SAFETY DATA SHEET

Section 1 – Identification of the Substance/Preparation and the Company/Undertaking

1.1 Product Identifier

Trade Name (As Labeled):	**Vyxeos™**
Chemical Name/Class:	For Active Ingredients: Daunorubicin Hydrochloride / Cytarabine
U.N. Number:	Not Applicable
U.N. Dangerous Goods Class/Subsidiary Risk:	Not Applicable
How Supplied:	Lyophilized solid for reconstitution
Date of Preparation:	September 28, 2017

1.2 Relevant Identified Uses of the Substance or Mixture and Uses Advised Against

Product Use:	Cancer treatment
Uses Advised Against:	All other uses

1.3 Details of the Supplier of the Substance or Mixture

Supplier/Manufacturer's Name:	Jazz Pharmaceuticals, Inc.
Address:	Palo Alto, CA 94304 USA
Phone:	+1-650-496-3777
Email address:	jazzpharma@medcomsol.com

1.4 Emergency Telephone Number +1-800-890-3098 (in US)
+1-800-520-5568 (from outside US)

Section 2 - Hazards Identification

2.1 Classification of the Substance or Mixture

GHS/OSHA/CLP (1272/2008) Classification:
Respiratory Sensitization Category 1 (H334)
Skin Sensitization Category 1 (H317)
Germ Cell Mutagenicity Category 2 (H341)
Carcinogenicity Category 2 (H351)
Reproductive Toxicity Category 1B (H360FD)
Aquatic Chronic Toxicity Category 3 (H412)

Note: Medicinal products as defined in Directive 2001/83/EC in their finished state, intended for the final user are not subject to the EU Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (Reg. No 1272/2008) or the requirement in REACH for a safety data sheet.

2.2 Label Elements

DANGER
H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H317 May cause an allergic skin reaction.
H341 Suspected of causing genetic defects.
H351 Suspected of causing cancer.
H360DF May damage fertility or the unborn child.
H412 Harmful to aquatic life with long lasting effects.
Prevention
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.

P261 Avoid breathing dust.
P272 Contaminated clothing must not be allowed out of the workplace.
P273 Avoid release to the environment.
P280 Wear protective gloves and eye protection.
P284 In case of inadequate ventilation wear respiratory protection.

Response
P302+P352 IF ON SKIN: Wash with plenty of soap and water.
P333+P313 If skin irritation or rash occurs: Get medical attention.
P362+P364 Take off contaminated clothing and wash it before reuse.
P304+P340 IF INHALED: remove person to fresh air and keep comfortable for breathing.
P342+P311 If experiencing respiratory symptoms: Call a POISON CENTER or doctor.
P308+P313 If exposed or concerned: Get medical advice.

Storage
Store locked up.

Disposal
Dispose of container and contents as pharmaceutical waste is accordance with national and local regulations.

2.3 Other Hazards: None

Section 3 - Composition Information on Ingredients

3.1 Mixture

Chemical Name	CAS Number / EINECS Number / REACH Reg. Number	% (w/w)	CLP/GHS Classification (1272/2008)
Cytarabine	147-94-4/205-705-9	3.4	Skin Irritation Category 2 (H315) Eye Irritation Category 2 (H319) Respiratory Sensitization Category 1 (H334) Skin Sensitization Category 1 (H317) Carcinogenicity Category 2 (H351) Reproductive Toxicity Category 1B (H360FD)
Copper(II) Gluconate (Elemental copper)	527-09-3/208-408-2	3.4 (0.48 Cu)	Aquatic Acute Toxicity Category 1 (H400) Aquatic Chronic Toxicity Category 1 (H410)
Daunorubicin Hydrochloride (as a free base)	23541-50-6 /245-723-4	1.5	Acute Oral Toxicity Category 3 (H301) Germ Cell Mutagenicity Category 2 (H341) Carcinogenicity Category 2 (H351) Reproductive Toxicity Category 1B (H360FD)
Non-hazardous ingredients	Mixture	Balance	Not Hazardous

