sanofi-synthelabo

MATERIAL SAFETY DATA SHEET

OXALIPLATIN

1. IDENTIFICATION OF MATERIAL AND SUPPLIER

Sanofi-Synthélabo, Centre de Recherche de Montpellier, 371, rue du Professeur J. Blayac, 34184 Montpellier Cedex 4, France. Téléphone: (33) 04.67.10.67.10

Sanofi-Synthélabo, Centre de Recherche de Chilly Mazarin, 1, Avenue Pierre Brossolette 91385 Chilly Mazarin Cedex, France. Téléphone : (33) 01.69.79.77.77

Sanofi-Synthélabo, Centre de Recherche de Porcheville, 2-8 route de Rouen, ZI Limay Porcheville - 78440 Gargenville, France. Telephone : 01.34.97.37.00.

Sanofi-Synthelabo Recherche Toulouse, 195, Route d'Espagne, 31036 Toulouse Cedex, France. Telephone: (33) 05.61.16.22.00

Sanofi-Synthelabo Limited, Alnwick Research Centre, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, England. Telephone: (01665).608300 for Emergency Information call and (01665).510011.

Sanofi-Synthelabo Inc., Sanofi-Synthelabo Research Division, 9 Great Valley Parkway, P.O. Box 3026, Malvern, PA 19355, USA. Telephone: (610)889-8911 for Emergency Information call and (610)889-8687)

Chinoin Pharmaceutical and Chemical Works Co. Ltd.
H-1045 Budapest - To u. 1-5 - Hungary. Telephone: 36.1.3690.900, 36.1.3692-500
For Technical Information call: (610) 889-8687

Sheet No:	**7**	**Version:**	**2**
Date of Issue:	**16/02/05**	**Supersedes:**	**01/04/04**

2. COMPOSITION / INFORMATION ON INGREDIENTS

Component(s)	Weight %	CAS#	SR#	Exposure Guideline
OXALIPLATIN	100	61825-94-3	SR96669	Sanofi-Synthelabo exposure band: 0.1-5 ug/m3

3. HAZARDS IDENTIFICATION

Only Authorized and Trained Personnel should handle this compound.

Internal Hazard Codes: I5 D5 F:U C:U **(see description last page)**

This is a substance from an experimental programme, and there is insufficient information available to assess the hazards fully. The material is therefore provided for laboratory investigations by competent investigators who must handle the material with appropriate care.

Hazard Summary:

WARNING: This is a CYTOTOXIC ANTI-CANCER DRUG available only with a prescription - use only as directed.

The drug substance oxaliplatin is mutagenic, cytotoxic, neurotoxic and fetotoxic. The drug substance is a possible carcinogen and known ocular irritant. Chemical and physical hazards have not been fully determined.

4. FIRST AID MEASURES

Signs and Symptoms:
Not available

Inhalation:
Remove to fresh air. Seek medical attention immediately.

Eyes:
In case of eye contact, flush with water for at least fifteen minutes. Seek medical attention if irritation develops.

Skin:
Flush area with large amounts of water for fifteen minutes. Use soap if available

Ingestion:
Seek medical attention

Note to physicians

The effects of overexposure are not known. Provide supportive treatment

5. FIRE FIGHTING MEASURES

A. Dust Explosion Risk:

A/B Classification: Group A (Flammable dust)

Minimum ignition energy (MIE) : 5-10 mJ
Take adequate precautions, finely divided solid materials (dusts and fines), when dispersed in the air, can fuel particularly violent and destructive explosions. This material presents an electrostatic discharge hazard.

B. Thermal Stability of Powder:

Data not fully determined.

C. Electrostatic Risk:

A/B classification : Group A (flammable)
Minimum ignition energy (MIE) : 5-10 mJ
Volume resisitivity (ohm.m) : ambient RH 3.2 x 10exp13, low RH >10exp14
Charge decay time : ambient RH : 1.4 h, low RH 46h

D. Special Fire-Fighting Procedures:

If rupture of containers is suspected, wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes. Use water spray to keep fire exposed containers cool.

Hazardous Combustion Products:

May include oxides of carbon and nitrogen

Means of Extinction:

Water spray, carbon dioxide or dry chemical. Try to minimize spread of powder.

