Safety Data Sheet
Oxaliplatin (lyophilised)

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

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MATERIAL IDENTIFICATION:

Product Name: Oxaliplatin (lyophilised)

Synomyms: Eloxatin, Eloxatine, Elplat, Dacplat, Lipoxal, 1-OHP, Orphenadrine, Oxalic Acid, Oxalatoplatin, Oxalaplatinum, Oxaliplatino (Spanish), Oxalato(1R,2R-cyclohexanediamine)platinum(II), RP 54780, JM-83, EP5.

Chemical Name: Platinum,(1,2-cyclohexanediamine-kN,kN')[ethandiato(2-)-kO1,kO2]-,[SP-4-2-(trans)]-.

Chemical Formula: $C_8H_{14}N_2O_4Pt$.

Product Type: Regulated freeze-dried sterile injectible prescription drug.

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

Product Supply: 50 mg/vial or 100 mg/vial 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 Oxaliplatin.**

Hazard: Product is a white, lyophilised cake. Cytotoxic. Eye irritant. May cause damage to the blood, liver, pulmonary, reproductive and

nervous systems. Harmful to the foetus. May cause allergic skin and/or respiratory reactions. Avoid contact with eyes, skin and clothing. Avoid exposure during pregnancy and while breastfeeding. Do not taste or swallow. Wash thoroughly after handling. Pre-existing blood, liver, lung and nervous systems may be aggravated by exposure (see Section 11).

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)

H315 Causes skin irritation.
H317 May cause an allergic skin reaction.
H319 Causes serious eye irritation.
H335 May cause respiratory irritation.
H341 Suspected of causing genetic defects.
H350 May cause cancer.

Precautionary statement(s)

P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P281 Use personal protective equipment as required.
P261 Avoid breathing dust/fume/gas/mist/vapours/spray.
P280 Wear protective gloves.
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.
P405 Store locked up.
P501 Dispose of contents/container in accordance with national regulations.

EU Risk Phrases: R23/24/25 – Toxic by inhalation, in contact with skin and if swallowed.
R36/37/38 – Irritating to eyes, respiratory system and skin.
R45 – May cause cancer.
R46 – May cause heritable genetic damage.

EU Indication of Danger: According to Regulation (EC) No1272/2008
Toxic.
Skin irritation (Category 2)
Eye irritation (Category 2)
Carcinogenic (Category 1)
Toxic to Reproduction (Category 2)

Mutagenic (Category 2)
Specific target organ toxicity – single exposure (Category 3)

According to European Directive 67/548/EEC as amended.
Irritating to eyes, respiratory system and skin. May cause sensitization by inhalation and skin contact. Limited evidence of a carcinogenic effect.

Principle Routes of Entry: Eye/skin contact or ingestion.

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

Ingestion: Harmful if swallowed (based upon animal data). Effects including myelosuppression including anaemia, leucopenia, neutropenia and thrombocytopenia, fever, anaemia, nausea, vomiting, diarrhoea, peripheral neuropathy and rare laryngeal dysaesthesias, abnormal liver function tests and mucositis may occur.

Skin Contact: May cause irritation and/or allergic reactions, particularly to cut or abraded skin. Allergic reactions have, on very rare occasions, been severe or life-threatening. Effects may include redness and a burning sensation on the 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	%
Oxaliplatin	61825-94-3	TP2275850	Mut. Cat. 2; R46; Repr. Cat. 2; R60; R61; Carc. Cat. 2; R45; T, R25	10

Non-Hazardous

Ingredients	CAS Number	EU EINECS/ ELINCS List	Classification	%
Lactose Monohydrate	64044-51-5	Not listed	None	90

This product needs to be reconstituted with water for injection prior to use.

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.

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. oxides of carbon, oxides of nitrogen and platinum-containing compounds). Some of these potential products may have carcinogenic potential.

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.

Oxaliplatin is inactivated by contact with undiluted bleach for ten minutes.

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 15-25 ºC and out of direct sunlight.

Incompatible products: Aluminium and organic solvents.

Special precautions: Persons with known hypersensitivities to oxaliplatin 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:

<u>Oxaliplatin</u>

Exposure limits of 2 mcg/m3, for soluble salts of platinum, expressed as an 8 hour Time Weighted Average have been assigned by OSHA (PEL), ACGIH (TLV), HSE (WEL).

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:	White freeze-dried crystalline solid
Odour:	No Data
pH:	4.0-7.0 (after reconstitution)
Molecular Weight:	397.3 g/mol
Boiling point:	193.6 ºC at 760 mmHg
Melting point:	No Data
Flashpoint:	75 ºC
Explosive properties:	No Data
Vapour pressure:	0.46 mmHg at 20 ºC
Relative density:	No Data
Viscosity:	No Data
Solubility:	Soluble in water (about 6 mg/ml at 20 ºC); practically insoluble in dehydrated alcohol; very soluble in methanol.

10. STABILITY AND REACTIVITY

Stability: Stable under normal temperature conditions.

Conditions to Avoid: Exposure to light.

Hazardous Polymerisation: Will not occur.

Incompatible Materials: Reactive with strong oxidizing or reducing agents. Avoid contact with chloride salts. Avoid contact with aluminium-containing products, as this may lead to the formation of a platinum precipitate.

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: myelosuppression including anaemia, leucopenia, neutropenia and thrombocytopenia, fever, anaemia, nausea, vomiting, diarrhoea, peripheral neuropathy and rare laryngeal dysaesthesias, abnormal liver function tests and mucositis may occur.

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

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

Oxaliplatin in bulk form

INTRAPERITONEAL LD_{50} (MOUSE):	17.5-19.8 mg/kg
INTRAPERITONEAL LD_{50} (RAT):	14.3 mg/kg
INTRAVENOUS LD_{50} (MOUSE):	16.5-22.5 mg/kg
ORAL LD_{50} (RAT):	>100 mg/kg

Irritation / Sensitisation:

The product is expected to be irritating to eyes, skin and the respiratory tract.

As with other platinum compounds, Oxaliplatin may produce allergic reactions that have, on very rare occasions, been severe or life-threatening.

Reproductive Effects:

This material is classified as a Pregnancy Category D (positive evidence of risk). Currently, there have been no studies in pregnant women.

Embryotoxicity/Teratogenicity:

In a fertility study, male rats were given Oxaliplatin at 0, 0.5, 1 or 2 mg/kg/day for five days every 21 days for a total of three cycles prior to mating with females that received two cycles of Oxaliplatin on the same schedule. A dose of 2 mg/kg/day did not affect the pregnancy rate, but caused developmental mortality (increased early resorptions, decreased live foetuses, decreased live births) and delayed growth (decreased foetal weight).

Mutagencity:

Oxaliplatin is positive in both *in vitro* and *in vivo* mutagenesis assays. It interacts with DNA, blocking DNA replication and transcription.

Carcinogenicity:

The carcinogenic potential of Oxaliplatin 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.

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

This product may be harmful to contaminated plant and animal life.

This product may be harmful to aquatic plant and animal life in contaminated bodies of water, especially if released in large quantities. It is not thought to bioaccumulate in aquatic organisms.

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.

EU Risk Phrases:
R23/24/25 – Toxic by inhalation, in contact with skin and if swallowed.
R36/37/38 – Irritating to eyes, respiratory system and skin.
R45 – May cause cancer.
R46 – May cause heritable genetic damage.

EU Safety Phrases:
S24 – Avoid contact with the skin.
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.
S45 – In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
S53 – Avoid exposure – obtain special instructions before use.
S60 – Material and its container must be disposed of as hazardous waste.

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).