Section 4 - First Aid Measures

4.1 Description of First Aid Measures

PERSONS ACCIDENTALLY OVEREXPOSED TO VYXEOS™ MUST RECEIVE MEDICAL ATTENTION IF ANY ADVERSE EFFECTS OCCUR! Take a copy of label and MSDS to health professional with victim.
Skin Exposure: Remove contaminated clothing. Wash contact area thoroughly with soap and water. If irritation persists or other symptoms develop, get medical attention.
Eye Exposure: If this material contaminates the eyes, flush eyes with gently running water for several minutes. If irritation persists or other symptoms develop, get medical attention.
Inhalation: Inhalation is an unlikely route of exposure for this material. If aerosols or mists of this material are inhaled, remove victim to fresh air. If irritation persists or other symptoms develop, get medical attention.
Ingestion: Ingestion is not anticipated to be a significant route of overexposure. If this material is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, DO NOT induce vomiting: Have the victim rinse their mouth and drink 2 glasses of water. Never induce vomiting or give diluents (water) to someone who is unconscious, having convulsions, or unable to swallow.

4.2 Most Important symptoms and effects, both acute and delayed: May cause eye and skin irritation. Ingestion or inhalation may cause effects similar to therapeutic use including bone marrow suppression, leukopenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, abdominal pain, cardiac toxicity, myelosuppression, infection, hemorrhage, alopecia (hair loss) and hepatic dysfunction. Cytarabine is a skin and respiratory sensitizer; subsequent exposure to small amounts may cause allergic reaction (e.g., sneezing, wheezing, difficulty breathing, skin rash) in susceptible individuals. This product is suspected to cause germ cell mutagenicity and cancer. It may cause adverse effects on fertility and the developing fetus.

4.3 Indication of Immediate Medical Attention and Special Treatment, if needed: Seek immediate medical attention if any adverse effects occur.
Recommendations to Physicians: Treat symptoms and eliminate overexposure. There is no known antidote for accidental exposure.

Section 5 - Fire-Fighting Measures

5.1 Suitable Extinguishing Media: Use any media that is suitable for the surrounding fire.
5.2 Specific Hazards arising from the Chemical: This product is not flammable or combustible. When involved in a fire, products of thermal decomposition may include irritating fumes and toxic gases (e.g., carbon oxides, nitrogen oxides, and hydrogen chloride).
5.3 Special Protective Equipment and Precautions for Fire Fighters: Firefighters should wear positive pressure self-contained breathing apparatus and full protective clothing for fires in areas where chemicals are used or stored.

Section 6 - Accidental Release Measures

6.1 Personal Precautions, Protective Equipment and Emergency Procedures: Clear spill area of unprotected people. Responders should wear appropriate protective clothing to avoid contact with material (see section 8).
6.2 Environmental Precautions: Avoid release to the environment. Report spills are required by local and national authorities.
6.3 Methods and Materials for Containment/Cleanup: For solid spills, carefully wipe up with a damp absorbent towel. If liquid, absorb small spills with paper towels or damp sponge. Clean exposed surfaces with water-wetted wipes followed by dilute bleach wipes followed by ethanol wipes followed by dilute HCl followed by soap and water. Solutions range from purple to orange and are easily removed from most surfaces using the above cleaning agents. Clean the area until colored areas which are water soluble have been eliminated.

Monitoring the cleanup process using color should avoid unintentionally spreading the contamination by the use of inappropriate cleaning technique (such as the use of copious volumes of cleaning solution). Place all spill residue and clean-up materials in an appropriate container and seal. Dispose of in accordance with applicable U.S. Federal, State, or local procedures or appropriate standards Canada or EU Member States (see Section 13, Disposal Considerations).

Section 7 - Handling and Storage

7.1 Precautions for Safe Handling: This product is a potent antineoplastic drug. Avoid contact with eyes, skin and clothing. Avoid creating and breathing aerosols or mists. Wash thoroughly after handling this material or equipment and containers that have been in contact with this material. Do not eat, smoke or drink while handling this product. Remove contaminated clothing immediately. Follow SPECIFIC USE INSTRUCTIONS supplied with this material. In addition, smokers who do not take simple protective measures such as gloving and hand washing may take in additional amounts of the drug orally through contaminated cigarettes, resulting in exposure. Particular care in working with this material must be practiced in pharmacies and other preparation areas, during manufacture of this compound, 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;
- Opening ampoules; and,
- Expulsion of air from drug-filled syringes.

DO NOT CLIP OR CRUSH NEEDLE WITH WHICH THIS PRODUCT WAS IN CONTACT.
Use of this product should meet the following provisions.

- Work should be performed in an appropriate, designated area;
- Contaminated waste must be properly handled; and,
- If necessary, work areas must be regularly decontaminated.

