

# CONTROL OF SUBSTANCES HAZARDOUS TO HEALTH (COSHH) SHEET

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

**PRODUCT NAME:**

Epirubicin Hydrochloride Injection 2 mg/mL, 5 mL, 10 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:**

Epirubicin Hydrochloride

**CHEMICAL NAME:**

(8-S-cis)-10-[(3-Amino-2,3,6-trideoxy- $\alpha$ -L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,10-trihydroxy-8-(hydroxylacetyl)-1-methoxy-5,12-naphthacendione Hydrochloride  
(8S,10S)-10-[(3-Amino-2,3,6-trideoxy- $\alpha$ -L-arabino-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracen-5,12-dione hydrochloride

**CHEMICAL FORMULA:**

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

**CHEMICAL FAMILY:**

Anthracycline cytotoxic agent

**HOW SUPPLIED:**

- 5 and 10 ml vials: Type I tubular glass vial with Teflon-coated rubber stopper and aluminium flip-off white seal
- 25 ml vial: Type I tubular glass vial with Teflon-coated rubber stopper and aluminium flip-off white/royal blue seal.
- 100 ml vial: Type I clear moulded glass vial with Teflon-coated rubber stopper and aluminium flip-off white / royal blue seal.

**Pack size:** 1 vial. Not all pack sizes may be marketed

**DATE OF PREPARATION:**

October 16, 2009

EPIRUBICIN HYDROCHLORIDE INJECTION

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

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

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

This material is intended for intravenous injection under the supervision of physicians. It must NOT be given by the intramuscular or subcutaneous route.

**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 may cause mild irritation. Effects may include stinging, watering, and redness of the eyes and redness and a burning sensation of the skin. Extraction during infusion may cause local pain, severe tissue lesions and necrosis. May cause an allergic reaction on the skin.

**INGESTION:**

Ingestion is not an anticipated route of occupational exposure. The active ingredient, Epirubicin Hydrochloride, is moderately toxic if swallowed. 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 bone marrow suppression with decreased blood cells, nausea, vomiting, severe gastrointestinal distress, loss of blood pressure, cardiac irregularities and hair loss may occur. See package insert for other 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, effects such as nausea, vomiting, diarrhea and loss of blood pressure may occur.

**Cancer:**

- Epirubicin Hydrochloride has not been specifically tested for cancer (see Section 11 for additional information).

**Chronic:**

- Based on animal data, Epirubicin Hydrochloride, is considered a potential developmental and reproductive toxicant (see Section 11).

**Target Organs:**

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

**PRE-EXISTING MEDICAL CONDITIONS:**

Pre-existing bone marrow, reproductive and heart disorders may be aggravated by exposure to this material.

**SECTION 3 – COMPOSITION, INFORMATION ON INGREDIENTS**

Chemical Name	CAS #	Wt %	EXPOSURE LIMIT IN AIR				
			ACGIH		OSHA		Other
			TLV	CEIL	PEL	CEIL	
Epirubicin Hydrochloride	5639-09-1	0.2	NE	NE	NE	NE	0.5 µg/m <sup>3</sup>
Sodium chloride	7647-14-5	< 1	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 \* Identified for a closely related antineoplastic compound, Doxorubicin

**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 – 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.

**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 Flammable

**AUTOIGNITION TEMPERATURE:**

Not applicable

**FLAMMABLE LIMITS (IN AIR BY VOLUME, %):**

Not applicable

**FIRE EXTINGUISHING EQUIPMENT:**

The size and nature of this product is such that it will not contribute to the intensity of a fire. 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:**

When heated to decomposition, this product may emit toxic fumes.

**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:	1 (Slight)
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 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**

**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. Protect from light. Keep away from any incompatible materials or conditions (see Section 10). Store refrigerated between 2-8°C (36-46°F). Do not freeze.

**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 95 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 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:

No special body protection required for routine, medical administration of this product. Wear lab coat, gown, or smock, as appropriate for procedure.

### 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):	No data
Specific Gravity (water = 1):	1.005
Solubility in Water:	Soluble
Vapor Pressure, mm Hg @ 25°C:	No data
Odor Threshold:	No data
Evaporation Rate (n-BuAc=1):	No data
Melting/Freezing Point:	~ 0°C
Boiling Point:	~ 100°C
pH	Between 2.5 and 3.5
Appearance and Color:	Clear red solution

## SECTION 10 – STABILITY AND REACTIVITY

Stability:	Stable under normal conditions of storage and handling.
Materials With Which Substance is Incompatible:	None known
Hazardous Polymerization:	Will not occur.
Hazardous Combustion Products	Heat may cause product to decompose, destroying the product or producing toxic fumes

## SECTION 11 – TOXICOLOGY INFORMATION

### TOXICITY DATA:

The following information is for Epirubicin Hydrochloride, the active ingredient.