6. ACCIDENTAL RELEASE MEASURES

Prevention:
To minimize hazards from accidental breakage of apparatus or containers, substance should be stored or transported within secondary containers, pans or trays. Use protective coatings and/or barrier sheeting where there is a possibility of spillage during handling.
Response:
Evacuate the area if spillage occurs and isolate air handling system if possible. Use appropriate personal protective equipment and minimize dust generation by using a high efficiency particulate (HEPA) vacuum cleaner to clean. If high efficiency vacuum cleaner is not available, wet the powder and contain the spill by surrounding and covering it with inert absorbent material (e.g. clay, vermiculite, etc.). Carefully place the waste in a labelled receptacle for safe disposal as a contaminated waste. Wash the area with damp towels or other inert scrubbing materials until all traces of residual contamination are removed. Remove any contaminated clothing, personal protective equipment, and other contaminated materials and place in a double sealed container for disposal (see Section 13).

7. HANDLING AND STORAGE

Only Authorized and Trained Personnel Shall Handle This Compound.
Handling and Storage Precautions:
Keep container closed. Store in a cool and dry place. Store and transport within secondary containers,
pans or trays. Label all containers with hazard information. (see Section 16). This material should be handled and stored per label instructions.
Work/Hygiene Practices:
Handle with extreme care. Do not breathe airborne substance, and do not allow contact with eyes, skin or clothing. Use only with containment or isolation facilities and equipment, personal protective equipment and safe work practices. Wash thoroughly after handling (see Section 8). Refer to recommendations for the 'Safe Handling of Cytotoxic Drugs', NIH Publication No. 92-2621.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

A workplace risk assessment must be carried out in order to determine the correct engineering control measures and personal protective equipment.

A. Exposure Limits:
This product is expected to be an extreme toxic hazard.
Sanofi Exposure Limit Band: 0.1 - 5 ug/m3
B. Preventive Measures:
Restrict access to the work area and take precautions to contain material within restricted area. Implement appropriate work practices and procedures to eliminate exposure.
Work only in accordance with workplace risk assessments and instructions for safe handling during both normal and emergency operations. Wash thoroughly immediately after use. Contain and control the emissions from experiments, and properly dispose of wastes generated.
C. Engineering Controls:
Use isolation equipment (glove box, physical barriers, contained process techniques) when there is risk of airborne exposure above recommended levels in order to prevent eye and skin contact and control airborne exposures. All operations must be conducted inside negatively ventilated rooms
currently verified as working properly.
D. Personal Protective Equipment:
Personal protective equipment can only be used in place of engineering controls as a temporary measure in emergency situations or when control by other means is not feasible. Respiratory protection must be selected according to the risk from the work task or situation. In general, positive pressure, supplied air respiratory protective equipment (hood, half suit or full suit), which provides high factors of protection, are used when there is risk of airborne exposure above recommended exposure levels. All respiratory protection should be in compliance with the OSHA Respiratory Protection Standard, 29 CFR 1910.134, or other regulations applicable to the country of use.

E. Eye Protection:
Avoid eye contact. Wear safety glasses with side shields, Chemical goggles or a full-face shield as appropriate to the risk.

F. Skin Protection:
Prevent skin exposure. If there is a risk of skin contamination, wear impervious chemical resistant clothing with long sleeves, a head cover and gloves to protect exposed skin.
G. Recommended Decontamination Facilities:
An eye wash, safety shower and washing facilities shall be available in the immediate area.

9. PHYSICAL AND CHEMICAL PROPERTIES

Molecular Formula : **C6H14N2 . C2O4Pt**
Molecular Weight : **397.33**
Physical Description: **Solid**
Solubility : **Molecular Formula: C8H14N2O4Pt**
Molecular Weight: 397.3
pH: 4.8 - 5.7 (in 2 mg/mL aqueous solution)
Vapour Pressure: N/A
Vapour Density (AIR = 1): N/A
Specific Gravity: N/A
Solubility (H2O @ 20 C): 6 mg/mL
Partition Coefficient (octanol/water) (Kow): 0.02, log = -1.67
Dissociation Constant (pKa at 25 C): None identified from pH = 5.87-11.12
Henry's Law Constant: Extremely low. Testing indicated no detectable volatilisation from water to air in 21 days
Melting Point (°C) **Decomposes**

10. STABILITY AND REACTIVITY

Thermal Stability: See Section 5.

Incompatibility: Incompatibility of this material has not been investigated.

By precaution avoid contact with oxidising agents, reactive organic compounds and strong acids and bases

11. TOXICOLOGICAL INFORMATION

Effects of Acute Exposure:

In Humans
In humans, anticipated effects of acute exposure include nausea, vomiting, diarrhea, peripheral neurotoxicity (with cold sensitivity and rare laryngeal dysesthesias [sensation of difficulty with breathing or swallowing]), and possible myelosuppression [low blood counts]. Mucositis [sore mouth, or soreness of other mucous membranes] and transient elevation of liver enzymes have been observed. As with other platinum compounds, allergic and very rare anaphylactoid – [severe, possibly life-threatening allergic reactions] have been observed.

