Safety Data Sheet
Gemcitabine Hydrochloride for Injection

1 - Identification of the substance/mixture and of the company undertaking

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MATERIAL IDENTIFICATION:

Product Name: **Gemcitabine Hydrochloride for Injection 40 mg/ml**

Synomyms: Gemzar, Gemcin, Gemtro, 188011, 264368.

Chemical Name: Cytadine, 2'-deoxy-2', 2'-difluoro-monohydrochloride.

Chemical Formula: $C_9H_{11}F_2N_3O_4.HCl$.

Product Type: Regulated sterile injectible prescription drug.

Intended Use: Antineoplastic DNA synthesis inhibitor primarily used in the treatment of lung and other cancers.

Product Supply: 200 mg/5 ml vial or 1000 mg/25 ml vial or 2000 mg/50 ml in amber glass vials.

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 labeling listed below is for bulk Gemcitabine Hydrochloride.**

Hazard Statement: Product is a white, or off-white powder. The active material may enter the body through the skin, alters genetic material and may be irritating to the eyes and skin. Effects of exposure may include decreased fertility, foetal changes and decreased blood cell counts.

Specific hazards: Possible foetal development hazard that may adversely affect the developing foetus.

EU Hazard Symbols:

Label elements

Pictogram

Signal word Warning

Hazard statement(s)

H312 Harmful in contact with skin.
H315 Causes skin irritation.
H319 Causes serious eye irritation.
H341 Suspected of causing genetic defects.

Precautionary statement(s)

P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P264 Wash hands thoroughly after handling.
P280 Wear protective gloves/eye protection.
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.
P405 Store locked up.
P501 Dispose of contents/container in accordance with national regulations.

EU Risk Phrases:
R21 – Harmful in contact with skin.
R22 – Harmful if swallowed.
R36/38 – Irritating to eyes and skin.
R46 – May cause heritable genetic damage.
R62 – Possible risk of impaired fertility.
R63 – Possible risk of harm to the unborn child.

EU Indication of Danger:
Harmful.
Irritant.
Toxic to Reproduction, Category 3.
Mutagenic, Category 2.

Principle Routes of Entry: Inhalation and skin absorption.

Inhalation: Inhalation is not considered likely under normal usage conditions, due to the small quantity of material within each vial. If inhaled, may cause fibrosis.

Ingestion: Harmful if swallowed (based upon animal data). Effects including decreased blood cell counts, mouth sores, diarrhoea, tiredness, weakness, wheezing, bruising, hair loss, bloody stools, headache, rhinitis, constipation, muscle pain, sweating, drowsiness, sleep disturbance, shortness of breath, nausea, vomiting, oedema, rash, fever, elevated liver enzymes and flu-like symptoms.

Skin Contact: May cause irritation and/or allergic reactions, particularly to cut or abraded skin.

Eye Contact: May cause eye irritation. May cause allergic reaction. Effects may include stinging, watering, redness and swelling of the eyes.

3. COMPOSITION

Hazardous

Ingredients	CAS Number	RTECS Number	Classification	%
Gemcitabine Hydrochloride	122111-03-9	HA3840000	Mut. Cat. 2; T, R46; Repr. Cat. 2; R60; R61; T; Xi, R36; R38; R21, R22	4.8
Sodium Hydrogen Phosphate Dodecahydrate	10039-32-4	TC5725000	Not Listed	-
Sodium Hydroxide 5 mol/l	1310-73-2	Not Applicable	R35	-
Ethanol	64-17-5	KQ6300000	R11	-

Note: Sodium hydroxide is used for pH adjustment only.

This document has been prepared in accordance with standards for workplace safety, which require the inclusion of all known hazards of the substances, regardless of the potential risk. This document does not serve as a risk assessment. The precautionary statements and warnings included may not apply in all cases. Any workplace risk assessment should take into account the hazards detailed within this document.

4. FIRST AID MEASURES

See patient insert for additional information.

Inhalation: Remove to fresh air and keep patient still. Seek medical attention immediately. If patient is unconscious, provide artificial respiration. If breathing is difficult, give oxygen.

Skin contact: Remove contaminated clothing and footwear. Flush affected area of skin with copious quantity of soap and water. Seek medical attention if irritation occurs. Wash contaminated clothing before reuse.

Eye contact: Immediately irrigate eye/s with water, whilst holding eyelids open, for at least 15 minutes. Seek medical attention if irritation occurs.

