If possible, do not leave victim unattended and observe closely for adequacy of breathing. Victims of chemical exposure must be taken for medical attention. Take a copy of the MSDS to the physician or health professional with victim. Physicians should refer to Section 11 (Toxicological Information) as well as the Physicians Desk Reference for additional treatment information.

SECTION 5 – FIRE FIGHTING MEASURES**FLASH POINT:**

Not applicable

AUTOIGNITION TEMPERATURE:

Not applicable

FLAMMABLE LIMITS (IN AIR BY VOLUME, %):

- Lower: Not applicable
- Upper: Not applicable

FIRE EXTINGUISHING EQUIPMENT:

Use extinguishing agent suitable for type of surrounding fire.

- Water Spray: OK
- Carbon Dioxide: OK
- Halon: OK
- Foam: OK
- Dry Chemical: OK
- Other: Any "ABC" Class

UNUSUAL FIRE AND EXPLOSION HAZARDS:

No unusual fire or explosion hazards are expected.

EXPLOSION SENSITIVITY TO MECHANICAL IMPACT:

Not sensitive.

EXPLOSION SENSITIVITY TO STATIC DISCHARGE:

Not sensitive

SPECIAL FIRE FIGHTING PROCEDURES:

For fires beyond the incipient stage, emergency responders in the immediate hazard area should wear bunker gear. When the potential chemical hazard is unknown, in enclosed or confined spaces, or when explicitly required by DOT, a self-contained breathing apparatus should be worn. In addition, wear other appropriate protective equipment as conditions warrant (see Section 8). Isolate immediate hazard area and keep unauthorized personnel out. Contain spill if it can be done with minimal risk. Move undamaged containers from immediate hazard area if it can be done with minimal risk. Cool equipment exposed to fire with water, if it can be done with minimal risk.

NFPA HAZARD CLASS:

- Health: 2 (Moderate)
- Flammability: 0 (Least)
- Reactivity: 0 (Least)

SECTION 6 – ACCIDENTAL RELEASE MEASURES**SPILL AND LEAK RESPONSE:**

For small releases of this product, wear latex or nitrile gloves and safety glasses. Absorb spilled liquid and rinse area thoroughly with soap and water.

For large or uncontrolled releases, stay upwind and away from spill. Isolate immediate hazard area and keep unauthorized personnel out. Contain spill if it can be done with minimal risk. Wear appropriate protective equipment including respiratory protection as conditions warrant (see Section 8). Prevent spilled material from entering sewers, storm drains, other unauthorized treatment drainage systems, and natural waterways. Dike far ahead of spill for later recovery or disposal. Spilled material may be absorbed into an appropriate absorbent material. Notify appropriate federal, state, and local agencies. Immediate cleanup of any spill is recommended.

SECTION 7 – HANDLING AND STORAGE

DOXORUBICIN HYDROCHLORIDE IS A CYTOTOXIC AGENT. ALL WORK PRACTICES MUST BE DESIGNED TO REDUCE HUMAN EXPOSURE TO THE LOWEST LEVEL

WORK AND HYGIENE PRACTICES:

As with all chemicals, avoid getting this product ON YOU or IN YOU. Do not eat, drink, smoke or apply cosmetics while handling the product. Wash hands thoroughly after handling.

Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this product, and during patient administration. Precautions should be taken during the following activities:

- Withdrawal of needles from drug vials.
- Drug transfers using syringes and needles or filter straws.
- Expulsion of air from drug-filled syringes.

STORAGE AND HANDLING PRACTICES:

Employees must be trained to properly use the product. Ensure vials are properly labeled. Store only in approved containers. Keep away from any incompatible materials or conditions (see Section 10). Store under refrigeration 2- 8°C (36-46°F). Avoid freezing.

PROTECTIVE PRACTICES DURING MAINTENANCE OF CONTAMINATED EQUIPMENT:

When cleaning non-disposable equipment, wear latex or nitrile gloves (double gloving is recommended), goggles, and lab coat. Wash equipment with soap and water. All needles, syringes, vials and other disposable items contaminated with this product should be disposed of properly.

SECTION 8 – EXPOSURE CONTROLS/PERSONAL PROTECTION

VENTILATION AND ENGINEERING CONTROLS:

Use with adequate ventilation. Follow standard medical product handling procedures.

RESPIRATORY PROTECTION:

Not normally required for routine, medical administration of this product. A NIOSH certified air-purifying respirator with a type 100 filter may be used under conditions where airborne concentrations are expected to be excessive. Protection provided by air purifying respirators is limited (see manufacturer's respirator selection guide). Use a positive pressure air supplied respirator if there is potential for uncontrolled release, exposure levels are not known or any other circumstances where air-purifying respirators may not provide adequate protection. A respiratory protection program that meets OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements must be followed whenever workplace conditions warrant a respirator's use.