Sensitization Potential: Oxaliplatin may produce allergic reactions that have, on very rare occasions, been severe or life-threatening.

11. TOXICOLOGICAL INFORMATION (continued)

Animal Studies
Vomiting and diarrhea have been observed following single parenteral doses of oxaliplatin. Cardiotoxicity was associated with deaths only in dogs at doses at ³ 7.5 mg/kg (which is equivalent to > 150 mg/m2).

LD10: 20.0 mg/kg Mouse IV, 17.5 mg/kg Mouse IP, 14.0 mg/kg Rat IP
LD50: >100 mg/kg Rat PO

Eye irritant based on data from in vivo tests.
Non-irritating to the skin based on an in vivo animal study with dry drug substance.

Effects of Chronic (Repeated) Exposure: Data obtained from studies (pre-clinical and clinical) conducted with parenteral administration only.

In Humans
Oxaliplatin has produced nausea, vomiting, diarrhea, and myelosuppression (including anemia [low red blood cell count], leucopenia, neutropenia [low white blood cell count, with possible increased risk of infection], and thrombocytopenia [low platelet count, with possible increased risk of bleeding]), acute and dose-related chronic, reversible neurotoxicity (with cold sensitivity and rare laryngeal dysesthesias [sensation of difficulty with breathing or swallowing]). Mucositis [sore mouth, or soreness of other mucous membranes] and transient elevation of liver enzymes have been reported. As with other platinum compounds allergic reaction and very rare anaphylactoid [sever, possibly life-threatening allergic reaction] reactions have been observed. Platinum may accumulate in red blood cells and plasma following repeat exposure to oxaliplatin.

Animal Studies
Oxaliplatin has produced hematotoxicity, vomiting, and diarrhea, and renal toxicity at high does in rats. Cardiotoxicity has been associated with fatal doses only in dogs.

Developmental Toxicity: In rats, the highest dose tested (2 mg/kg/day) for five days caused almost 100% resorption of the uterine contents. No malformations were detected at lower doses.

Reproductive Toxicity: There was no impairment of fertility of treated rats. However, testicular hypoplasia has been detected in dogs following repeated doses of oxaliplatin.

Genotoxicity: Positive genotoxic agent in both in vitro and in vivo tests. Oxaliplatin interacts with DNA , blocking DNA replication and transcription. Cytotoxicity has been observed in the bone marrow of mice.

Carcinogenicity: May be carcinogenic based on cytotoxic and genotoxic data.

12. ECOLOGICAL INFORMATION

Oxaliplatin and its metabolites are expected to enter the surface water compartment of the environment after human excretion and entry into sewage treatment systems.

Ecotoxicity
Dosages refer to the dose of oxaliplatin pure drug substance used
Oxaliplatin is expected to have no significant effect on the environment since it is predicted to be present in an extremely low concentration resulting from manufacturing, distribution and use.
Microbial Inhibition (minimum inhibitory concentration, mg/L):
Aspergillus, Penicillium and *Chaetomium* >1,000
Pseudomonas and *Anabaena* 800
Bacillus 400
Azobacter 20

Mobility
Water Solubility, Kow and Henry's Law Constant data indicate that Oxaliplatin will migrate to the water compartment of the environment.

Persistence and degradability
Hydrolysis test data indicate that Oxaliplatin will not readily hydrolyse in the environment.
Hydrolysis ($t_{1/2}$ at 25°C): pH = 9: 1.09 days
pH = 7: 27.4 days
pH = 5: 49.19 days

Bioaccumulation Potential
The octanol/ water partition coefficient (Kow) value of 0.02 indicates that oxaliplatin is not likely to bioaccumulate. Dissociation constant (pKa) data indicate that Oxaliplatin will not dissociate in the environmental pH range.

13. DISPOSAL CONSIDERATIONS

Discharge, treat and/or dispose of in accordance with federal, state and local regulations. Collect in an impervious waste container. Contaminated clean up materials and disposable personal protective equipment should be double contained (e.g. double sealed bags), marked and disposed by incineration. Outer waste containers should be labeled or marked to indicate contents and hazards for safe handling and disposal. Contents should be burned in an incinerator with environmental control devices operating under applicable regulatory requirements.

14. TRANSPORTATION INFORMATION

Proper Shipping Name and Classification (IATA, USA DOT):

Organometallic compound, toxic, solid, n.o.s. (oxaliplatin), 6.1, UN 3467, PG III

15. REGULATORY INFORMATION

OSHA chemical hazards according to 29 CFR 1910.1200: Toxic.