7.2 Conditions for Safe Storage, Including Any Incompatibilities: Store as directed on the package insert, refrigerated at 5ºC in an upright position.

7.3 Specific end use(s):
Industrial uses: None identified
Professional uses: Pharmaceutical use only

Section 8 - Exposure Controls / Personal Protection

8.1 Control Parameters

CHEMICAL	EXPOSURE LIMIT
Daunorubicin Hydrochloride	None Established
Copper Gluconate (as Cu dust/mist)	1 mg/m^3 TWA ACGIH TLV, Belgium, Denmark, France, Spain, Sweden, UK 2 mg/m^3 STEL Denmark, France, UK 0.01 mg/m^3 TWA, 0.02 mg/m3 STEL (respirable) Germany
Cytarabine	None Established

8.2 Exposure Controls:

Appropriate Engineering Controls: Use with adequate process enclosures or local exhaust ventilation to minimize exposure. Follow standard cancer drug handling procedures.
Personal Protective Equipment
Respiratory Protection: Respiratory protection is not generally needed during routine use of this material. If mists or aerosols are generated, appropriate respiratory protection should be worn. Equipment selection depends on

contaminant type and concentration. Select and use in accordance with 29 CFR 1910.134, EN136, EN143 or other applicable regulations and good industrial hygiene practice. For firefighting, use self-contained breathing apparatus.
Eye Protection: Wear eye protection as required to avoid eye contact. Refer to U.S. OSHA 29 CFR 1910.133, appropriate Canadian Standards, or the European Standard EN166 for further information.
Hand Protection: Wear Nitrile NBR gloves for routine use. If necessary, refer to U.S. OSHA 29 CFR 1910.138, appropriate Standards of Canada or EN374.
Other Protective Equipment/Clothing: Appropriate protective clothing as needed to minimize skin contact. Suitable washing and eye flushing facilities should be available in the work area. Contaminated clothing should be removed and laundered before re-use.

Section 9 - Physical and Chemical Properties

9.1 Information on basic Physical and Chemical Properties

Appearance:	Opaque purple solid in a clear vial	**Odour:**	Odourless
Odour Threshold:	Not applicable	**pH:**	6-8
Melting/Freezing Point:	Not established	**Boiling Point/Range:**	Not applicable
Flash Point:	None	**Evaporation Rate:**	Not applicable
Flammability (Solid, Gas)	Not flammable	**Flammability Limits:**	Not applicable
Vapor Pressure:	Not applicable	**Vapor Density:**	Not applicable
Relative Density:	Not established	**Solubilities**	Water: Soluble
Partition Coefficient (n-Octanol/Water)	Not established	**Autoignition Temperature:**	Not established
Decomposition Temperature:	Not established	**Viscosity:**	Not applicable

9.2 Other Information: None available

Section 10 - Stability and Reactivity

10.1 Reactivity: Normally unreactive
10.2 Chemical Stability: Stable
10.3 Possibility of Hazardous Reactions: None known.
10.4 Conditions to Avoid: Exposure to or contact with extreme temperatures and incompatible chemicals.
10.5 Incompatible Materials: This material is generally compatible with other common materials in a medical facility. Acids, caustics, strong oxidizers, and other chemicals that could affect its performance should be avoided.
10.6 Hazardous Decomposition Products: Discard if exposed to high temperatures (>50ºC/120ºF). The materials of thermal decomposition may include irritating fumes and toxic gases (e.g., carbon oxides, nitrogen oxides and hydrogen chloride).

Section 11 - Toxicological Information

11.1 Information on Toxicological Effects:

POTENTIAL HEALTH EFFECTS:
Symptoms of Overexposure by Route of Exposure: The extent of entry into the body by most routes has not been fully investigated. Occupational exposures to this product may cause acute effects in humans, as described in the following paragraphs.
Inhalation: Inhalation of vapors, mists, or sprays of this product may slightly irritate the nose, throat, and lungs. Severe inhalation overexposure may cause symptoms such as those described for "Other Potential Health Effects".