EYE PROTECTION:

Approved eye protection (e.g., safety glasses with side shields) to safeguard against potential eye contact, irritation or injury is recommended. Depending on conditions of use, a face shield may be necessary.

HAND PROTECTION:

Use latex, nitrile, or rubber gloves. Check gloves for leaks. Wash hands before and after using gloves.

BODY PROTECTION:

A full body gown which is closed at the front and has long sleeves is recommended.

PRODUCT PREPARATION INSTRUCTIONS FOR MEDICAL PERSONNEL:

Follow standard procedure for handling pharmaceutical materials and recommendations presented on the Package Insert.

SECTION 9 – PHYSICAL AND CHEMICAL PROPERTIES

Relative Vapor Density (air = 1):	>
Specific Gravity (water = 1):	~1
Solubility in Water:	Soluble
Vapor Pressure, mm Hg @ 25°C.	ND
Odor Threshold:	Odorless
Evaporation Rate (n-BuAc=1):	> 1
Melting/Freezing Point:	ND
Boiling Point:	100-105°C (212-221°F)
pH	Between 2.5 and 3.5
Appearance and Color:	Translucent, red solution

ND = No data

SECTION 10 – STABILITY AND REACTIVITY**STABILITY:**

Stable under normal conditions of storage and handling.

MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE:

This product is generally compatible with other common materials in a medical facility. Keep away from strong oxidizers and strong acids.

HAZARDOUS POLYMERIZATION:

Will not occur.

CONDITIONS TO AVOID:

Heat may cause this product to decompose, destroy the product and produce irritating vapors and toxic gases. Keep refrigerated 2- 8°C (36-46°F). Avoid freezing.

SECTION 11 – TOXICOLOGY INFORMATION

Toxicity Data: The following information is for Doxorubicin Hydrochloride

IV LD50(rat) = 12510 ug/kg		SubQ LD50 (mouse) = 7678ug/kg
IV LD50(mouse) = 1245 ug/kg	Oral LD50(mouse) = 698 mg/kg	SubQ LD50 (rat) = 21840 ug/kg
IV LD50(rabbit) = 5980 ug/kg	Oral LD50(mouse) = 570 mg/kg	SubQ LD50(mouse) = 13.5 mg/kg

SUSPECTED CANCER AGENT:

Considered a carcinogen based on studies in laboratory animals and cancer cases in humans administered the drugs. It has been identified as a carcinogen by NTP and IARC.

IRRITANCY OF PRODUCT:

This product is irritating to contaminated skin, eyes and other tissues.

SENSITIZATION TO THE PRODUCT:

Rare instances of allergic reaction have occurred from clinical use. No data on allergic sensitization potential from repeated skin contact.

REPRODUCTIVE TOXICITY INFORMATION:

Listed below is information concerning the effects of Doxorubicin Hydrochloride on human and animal reproductive systems. This material is classified as a Pregnancy Category D (Positive Evidence of Risk).

MUTAGENICITY:

Doxorubicin is mutagenic in a battery of studies. Embryotoxicity/ Teratogenicity/ Reproductive Toxicity: In humans, there have been reports of fetal abnormalities and fetal deaths in the offspring of patients administered doxorubicin. There is conflicting data on whether nurses who were occupationally exposed to antineoplastic agents, including doxorubicin, had an increased risk of fetal loss. It is embryotoxic and an abortifacient (causes spontaneous abortions) in laboratory animals. Increased frequencies of gastrointestinal anomalies, cardiovascular malformations, bladder hypoplasia, dilatation of the renal pelvis and ureter, skeletal anomalies, and other abnormalities were observed among the offspring of rats treated during pregnancy with doxorubicin in doses 1-5 times those used in humans. With doses that were somewhat smaller but still within the human therapeutic range, malformations were not increased among the offspring of pregnant rats, mice, or rabbits treated with doxorubicin, but fetal loss and growth retardation were common.

Affects both male and female fertility based on studies in laboratory animals (ovarian atrophy in females and testicular atrophy and effects on sperm in males).

TARGET ORGAN TOXICITY INFORMATION:

This product may produce adverse effects on the heart and blood effects. When administered clinically by intravenous injection, Doxorubicin Hydrochloride can cause myocardial toxicity leading to congestive heart failure. Cardiac toxicity is more common in patients who have received prior anthracyclines or who have pre-existing cardiac disease. Severe myelosuppression will occur in all patients given a therapeutic dose. ACGIH Biological Exposure Indices: Currently there are no Biological Exposure Indices (BEIs) associated with the components of this product.