Ingestion: Wash out mouth with water. Do NOT induce vomiting unless directly by medical personnel. Seek medical attention immediately. Activated charcoal (6-8 heaped teaspoons) can be administered with two-three glasses of water.

5. FIRE FIGHTING MEASURES

Suitable extinguishing media: Use carbon dioxide, dry chemical or water spray as appropriate to surroundings.

Unsuitable extinguishing media: Not known.

Special hazards in fire: During thermal decomposition, the formation of irritating vapours or fumes may be possible (i.e. chlorides and fluorides, carbon dioxide, carbon monoxide and oxides of nitrogen).

Firefighting instructions: Wear appropriate personal protective equipment, including self-contained breathing apparatus (SCBA).

6. ACCIDENTAL RELEASE MEASURES

Personnel precautions: Wear suitable protective clothing and gloves (see Section 8 – Exposure Controls).

Environmental precautions: Eliminate releases to drains, water courses and emissions to atmosphere.

Methods for cleaning: Contain spills with absorbent material (i.e. booms, towels, granules) and then place soiled materials in suitable sealed container for disposal as chemical waste. Clean affected area with soapy water.

Decontaminate spill site with 10 % caustic solution.

Additional considerations: If a large spill occurs, evacuate non-essential personnel. Report emergency situations immediately. Clean-up operations should only be performed by trained personnel.

7. HANDLING AND STORAGE

Handling: Wash hands thoroughly after handling and before eating, drinking or smoking.

As with all potent pharmaceutical products, avoid contact and inhalation of dust, fumes, mist and/or vapours associated with the product.

Storage: To prevent deterioration of the product, keep in sealed container until time of use. Store between 15-30 ºC and out of direct sunlight. Do not freeze or refrigerate.

Incompatible products: Strong oxidisers.

Special precautions: Persons with known hypersensitivities to gemcitabine products, pregnant women, or women who want to become pregnant, should

consult an occupational health and/or safety professional prior to handling this material.

8. EXPOSURE CONTROLS

Engineering measures: During reconstitution, use a biological safety cabinet or other ventilated enclosure designed to miminise airborne exposure. This should discharge HEPA filtered air external to the room environment.

Ensure a safety shower and eye wash is available for personnel involved in handling larger quantities of product (i.e. during reconstitution). Ensure an eyewash is available during drug administration.

Respiratory protection: Not usually required for normal final use conditions. Where there is potential to exceed the exposure limit, suitable respiratory protective equipment will be required.

Personal protection: Wear suitable disposable protective clothing. For reconstitution, wear close-front lab coat, gown or smock with long sleeves and knit cuffs, as appropriate.

Eye protection: Wear suitable eye protection during dilution or reconstitution. Where eye contact is possible during final product use, wear suitable eye protection.

Hand protection: Wear suitable chemical-resistant impervious gloves (i.e. nitrile rubber).

Hygiene measures: Wash hands and arms thoroughly after handling this product.

Exposure limits:

Gemcitabine Hydrochloride
None have been assigned by any regulatory authority, however, for the bulk material the innovators of the drug utilised an in-house control limit during manufacture of 0.3 mcg/m3, expressed as an 8 hour Time Weighted Average.

Analytical Methods: Contact Sindan Pharma for further details on available analytical methods for occupational hygiene personal exposure monitoring to the active ingredient.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	Off-White colour solution
Odour:	No Data
pH:	No Data
Molecular Weight:	299.7 g/mol
Boiling point:	No Data
Melting point:	290 ºC (for solid compound)
Flashpoint:	No Data
Explosive properties:	No Data
Vapour pressure:	No Data
Relative density:	0.945
Viscosity:	No Data
Solubility:	Soluble in water.

10. STABILITY AND REACTIVITY

Stability: Stable under normal temperature conditions.

Conditions to Avoid: None.

Hazardous Polymerisation: Will not occur.

Incompatible Materials: Reactive with strong oxidizing or reducing agents. Avoid contact with peroxides, permanganates, nitric acid, etc.

11. TOXICOLOGICAL INFORMATION

This product is intended for therapeutic use only when prescribed by a physician. Potential adverse reactions from prescribed doses are described in the package insert. Reported warnings and adverse patient effects may include: decreased blood cell counts, mouth sores, diarrhoea, tiredness, weakness, wheezing, bruising, hair loss, bloody stools, headache, rhinitis, constipation, muscle pain, sweating, drowsiness, sleep disturbance, shortness of breath, nausea, vomiting, oedema, rash, fever, elevated liver enzymes and flu-like symptoms.