Cytarabine is a respiratory sensitizer; subsequent exposure to small amounts may cause allergic reaction (e.g., sneezing, wheezing, difficulty breathing) in susceptible individuals.
Skin: Skin contact with this material may be mildly irritating. Symptoms of skin contact may include redness and itching. Repeated skin contact may cause dermatitis (dry, red skin). Cytarabine is a skin sensitizer; subsequent exposure to small amounts may cause allergic reaction (e.g., rash, redness, itching) is susceptible individuals. Persons susceptible to sensitization who are repeatedly exposed to low-levels of this product by skin contact may experience allergic reaction.
Eyes: Eye contact with this material may be irritating. Symptoms of eye contact may include redness, pain, and tearing.
Skin Absorption: This material is not known to be absorbed through the skin.
Ingestion: Ingestion is not anticipated to be a significant route of occupational overexposure for this material. If this material is swallowed (i.e., through poor hygiene practices), it may slightly irritate the mouth and throat. Severe ingestion overexposure of this material may cause symptoms described for "Other Potential Health Effects". Cytarabine may cause an allergic reaction when ingested.
Injection: Though not anticipated to be a significant route of overexposure for this material, injection (via punctures or lacerations by contaminated objects) may cause redness at the site of injection. Symptoms may include those described for "Other Potential Health Effects".
Other Potential Health Effects: This product is a potent antineoplastic drug. Therapeutic use of this product has caused bone marrow suppression, leukopenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, abdominal pain, cardiac toxicity, myelosuppression, infection, hemorrhage, alopecia (hair loss) and hepatic dysfunction. Cytarabine is a skin and respiratory sensitizer; subsequent exposure to small amounts may cause allergic reaction (e.g., sneezing, wheezing, difficulty breathing, skin rash) in susceptible individuals. This product is suspected to cause germ cell mutagenicity and cancer. It may cause adverse effects on fertility and the developing fetus.

Toxicity Data: The following data are for the active ingredients in this product:
Cytarabine: LD50 (oral, rat)>5000 mg/kg; LD50 (intravenous, rat) >5000 mg/kg
Daunorubicin Hydrochloride: LD50 (oral, rat) = 290 mg/kg; LD50 (oral mouse) = 250 mg/kg

Carcinogenicity: Daunorubicin is classified by IARC as a possible carcinogen (group 2B) (listed as Daunomycin) and by the US EPA as a probable human carcinogen (group 2). Daunorubicin Hydrochloride caused fibrosarcomas at the injection site in mice. No carcinogenic effects were observed when administered 3xweekly to mice for 18 months. In male rats, administration of Daunorubicin Hydrochloride 3xweek for 6 months resulted in the development of peritoneal sarcomas.
Irritancy of Material: This material may be irritating to the eyes and skin.
Sensitization to The Material: Cytarabine is a respiratory and skin sensitizer; subsequent exposure to small amounts may cause allergic reaction in susceptible individuals.
Reproductive Toxicity Information: There are no adequate and well-controlled studies in pregnant women. Intravenous administration of Daunorubicin in male dogs at a dose of 0.25 mg/kg/day caused testicular atrophy and total aplasia of the spermatocyte series in the seminiferous tubules with aspermatogenesis. Reproduction studies in rats treated with liposomal Daunorubicin dose of 2 mg/kg/day revealed evidence of severe maternal and embryo toxicity and fetal malformations (characterized by anophthalmia, microphthalmia and incomplete ossification). Administration of Cytarabine to rats resulted in fetotoxicity.

Germ Cell Mutagenicity: Daunorubicin Hydrochloride was mutagenic *in vitro* (Ames assay, V79 hamster cell assay), and clastogenic *in vitro* (CCRFCEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow) tests. Extensive chromosomal damage, including chromatid breaks have been produced by Cytarabine and malignant transformation of rodent cells in culture has been reported.

Aspiration Toxicity: Components are not aspiration hazards.

ACGIH Biological Exposure Indices: Currently, there are no ACGIH Biological Exposure Indices (BEIs) determined for the components of this material.

Section 12 - Ecological Information

12.1 Ecotoxicity: No data available. Copper gluconate is classified as very toxic to aquatic life based on the copper content.
12.2 Persistence And Degradability: No data available.
12.3 Bioaccumulative Potential: No data available.
12.4 Mobility in Soil: This material would be expected to be mobile in soil.
12.5 Results of PVT and vPvB assessment: Components do not meet the criteria of PBT or vPvB.
12.6 Other Adverse Effects: No data available.