SECTION 12 – ECOLOGICAL INFORMATION

All work practices must be aimed at eliminating environmental contamination.

ENVIRONMENTAL STABILITY:

This product will be relatively stable under ambient environmental conditions.

EFFECT OF MATERIALS ON PLANTS OR ANIMALS:

No specific information is available on the effect of Doxorubicin Hydrochloride on plants or animals in the environment.

EFFECT OF CHEMICALS ON AQUATIC LIFE:

No specific information is available on the effect of Doxorubicin Hydrochloride on plants or animals in the aquatic environment.

SECTION 13 – DISPOSAL CONSIDERATIONS**PREPARING WASTES FOR DISPOSAL:**

This material, if discarded as produced, is not a RCRA “listed” or “characteristic” hazardous waste. Use resulting in chemical or physical change or contamination may subject it to regulation as a hazardous waste. Along with properly characterizing all waste materials consult state and local regulations regarding the proper disposal of this material.

U.S. EPA WASTE NUMBER:

None

SECTION 14 – TRANSPORTATION INFORMATION

This Material is not Hazardous as Defined by 49 CFR 172.101 by the U. S. Department of Transportation.

PROPER SHIPPING NAME:

Not applicable

HAZARD CLASS NUMBER AND DESCRIPTION:

Not applicable

UN IDENTIFICATION NUMBER:

Not applicable

PACKING GROUP:

Not applicable

DOT LABEL(S) REQUIRED:

Not applicable

NORTH AMERICAN EMERGENCY RESPONSE GUIDEBOOK NUMBER (1996):

Not applicable.

MARINE POLLUTANT:

No component of this product is listed as a Marine Pollutant (49 CFR 172.101, Appendix B)

TRANSPORT CANADA TRANSPORTATION OF DANGEROUS GOODS REGULATIONS:

Not applicable

SECTION 15 – REGULATORY INFORMATION**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 II of the Superfund Amendments and Reauthorization Act.

U.S. SARA THRESHOLD PLANNING QUANTITY:

Not applicable

U.S. CERCLA REPORTABLE QUANTITIES (RQ):

Not applicable

U.S. TSCA INVENTORY STATUS:

Doxorubicin Hydrochloride is a "drug" as defined by the Federal Food, Drug and Cosmetic Act and is therefore not a chemical substance under TSCA.

California Safe Drinking Water and Toxic Enforcement Act (Proposition 65):

This product does contain a chemical known to the State of California to cause cancer, developmental and male reproductive effects – Doxorubicin hydrochloride.

OTHER U.S. FEDERAL REGULATIONS:

Based on this product's use, the requirements of the OSHA Bloodborne pathogen Standard (29 CFR 1910.1030) are applicable.

ANSI LABELING (BASED ON 129.1, PROVIDED TO SUMMARIZE OCCUPATIONAL EXPOSURE HAZARDS):

OVEREXPOSURE MAY CAUSE DAMAGE TO THE HEART, BONE MARROW AND REPRODUCTIVE SYSTEMS. PROBABLE CANCER HAZARD. HAZARD TO THE FETUS. MAY CAUSE ALLERGIC REACTIONS. Doxorubicin Hydrochloride should be administered under the supervision of a qualified physician. Avoid over-exposure. Avoid exposure during pregnancy. Avoid breathing vapor. Avoid contact with eyes, skin and clothing. Do not eat, drink or smoke when handling Doxorubicin Hydrochloride. Do not taste or swallow. Wash thoroughly after handling. Clean up spills promptly.

CANADIAN REGULATIONS:**CANADIAN DSL/NDL STATUS:**

Doxorubicin Hydrochloride is regulated by the Food and Drug Administration of Health Canada and is therefore exempt from the requirements of CEPA.

SECTION 16 – OTHER INFORMATION**ISSUE DATE:**

October 16, 2009

The information in this document is believed to be correct as of the date issued.

HOWEVER, NO WARRANTY OF MERCHANTABILITY, FITNESS FOR ANY PARTICULAR PURPOSE, OR ANY OTHER WARRANTY IS EXPRESSED OR IS TO BE IMPLIED REGARDING THE ACCURACY OR COMPLETENESS OF THIS INFORMATION, THE RESULTS TO BE OBTAINED FROM THE USE OF THIS INFORMATION OR THE PRODUCT, THE SAFETY OF THIS PRODUCT, OR THE HAZARDS RELATED TO ITS USE. This information and product are furnished on the condition that the person receiving them shall make his own determination as to the suitability of the product for his particular purpose and on the condition that he assumes the risk of his use thereof.