

Corazon Alvarado, R.N.  
Medical Information Associate  
Clinical Affairs



~~Ortho Biotech Products, L.P.~~  
700 U.S. Highway 202  
P. O. Box 670  
Raritan, NJ 08869-0670

(800)325-7504, prompt #2 Phone  
(908) 526-9230 Fax

August 15, 2002

Tiffany Anderson  
PROZAR  
1295 Vandaner Blvd  
Saint Paul, MN 55108

Dear Ms. Anderson:

Thank you for your interest in DOXIL<sup>®</sup> (doxorubicin HCl liposome injection). In the United States, DOXIL<sup>®</sup> is marketed by Ortho Biotech Products, L.P. for:

1. The treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment.
2. The treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior chemotherapy or in patients who are intolerant to such therapy.

These indications are based on objective tumor response rates. No results are available from controlled studies that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

The active ingredient of DOXIL is doxorubicin HCl. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

DOXIL is doxorubicin HCl encapsulated in long-circulating STEALTH<sup>®</sup> liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect the liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Information specific to your inquiry in the following area(s) is attached:

- Doxil Material Data Safety Sheet

Ortho Biotech has supplied this information to you as a service because of your specific request and is not intended as an endorsement or promotion of any usage not contained in the package insert.

If you have any other questions or require information, please do not hesitate to contact me or any member of the Medical Information Group, at (800) 325-7504, prompt #2.

Sincerely,

  
Corazon Alvarado, R.N.

Enclosures

Doxil Material Data Safety Sheet

DOXIL (doxorubicin HCl liposome injection) PACKAGE INSERT, Distributed by Ortho Biotech Products, L.P.,  
Raritan, New Jersey Revd September 2001

Inquiry No: 111571



## Material Safety Data Sheet

### SECTION 1. COMPANY AND MATERIAL IDENTIFICATION

Supplier of Data ALZA Corporation  
1900 Charleston Road  
Mountain View, CA 94039-7210

In case of emergency, call: (650)564-2526

Generic names: doxorubicin HCl liposome injection,  
doxorubicin HCl [pegylated liposomal]

Trade names: DOXIL<sup>®</sup>, CAELYX<sup>™</sup>

Note: This MSDS is written to provide health and safety information for personnel that will be handling the final product (i.e. transportation, distribution and health care workers). For health and safety information during manufacturing, refer to the appropriate MSDS of each component.

### SECTION 2. PRODUCT COMPOSITION

Component	CAS#	Formula	Percent
Doxorubicin Hydrochloride	25316-40-9	$C_{27}H_{29}NO_{11}-HCl$	0.2 %
Liposomal carrier*	not applicable	not applicable	99.8 %

\*Contains N-(carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycerol-3-phosphoethanolamine sodium salt (MPEG-DSPE), fully hydrogenated soy phosphatidylcholine (HSPC), cholesterol, ammonium sulfate, histidine, sucrose and hydrochloric acid and/or sodium hydroxide for pH control.

### SECTION 3. HEALTH HAZARDS

#### WARNING STATEMENT

**CAUTION:** Contains Doxorubicin Hydrochloride an antineoplastic agent used in chemotherapy. Doxorubicin Hydrochloride is a known carcinogen in animals and a probable carcinogen in humans. This drug is intended for human pharmaceutical use by intravenous infusion as prescribed by a physician.

---

### SECTION 3. HEALTH HAZARDS (CONTINUED)

---

#### Precautionary statement

Irritant

Irritating to eyes, skin and mucosa

#### Potential routes of exposure

Skin, eyes, ingestion, inhalation, accidental injection

#### Systemic

Acute: Due to the nature of the use (intravenous infusion) of this drug no oral or inhalation toxicity data exists.

Chronic: Due to the nature of the use (intravenous infusion) of this drug no oral or inhalation toxicity data exists.

#### Reproductive and Developmental Toxicity

DOXIL<sup>®</sup> is embryotoxic at doses of 1 mg/kg/day (about 1/3 of the recommended human dose on mg/m<sup>2</sup> basis) in rats.

DOXIL<sup>®</sup> is embryotoxic and abortifacient at 0.5 mg/kg/day (about 1/4 the recommended human dose on mg/m<sup>2</sup> basis) in rabbits.

No data exists, for tests in humans, to confirm or deny the results of the animal models.

#### Carcinogenicity and Mutagenicity

Although no studies have been conducted with DOXIL<sup>®</sup>, doxorubicin HCl has been shown to have mutagenic and carcinogenic properties when tested in animal models.

No data exists, for tests in humans, to confirm or deny the results of the animal models.

#### Permissible Exposure Limit

No OSHA or ACGIH exposure limits have been set.

---

### SECTION 4. FIRST AID MEASURES

---

#### Eye contact

Immediately flush eyes with copious amounts of water for at least 15 minutes. If irritation develops seek medical attention.

#### Skin contact

Remove contaminated clothing and wash area thoroughly with soap and water for at least 15 minutes. Thoroughly wash with soap and water any garments that might have been contaminated before using again. If irritation develops seek medical attention.

#### Inhalation

Remove person to fresh air and notify emergency medical personnel.

---

**SECTION 4. FIRST AID MEASURES (CONTINUED)**

---

**Ingestion**

Do not induce vomiting. Notify emergency medical personnel.