Section 13 - Disposal Considerations

13.1 Preparing Wastes for Disposal: Waste disposal must be in accordance with appropriate U.S. Federal, State, and local regulations or with regulations of Canada or EU Member States. This material, 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 gowns, gloves, and disposable materials used in the preparation or handling of this drug should be disposed of in accordance with established medical waste disposal procedures. Incineration is recommended. Reusable equipment should be cleaned with soap and water.
U.S. EPA Waste Number: Not applicable to wastes consisting only of this material.

Section 14 - Transport Information

	14.1 UN Number	14.2 UN Proper Shipping Name	14.3 Hazard Class(s)	14.4 Packing Group	14.5 Environmental Hazards
US DOT	None	Not Regulated	None	None	No
Canadian TDG	None	Not Regulated	None	None	No
EU ADR/RID	None	Not Regulated	None	None	No
IMDG	None	Not Regulated	None	None	No
IATA/ICAO	None	Not Regulated	None	None	No

14.6 Special Precautions for User: None
14.7 Transport in Bulk According to Annex III MARPOL 73/78 and the IBC Code: Not applicable, transported only in packaged form

Section 15 - Regulatory Information

15.1 Safety, Health and Environmental Regulations/Legislation Specific for the Substance or Mixture

UNITED STATES REGULATIONS:
U.S. SARA Reporting Requirements: This material is not subject to the reporting requirements of Sections 302, 304, and 313 of Title Ill of the Superfund Amendments and Reauthorization Act.
U.S. SARA Threshold Planning Quantity: There are no specific Threshold Planning Quantities for this material. The default Federal MSDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) may apply, per 40 CFR 370.20.
U.S. CERCLA Reportable Quantity (RQ): Not applicable.
U.S. TSCA Inventory Status: This material is regulated by the Food and Drug Administration; it is exempt from the requirements of TSCA.

California Safe Drinking Water and Toxic Enforcement Act {PROPOSITION 65}: Daunorubicin hydrochloride and Cytarabine are listed as developmental toxins.

CANADIAN REGULATIONS:
Canadian DSL/NDSL Status: This material is regulated by the Therapeutic Materials Programme (TPP) of Health Canada; it is exempt from the requirements of CEPA.
Canadian WHMIS IDL Disclosure Status: Not applicable.
Canadian Environmental Protection Agency (CEPA) Priority Substances Lists: This material is not on the Priority Substances Lists.

Vyxeos™ (Cytarabine:Daunorubicin) Liposome Injection is registered with the Health Canada under Clinical Trial Application File # 9427-C2874-21C and is limited to investigational use only.

EUROPEAN UNION INFORMATION FOR MATERIAL:
Vyxeos™ (Cytarabine: Daunorubicin) Liposome Injection is registered with the European Medicine Agency under EUDRA CT# 2009-010951-28 and is limited to investigational use only.

This product is classified in accordance with EC CLP (Regulation No. 1272/2008). This Safety Data Sheet complies with the requirements of Regulation (EC) No 1907/2006 (REACH). Regulation EU No. 1272/2008 on classification labeling and packaging of hazardous substances and mixtures (CLP) does not apply to medicinal products for human use defined by directive 65/65/CEE, at the finished stage, intended for the final user.

Section 16 - Other Information

CLP/GHS Classification and H Phrases for Reference (See Section 3)
H302 Harmful if swallowed.
H315 Causes skin irritation.
H319 Causes serious eye irritation.
H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H317 May cause an allergic skin reaction.
H341 Suspected of causing genetic defects.
H351 Suspected of causing cancer.
H360DF May damage fertility or the unborn child.
H400 Very toxic to aquatic life
H410 Very toxic to aquatic life with long lasting effects

Prepared by: Industrial Health & Safety Consultants, Inc. Shelton, CT 06484

Version: 2
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Supersedes SDS Dated: July 7, 2017

This SDS conforms to Regulation (EU) No. 1907/2006 and 2015/830, US OSHA Hazcom 2012 (29 CFR1910.1200) and Canada WHMIS 2015.

Disclaimer: The above mentioned information is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. The information in this document is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. It does not represent any guarantee of the properties of the product. Jazz Pharmaceuticals shall not be held liable for any damage resulting from handling or use of this product.

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Approvals:

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Sean Hunt; Environmental, Health & Safety Specialist; Document Consolidator

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Kieran O'Donoghue; Dir, Global Regulatory Affairs CMC; Signing as Approver; 10-Oct-2017 08:18:34 IST

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