This product does not contain any ingredients which are regulated on the US EPA List of Toxic Chemicals (40 CFR Part 372) and is therefore not subject to release reporting under section 313 of EPCRA.

Labelling symbol:

T+: Very Toxic

Risk phrases: 45-48/23/25-46-48-60-61

26/28: Very toxic by inhalation and if swallowed
48: Danger of serious damage to health by prolonged exposure
61: May Cause harm to the unborn child

Safety phrases: S-53; S-3/7/9; S-36/37/39

Avoid exposure - obtain special instruction before use.
Keep container tightly closed, in a cool, well-ventilated place.
Wear suitable protective clothing, gloves and eye/face protection.

16. OTHER INFORMATION

Hazard label for this substance should state: "Sanofi-Synthelabo I5, D5, F-U, C-U for research and development purposes only by trained personnel".

This material safety data sheet is intended for personnel handling of this material in research, development and clinical manufacturing. It does not address the therapeutic use of this product. Therapeutic agents are intended for use under direction of a physician. As a general precaution, personnel who handle drug product should avoid contact (ingestion, inhalation, skin and eye) with this substance. This substance is presumed toxic; with danger of possible serious, irreversible effects through inhalation, in contact with skin or eyes, and if swallowed.

For use within Sanofi-Synthelabo. Prior approval by Health, Safety and Environmental Affairs is required for distribution of this MSDS to anyone other than a Sanofi-Synthelabo Research employee.

The information found in this sheet should not be considered as exhaustive. This information is given in good faith and based on the scientific and technical knowledge reasonably available to Sanofi-Synthelabo at the date of production of the sheet

If this information should be found to be inexact or partial users are expressly requested to inform Sanofi-Synthelabo as soon as possible in order that all necessary actions should be taken

Sanofi-Synthelabo would also like to point out that all persons obtaining or using a hazardous chemical substance or preparation have the duty to inform themselves of the actions necessary to prevent the risks arising from handling the product

GUIDE FOR SANOFI-SYNTHELABO RESEARCH HAZARD CODES

HEALTH HAZARDS:

I = Inhalation hazard

I1 = Indicates a substance with a low respiratory hazard. Inhalation of substances classified I1 will only cause minor and easily reversible effects.

I2 = Indicates a substance with a moderate respiratory hazard. Inhalation of substances classified I2 can cause respiratory irritation or acute or delayed harmful health effects.

I3 = Indicates a substance with a serious respiratory hazard. Inhalation of substances classified I3 can cause significant respiratory irritation, toxic systemic effects, pharmacological effects or result in long term damage to health.

I4 = Indicates a substance with a very serious respiratory hazard. Inhalation of substances classified I4 can cause severe respiratory sensitization, very toxic systemic effects, potent pharmacological effects or result in serious long term damage to health

I5 = Indicates a substance with an extremely serious respiratory hazard. The effects of inhalation of substances classified I5 are so serious and can occur at such low levels that total containment is required to handle these products.

D =

D1 = Dermal hazard

Indicates a substance with a low hazard by skin contact.

D2 = Minor skin irritation may be caused by these substances.

Indicates a substance with a medium hazard by skin

D3 = contact. These substances may cause skin irritation, allergic reaction or may be harmful by skin absorption.

Indicates a substance with a high hazard by skin contact.

D4 = These substances may be corrosive, a potent cause of allergic reactions or toxic by skin absorption.

Indicates a substance with a very high hazard by skin

D5 = contact. These substances may be potent skin sensitizing agents or very toxic by skin absorption.

Indicates a substance with an extremely serious hazard by skin contact. The effects of skin contact with these substances are so dangerous and can occur at such low levels that total containment must be used to handle these compounds.

PHYS/CHEM HAZARDS:

F = Fire and explosion hazard

F0 = Basically inert

F1 = Low hazard

F2 = Moderate hazard - combustible

F3 = Severe hazard - flammable, readily ignites

F4 = Extreme hazard - very flammable

C = Reactivity hazard

C0 = Basically inert

C1 = Low hazard

C2 = Moderate hazard - heat sensitive, decomposes when heated

C3 = Severe hazard - decomposes violently when heated

C4 = Extreme hazard - decomposes very violently when heated

U = Unknown

O = Indicates a special risk by eye contact

S = Indicates that specific health surveillance is indicated

R = Reproductive hazard - special considerations apply to handling by pregnant employees

G = Indicates those substances with a very high hazard for pregnancy. It is advised that pregnant employees should not be employed at workstations where these materials are manipulated.