SAFETY DATA SHEET

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

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Additional Address	Sindan Pharma Ion Mihalache Blvd, 11 011171 Bucharest 1 Romania Tel: (+40) 21 318 17 67 Fax: (+40) 21 312 44 99
Product identifier	Doxorubicin Hydrochloride Powder for Injection
Synonyms	None identified
Trade names	Sindroxocin 10 mg, 50 mg
Chemical family	Mixture. Doxorubicin hydrochloride is an anthracycline antibiotic.
Relevant identified uses of the substance or mixture and uses advised against	Bulk formulated pharmaceutical product/Formulated pharmaceutical product packaged in final form and intended for the final user; indicated for the treatment of certain types of cancer.
Note	The toxicological and ecological properties of this mixture and/or its ingredients have not been fully characterized. This SDS will be revisited as more data become available.
Issue Date	6 January 2011

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture	**Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada.** Please consult the prescribing/packaging information. **The classification and labelling listed below is for bulk Doxorubicin Hydrochloride Powder for Injection.**

Regulation (EC) 1272/ 2008 [GHS]	Acute toxicity - oral - Category 4. Irritant (skin) - Category 2. Irritant (eye) - Category 2. Reproductive Toxicity - Category 1B. Germ Cell Mutagenicity - Category 1B. Carcinogenic - Category 1B. Specific Target Organ Toxicity (repeated exposure) - Category 1.
Directive 67/548/EEC or 1999/45/EC	T - R22, R36/38, R45 (Carc. Cat. 2), R46 (Muta. Cat. 2), R60 (Repr. Cat. 2), R61 (Repr. Cat. 2)

Label elements

CLP/GHS hazard pictogram

CLP/GHS signal word	Danger
CLP/GHS hazard statements	H302 - Harmful if swallowed. H315 - Causes skin irritation. H319 - Causes serious eye irritation. H340 - May cause genetic defects. H350 - May cause cancer. H360FD - May damage fertility. May damage the unborn child. H372 - Causes damage to the blood, bone marrow, gastrointestinal tract, heart and reproductive organs through prolonged or repeated exposure.
CLP/GHS precautionary statements	P201 - Obtain special instructions before use. P260 - Do not breathe dust. P280 - Wear protective gloves/eye protection/face protection. P281 - Use personal protective equipment as required. P302 + P352 - If on skin: Wash with plenty of soap and water. P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P308 + P313 - If exposed or concerned: get medical advice/attention. P337 + P313 - If eye irritation persists: Get medical advice/attention. P362 - Take off contaminated clothing and wash before reuse. P501 - Dispose of contents/ container to location in accordance with local/regional/national/international regulations.
EU symbol/indication of danger	 T - Toxic
Risk (R) Phrase(s)	R22 - Harmful if swallowed. R36/38 - Irritating to eyes and skin. R45 - May cause cancer. R46 - May cause heritable genetic damage. R60 - May impair fertility. R61 - May cause harm to the unborn child.

Safety Advice	S24 - Avoid contact with skin. S26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S36/37 - Wear suitable protective clothing and gloves. S53 - Avoid exposure - Obtain special instructions before use.
Other hazards	Contains doxorubicin hydrochoride, a cytotoxic agent. Commonly reported effects seen with the therapeutic use of doxorubicin include severe bone marrow suppression (often dose-limiting), gastrointestinal toxicity, increased susceptibility to infection, and hair loss. Red discoloration of the urine may occur for 1-2 days after treatment. Doxorubicin, like other anthracyclines, may also produce cardiotoxicity, which manifests both as an acute, transient cardiac dysfunction and as delayed, irreversible and sometimes fatal congestive heart failure. Extravasation of the drug following IV administration can cause severe skin irritation. Doxorubicin can cause mutations in sperm and a reduction in sperm count, which may be permanent. Although reversible disruption of the menstrual cycle as well as premature menopause have been reported in female patients, one retrospective study of young women with breast cancer who were treated with doxorubicin found that a large number maintained intact ovarian function. There was no increased risk of anomalies in subsequent pregnancies. Secondary leukemia has occurred in cancer patients treated with anthracyclines, most frequently when the drugs are administered as part of combination therapies. There are scientific studies that suggest personnel (*e.g.*, nurses, pharmacists) who prepare and administer parenteral antineoplastics may be at some risk due to potential mutagenicity, adverse effects on reproduction and/or carcinogenicity if these materials are not properly controlled in the workplace. The actual risk in the workplace is not known.
US Signal word	Warning
US Hazard overview	Mixture contains doxorubicin hydrochloride - a cytotoxic anticancer agent. May be harmful if swallowed. Causes skin/eye irritation. Possible Reproductive/ Developmental hazard - may cause adverse reproductive/developmental effects. Possible birth defect hazard - May cause birth defects. Genotoxic. Can cause blood, bone marrow, and gastrointestinal, reproductive organ and heart damage.
Note	This mixture is classified as dangerous/hazardous according to Directive 67/548/ EEC, Regulation EC No 1272/2008 (EU CLP), and applicable US regulations. The GHS classifications are based on Regulation (EC) 1272/2008. The EU symbol/ indicator of danger, R Phrases and Safety Advice are based on Directive 67/548/ EEC or 1999/45/EC.