Signs and Symptoms of Exposure/Overexposure: Occupational exposure has not been fully investigated.

Medical Conditions Aggravated by Exposure: Individuals with hypersensitivity to Gemcitabine Hydrochloride Injection or any of its excipients. Pre-existing bone marrow, blood, cardiovascular, gastrointestinal, central nervous system, pulmonary, liver or skin ailments; or pregnancy.

Gemcitabine Hydrochloride in bulk form

ORAL LD_{50} (RAT): >500 mg/kg
INTRAVENOUS LD_{50} (RAT): 236 mg/kg

Skin absorption:

Gemcitabine hydrochloride for injection. Rabbit, median lethal dose estimated greater than 1000 mg/kg caused mortality, reduced activity, diarrhoea, weight loss, few faeces, pale eyes, salivation.

Irritation / Sensitisation:

The product is expected to be irritating to eyes, skin and the respiratory tract. In guinea pig sub-cutaneous tests, a negative systemic response was observed.

Reproductive Effects:

Decreased sperm formation and decreased fertility in males, as well as reproductive tissue changes. Currently, there have been no studies in pregnant women.

Embryotoxicity/Teratogenicity:

Depressed foetal viability and weight, as well as increased malformations at doses toxic to the mother.

Mutagencity:

Positive in both mouse lymphoma cells assay and mouse micronucleus test. Not mutagenic in bacterial cells and other mammalian cell tests.

Carcinogenicity:

The carcinogenic potential of Gemcitabine has not been examined in test animals; however, compounds with similar mechanisms of action (e.g., cytotoxic) and mutagenicity profiles have been reported to be carcinogenic. It is not listed as carcinogenic by NTP, IARC or OSHA.

12. ECOLOGICAL INFORMATION

The environmental characteristics of this material have not been fully evaluated. Releases to environment should be prevented.

Practically non-toxic to fish and micro-organisms and moderately toxic to green algae. Low potential to bioaccumulate in aquatic organisms. Expected to be persistent in the environment, due to slow rates of hydrolysis and biodegradation.

13 DISPOSAL CONSIDERATIONS

Dispose of waste by incineration in accordance with all applicable laws and regulations. EU Member State-specific and Community-specific provisions must be considered.

Packaging should be disposed of in keeping with all local and national legislation.

Treat all contaminated waste as bulk product and dispose of as pharmaceutical waste.

14. TRANSPORT INFORMATION

Classification data: Not regulated for transport under USDOT, IATA or IMDG regulations. May be subject to state and/or local transportation requirements.

15. REGULATORY INFORMATION

Ingredients are not listed as carcinogenic by IARC, NTP or OSHA.
Classification and Labeling According to EU Directives

EU Risk Phrases:
R21 – Harmful in contact with skin.
R22 – Harmful if swallowed.
R36/38 – Irritating to eyes and skin.
R46 – May cause heritable genetic damage.
R62 – Possible risk of impaired fertility.
R63 – Possible risk of harm to the unborn child.

EU Safety Phrases:
S24/25 – Avoid contact with the skin and eyes.
S26 – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S36/37/39 – Wear suitable protective clothing, gloves and eye/face protection.
S53 – Avoid exposure – obtain special instructions before use.

16. OTHER INFORMATION

Recommendations/ restrictions:	The information relates only to the specific material designated and may not be valid for such materials used in combination with other materials or in any process. Such information is, to the best of the company's knowledge and belief, accurate and reliable as of the date of issue. However, no warranty guarantee of representation is made to its accuracy, reliability or completeness. It is the user's responsibility to satisfy himself as to the suitability of such information for his own particular use.
Note:	There is limited evidence that personnel involved in the preparation and administration or parenteral antineoplastic agents may be at some risk due to mutagenicity and/or teratogenicity and/or carcinogenicity of these agents. The actual risk has not been adequately quantified. Cautious handling is required in both preparation and disposal of antineoplastic agents. Precautions suggested include the use of biological safety cabinets during reconstitution and dilution of parenteral medications, use of surgical gloves and masks good techniques to prevent worker and workplace contamination and proper disposal of needles, syringes, vials or ampoules.
Data Sources:	Proprietary drug development information and publicly available toxicity information.
Prepared by:	Registered professional occupational hygienists working for Actavis Corporate Environmental, Health and Safety.
Reasons for Revision:	Not applicable (first issue).