**Accidental Injection**

In studies with rabbits, lesions that developed after subcutaneous injection of DOXIL<sup>®</sup> were minor and reversible compared to the more severe and irreversible lesions and tissue necrosis that developed after subcutaneous injection of conventional doxorubicin HCl. Clean the puncture wound to prevent infection. Follow the local procedures concerning the possible exposure to blood borne pathogens, if needle was previously used. Seek medical attention.

---

**SECTION 5. FIRE PROTECTION**

---

**Extinguishing media**

Water spray, carbon dioxide, dry chemical powder or foam

**Special fire fighting procedures**

Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.

---

**SECTION 6. ACCIDENTAL RELEASE MEASURES**

---

If material is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment. Deny access to the spill area and minimize the spreading of the material. Be aware of broken glass. Carefully soak up any spilled material using Chemo-pads or other absorbent pads. Wipe area to remove as much of the liquid as possible. Apply bleach, or 5-6% sodium hypochlorite solution, to the affected area and let sit for at least two hours. Wipe the area down to remove the bleach and wash the area with soap and water. Collect all materials generated during the clean up in a suitable container and dispose of in accordance with the applicable local, state and federal waste disposal laws.

---

**SECTION 7. HANDLING AND STORAGE**

---

Avoid contact with skin, eyes and mucosa. Wash thoroughly after handling. Refrigerate at between 2°C and 8°C (36°F and 46°F).

---

**SECTION 8. EXPOSURE CONTROL**

---

Wear latex gloves suitable for handling chemotherapy agents, safety goggles or glasses with side shields and a laboratory coat. Prepare syringes in a bio-safety cabinet or fume hood. Avoid generating aerosols when priming syringes.

---

**SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES**

---

Appearance:	Translucent liquid	% Volatile:	Not Available
Color:	Red	Evaporation:	Not Available
Odor:	Unknown	Melting Point:	Not Available
Boiling Point:	Not Available	Vapor Press.:	Not Available
Solubility in water:	Good	pH:	6.5
Spec. Gravity:	1.03	Vapor Dens.:	Not Available

---

**SECTION 10. STABILITY AND REACTIVITY**

---

Stability:

Stable.

Hazardous combustion or decomposition products:

Nature of decomposition products is not known.

Hazardous Polymerization:

Will not occur

---

**SECTION 11. TOXICOLOGICAL INFORMATION**

---

Acute effects

May be harmful by inhalation and ingestion. Causes irritation to the skin, eyes and mucosa

Chronic effects

Confirmed Carcinogenic, mutagenic and teratogenic in animal models.

Probable Carcinogenic, mutagenic and teratogenic in humans.

Possible adverse effects on male and female fertility have not been adequately evaluated, but it is suspected that the effects are adverse to human fertility.

RTECS data supplied is for the most abundant hazardous component of this product.

RTECS # 019295900 - Doxorubicin Hydrochloride.

Only selected RTECS data is presented here. See actual entry in RTECS for complete information.

Toxicity data

LDLo:	2571 µg/Kg/2Y	Intermittent intravenous - man
TDL0:	12 mg/Kg/26W	Intermittent intravenous - man
LD <sub>50</sub> :	16030 µg/Kg	intraperitoneal - rat
LD <sub>50</sub> :	21800 µg/Kg	subcutaneous - rat
LD <sub>50</sub> :	12510 µg/Kg	intravenous - rat
LD <sub>50</sub> :	16 mg/Kg	intramuscular - rat
LD <sub>50</sub> :	698 mg/Kg	oral - mouse

LD <sub>50</sub> :	11160 µg/Kg	intraperitoneal - mouse
LD <sub>50</sub> :	7678 µg/Kg	subcutaneous - mouse
LD <sub>50</sub> :	1245 µg/Kg	intravenous - mouse
LD <sub>50</sub> :	13700 µg/Kg	intramuscular - mouse
LD <sub>50</sub> :	6 mg/Kg	intravenous - rabbit

---

**SECTION 11. TOXICOLOGICAL INFORMATION (CONTINUED)**

---

Mutagenicity Data	[RTECS]
Carcinogenicity Data	[RTECS]
Reproductive Effects Data	[RTECS]

Target organs

Bone marrow, heart, immune system, reproductive system (male)

---

**SECTION 12. ECOLOGICAL INFORMATION**

---

Data not available

---

**SECTION 13. DISPOSAL CONSIDERATIONS**

---

Mix material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Follow all local, state and federal Environmental, Health and Safety regulations.

---

**SECTION 14. TRANSPORTATION INFORMATION**

---

DOXIL<sup>®</sup> is not classified as a hazardous material according to regulations of the US Department of Transportation (49 CFR 173) nor the United Nations Recommendations on the Transport of Dangerous Goods.

---

**SECTION 15. REGULATORY INFORMATION**

---

UN number:	Not listed
RID/ADR:	Not listed
EINECS:	Not listed (DOXIL <sup>®</sup> is not listed. The active ingredient, doxorubicin hydrochloride, is listed as 246-818-3.)
TSCA:	Not listed*
RCRA:	Not listed*
SARA (302):	Not listed*
SARA (313)	Not listed*
OSHA:	No exposure limits set*

\* Neither DOXIL<sup>®</sup> nor its active ingredient, doxorubicin hydrochloride, is listed.

---

**SECTION 16. OTHER INFORMATION**

---

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. SEQUUS Pharmaceuticals, Inc. shall not be held liable for any damage resulting from handling or from contact with the above product. See your invoice or packing slip for any additional terms and conditions.