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	EU Classification	GHS Classification
Doxorubicin Hydrochloride	25316-40-9	246-818-3	10-20%	T - Toxic: R22, R36/38, R45, R46, R60, R61	ATO4: H302; SI2: H315; EI2: H319; RT1B: H360FD; GCM1B: H340; Carc1B: H340, STOT-R1: H372
Methyl Paraben	99-76-3	202-785-7	1-2%	Xi - Irritant: R36	EI2: H319

Note The ingredient(s) listed above are considered dangerous/hazardous. The remaining components are non-dangerous/not hazardous and/or present at amounts below reportable limits. See Section 16 for full text of EU and EU-CLP/GHS classifications. The EU classification is based on Directive 67/548/EEC and the GHS classification is based on Regulation (EC) 1272/2008.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed Yes

Eye Contact If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.

Skin Contact Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

Inhalation Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.

Ingestion Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.

Protection of first aid responders See Section 8 for Exposure Controls/Personal Protection recommendations.

Most important symptoms and effects, both acute and delayed See Sections 2 and 11.

SECTION 4 - FIRST AID MEASURES …continued

Indication of immediate medical attention and special treatment needed, if necessary	Contains doxorubicin hydrochloride - a cytotoxic anticancer agent. Medical conditions aggravated by exposure: Hypersensitivity to doxorubicin or other anthracyclines, myelosuppression, cardiac conditions, previous treatment with other anthracyclines, liver impairment. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	No information identified. May emit toxic fumes of carbon monoxide, carbon dioxide, and oxides of nitrogen.
Flammability/ Explosivity	No explosivity or flammability data identified. High concentrations of finely divided airborne organic particles can potentially explode if ignited.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Area should be adequately ventilated. Do not breathe dust.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	Do not cause material to become airborne. Surround spill or powder with absorbents and place a damp cloth or towel over the area to minimize entry of powder into the air. Add excess liquid to allow the material to enter solution. Capture remaining liquid onto spill absorbents. Place spill materials into a leak-proof container suitable for disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling potent cytotoxic pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Avoid breathing dust. Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at room temperature (~15-25°C) away from incompatible materials. Do not refrigerate or freeze. Keep away from direct light. Keep container tightly closed in a dry and well-ventilated place.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note	Wash hands, face and other potentially exposed areas immediately in the event of physical contact.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Doxorubicin Hydrochloride	--	--	--

Exposure/Engineering controls	Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.
Respiratory protection	Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with appropriate HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where air purifying respirators may not provide adequate protection.
Hand protection	Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered. When the material is dissolved or suspended in an organic solvent, wear gloves that provide protection against the solvent.
Skin protection	Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.
Eye/face protection	Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Lyophilized powder
Color	Red
Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	Not applicable.
Flash point	No information identified.
Evaporation rate	Not applicable.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified.
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	Soluble.
Solvent solubility	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.
Other information	
Molecular weight	579.99 (doxorubicin HCl)
Molecular formula	$C_{27}H_{29}NO_{11} \cdot HCl$ (doxorubicin HCl)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Chemically stable; pharmacological stability not guaranteed beyond expiration date imprinted on package..
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	Light sensitive; protect from light.
Incompatible materials	Oxidizing agents.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note	**The following data describe the active ingredient and/or the individual ingredients where applicable.**
Information on toxicological effects	
Route of entry	May be absorbed by inhalation, skin contact and ingestion.

SECTION 11 - TOXICOLOGICAL INFORMATION …continued

Acute toxicity

Compound	Type	Route	Species	Dose
Doxorubicin Hydrochloride	LD_{50}	Oral	Mouse	698 mg/kg
	LD_{50}	Intravenous	Rat	12.5 mg/kg
	LD_{50}	Intravenous	Mice	1.2 mg/kg
	LD_{50}	Oral	Mouse	570 mg/kg
Methyl Paraben	LD_{50}	Oral	Rat	2100 mg/kg
	LD_{50}	Oral	Mouse	>8000 mg/kg

Irritation/Corrosion Doxorubicin hydrochloride may cause severe eye/skin irritation

Sensitization Methyl paraben may cause allergic skin reactions if applied to damaged skin, however sensitization reactions are rare when applied to intact skin.

STOT-single exposure No data available.