Oral LD50(rat) = 1350 mg/kg	IV LD50(rat) = 17 mg/kg	IP LD50(rat) = 10800 ug/kg
Oral LD50(Mouse) > 2 gm/kg	IV LD50(mouse) = 31500 ug/kg	IP LD50(mouse) = 64 mg/kg
SubQ(mouse) = 37500 ug/kg	IV LD50(dog) = 2250 ug/kg	SubQ(rat) = 17600 ug/kg

### SUSPECTED CANCER AGENT:

Conventional long-term studies to evaluate the carcinogenic potential of Epirubicin Hydrochloride have not been performed; however, intravenous administration of a single 3.6 mg/kg dose to female rats (one-fifth the recommended human dose on a surface area basis) approximately doubled the incidence of mammary tumors observed at one year. Subcutaneous administration of 0.75 or 1.0 mg/kg/day (about one-sixtieth the maximum recommended dose in humans on a surface area basis), to newborn rats for four days on the first and tenth day after birth (for a total of eight doses) increased the incidence of animals evidencing tumors over a 24 month observation period. It is not listed as carcinogenic by NTP, IARC or OSHA.

### IRRITANCY OF PRODUCT:

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

### SENSITIZATION TO THE PRODUCT:

Dermatological reactions have been observed with exposure to this compound. No data on allergic sensitization potential from repeated skin contact.

### TARGET ORGAN(S):

Causes bone marrow suppression (decreased white blood cell count and platelets, neutropenia and thrombocytopenia) and changes in the liver.

### REPRODUCTIVE TOXICITY INFORMATION:

Listed below is information concerning the effects of Epirubicin Hydrochloride on human and animal reproductive systems. This material is classified as a Pregnancy Category D (Positive evidence of risk). Currently, there have been no studies in pregnant women

**MUTAGENICITY:**

Epirubicin Hydrochloride was mutagenic *in vitro*, testing positive in the Ames bacterial cell mutagenicity assay and in a mammalian cell assay (HGPRT in Chinese hamster lung fibroblasts). Epirubicin was clastogenic *in vitro* (positive for chromosome aberrations in human lymphocytes) and *in vivo* (positive for chromosome aberrations in mouse bone marrow).

**EMBRYOTOXICITY/TERATOGENICITY/REPRODUCTIVE TOXICITY:**

Epirubicin Hydrochloride doses of 0.1 mg/kg/day in rats were associated with increased embryoletality, while an increase in fetal growth retardation was associated with doses of 0.03 mg/kg/day (about one-six-hundredth the maximum recommended dose in humans on a surface area basis). Administration of 2 mg/kg/day intravenously to rats (about one-tenth the maximum recommended dose in humans on a surface area basis) on days 9 and 10 of gestation was embryotoxic (e.g., decreased numbers of viable fetuses), retarded fetal growth, induced decreased placental weight, and was associated with birth defects (e.g., caused numerous external, visceral, and skeletal anomalies). Rabbits given maternally toxic doses of 0.32 and 1.0 mg/kg/day evidenced increased abortions and delayed ossification in offspring, but no other overt signs of fetal toxicity or teratogenicity.

Epirubicin reportedly impairs fertility in rats at a dose of 0.3 mg/kg/day (about one-sixtieth the maximum recommended dose in humans on a surface area basis). At a dose of 0.1 mg/kg/day, male rats evidenced atrophy of the testes and epididymis and reduced spermatogenesis. Multiple daily doses of epirubicin given to rabbits and dogs induced atrophy of male reproductive organs. Similarly, single intravenous doses of 20.5 and 12 mg/kg (both about one-half the maximum recommended dose in humans on a surface area basis) given to mice and rats, respectively, were associated with testicular atrophy. A single dose of 16.7 mg/kg was associated with uterine atrophy in female rats.

**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:**

It is anticipated that this compound will decompose into a variety of organic compounds.

**EFFECT OF MATERIALS ON PLANTS OR ANIMALS:**

This product may be harmful to contaminated plant and animal life. See Section 11 (Toxicological Information) for additional information.

**EFFECT OF CHEMICALS ON AQUATIC LIFE:**

This product may be harmful to aquatic plant and animal life in contaminated bodies of water, especially if released in large quantities.

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



This material, if discarded as produced, is not a RCRA "listed" 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. TSCA INVENTORY STATUS:**

Epirubicin 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 NOT contain chemicals known to the State of California to cause cancer or reproductive effects.

**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.

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

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

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

Harmful to the Fetus. May Cause Damage to the Bone Marrow, Heart and Reproductive System. Epirubicin Hydrochloride should be administered under the supervision of a qualified physician. Avoid over-exposure. Avoid contact with eyes, skin and clothing. Avoid exposure during pregnancy. Avoid accidental injection. Do not eat, drink or smoke when handling. Do not taste or swallow. Wash thoroughly after handling. Clean up spills promptly.

**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.