STOT-repeated exposure/Repeat-dose toxicity Daily IV doses of 0.125 mg/kg doxorubicin given to rabbits and dogs did not cause deaths or clinical signs of toxicity. A dosage of 0.5 mg/kg/day caused lethality in rats and dogs. Target organs of toxicity were the gastrointestinal tract, hematopoietic system, testes, kidney (rabbits only), and skin (dogs only).

Reproductive toxicity Doxorubicin was positive when tested in the mouse dominant lethal assay, and was toxic to male reproductive organs in repeat-dose studies. Intraperitoneal dosages of 0.05 and 0.1 mg/kg/day caused effects on fertility in female and male rats, respectively.

Developmental toxicity Pregnant rats and rabbits treated IV with 0.8 and 0.6 mg/kg/day doxorubicin, respectively, during organogenesis had increased resorptions and abortions as well as fetal skeletal and soft tissue malformations. Single doses (?2 mg/kg) given to rabbits also blocked implantation and were abortifacient.

Genotoxicity Doxorubicin was positive when tested in a number of short-term mutagenicity and clastogenicity assays, both *in vitro* and *in vivo.*

Carcinogenicity Mammary tumors were seen in rats treated with single IV doses of 8 mg/kg doxorubicin. Doxorubicin has been classified by the International Agency for Research on Cancer (IARC) as an IARC Group 2A carcinogen (probably carcinogenic to humans). According to NTP, doxorubicin is reasonably anticipated to be a human carcinogen. Doxorubicin is also listed as a carcinogen under OSHA. No other components of the product present at levels greater than or equal to 0.1% are listed by NTP, IARC, ACGIH or OSHA as a carcinogen.

Aspiration hazard No data available.

Human health data See "Section 2 - Other Hazards"

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Doxorubicin Hydrochloride	--	--	--

SECTION 12 - ECOLOGICAL INFORMATION …continued

Persistence and Degradability	No data available.
Bioaccumulative potential	No data available.
Mobility in soil	No data available.
Results of PBT and vPvB assessment	Not performed.
Other adverse effects	No data available.
Note	The environmental characteristics of the formulated product have not been fully investigated. Data above describe the active ingredient and/or the individual ingredients where applicable. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods	Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this substance is not regulated as a hazardous material/ dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG.
UN number	None assigned.
UN proper shipping name	None assigned.
Transport hazard classes and packing group	None assigned.
Environmental hazards	Based on the available data, this product/mixture is not regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS complies with the requirements under US, EU and GHS (EU CLP - Regulation EC No 1272/2008) guidelines. Consult your local or regional authorities for more information.
Chemical safety assessment	Not conducted.
OSHA Hazardous	Yes. Warning. Mixture contains doxorubicin hydrochloride - a cytotoxic anticancer agent. May be harmful if swallowed. Causes skin/eye irritation. Possible Reproductive/Developmental hazard - may cause adverse reproductive/ developmental effects. Possible birth defect hazard - May cause birth defects. Genotoxic. Can cause blood, bone marrow, and gastrointestinal, reproductive organ and heart damage.
WHMIS classification	Not required. Drugs are not subject to WHMIS. This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the SDS contains all of the information required by those regulations.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	This product contains chemical(s) (doxorubicin) known to the state of California to cause cancer, developmental toxicity and male reproductive toxicity.
Additional information	Doxorubicin hydrochloride is considered a hazardous drug by NIOSH.

SECTION 16 - OTHER INFORMATION

Full text of R phrases and EU Classifications	X_i - Irritant. T - Toxic. R22 - Harmful if swallowed. R36 - Irritating to eyes. R36/ 38 - Irritating to eyes and skin. R45 - May cause cancer. Carc. Cat. 2 - Carcinogenic Category 2. R46 - May cause heritable genetic damage. Muta. Cat. 2 - Mutagenic Category 2. R60 - May impair fertility. R61 - May cause harm to the unborn child. Repr. Cat. 2 - Toxic for reproduction Category 2.
Full text of H phrases, P phrases and GHS classification	ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. SI2 - Skin irritant Category 2. H315 - Causes skin irritation. EI2 - Eye irritant Category 2. H319 - Causes serious eye irritation. RT1B - Reproductive toxicity Category 1B. H360FD - May damage fertility. May damage the unborn child. GCM1B - Germ Cell Mutagenicity Category 1B. H340 - May cause genetic defects. Carc1B - Carcinogenic Category 1B. H350 - May cause cancer. STOT-R1 - Specific Target Organ Toxicity Following Repeat Exposure Category 1. H372 - Causes damage to the blood, bone marrow, gastrointestinal tract, heart and reproductive organs through prolonged or repeated exposure.
Sources of data	Information from published literature and internal company data.

SECTION 16 - OTHER INFORMATION …continued

Abbreviations

ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System

Revisions

This is the first version of this SDS.

Disclaimer

The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions.

No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse incident associated with this product, this Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.