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MATERIAL SAFETY DATA SHEET

PACLITAXEL INJECTION, USP

Section One: Product and Company Identification

Common Brand Name: **PACLITAXEL INJECTION, USP** **Formula:** $C_{47}H_{51}NO_{14}$

Chemical Name: 5ß,20-Epoxy-1,2α,4,7ß,10ß,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.

Therapeutic Category: Antineoplastic

Controlled Substance: no

Section Two: Composition/Information on Ingredients

Components	Percent	Exposure Limits
paclitaxel	0.65	NF
purified Cremophor® EL* (polyoxyethylated castor oil	56.17	NF
Dehydrated alcohol	43.18	NF

Section Three: Hazard Information

Usual Adult Dosage: All patients should be premedicated prior to Paclitaxel Injection, USP administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone20 mg PO administered approximately 12 and 6 hours before Paclitaxel Injection, USP, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Paclitaxel Injection, USP, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel Injection, USP.

For patients with **carcinoma of the ovary**
a. Paclitaxel Injection, USP administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or
b. Paclitaxel Injection, USP administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.

For patients with **carcinoma of the breast**
For previously untreated patients with carcinoma of the ovary one of the following regimens may be given every 3 weeks.
1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is Paclitaxel Injection, USP, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for four courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used four courses of doxorubicin and cyclophosphamide.
2) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

In patients previously treated with chemotherapy for carcinoma of the ovary, Paclitaxel Injection, USP has been used at several doses and schedules; however the optimum schedule is not yet clear. The recommended schedule is Paclitaxel

Injection, USP 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with **non-small cell lung carcinoma**, the recommended regimen, given every 3 weeks, is Paclitaxel Injection, USP administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

For patients with **AIDS related Kaposi´s sarcoma**, Paclitaxel Injection, USP administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45–50 mg/m^2/week). In the two clinical trials evaluating these schedules, the former schedule (135 mg/m^2 every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m^2 every 2 weeks).

Overdose Effects: There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity

Adverse Effects:

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm3 in 14% of the patients treated with a dose of 135 mg/m^2 compared to 27% at a dose of 175 mg/m^2 (p=0.05). In the same study, severe neutropenia (<500 cells/mm3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent or more severe for patients previously treated with radiation therapy.

Hypersensitivity Reactions (HSRs): All patients received premedication prior to paclitaxel. The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel administration. In the Phase 3 second-line ovarian study, the 3-hour infusion was not associated with a greater increase in HSRs when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia. The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period. Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of paclitaxel safety.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 second-line ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy. Significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with Paclitaxel at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy, and complete AV block requiring pacemaker placement. Among patients with NSCLC treated with paclitaxel in combination with cisplatin in the Phase 3 study, significant cardiovascular events occurred in 12%–13%. This apparent increase in cardiovascular events is possibly due to an increase in cardiovascular risk factors in patients with lung cancer.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities. Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.

Respiratory: Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Neurologic: In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent paclitaxel. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34%–51% from course 2 to 10. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of Paclitaxel and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after paclitaxel administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of paclitaxel administration. Among patients with normal baseline liver function 7%, 22% and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity. Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.

Renal: Among the patients treated for Kaposi´s sarcoma with paclitaxel, five patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other four patients had renal insufficiency with reversible elevations of serum creatinine.

Gastrointestinal (GI): Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion. In patients with poor-risk AIDS-related Kaposi´s sarcoma, nausea/vomiting, diarrhea, and mucositis were reported by 69%, 79% and 28% of patients, respectively. One third of patients with Kaposi´s sarcoma complained of diarrhea prior to study start.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., “recall”, has been reported rarely.

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to paclitaxel related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Medical Conditions Aggravated by Exposure: None

Cross Sensitivity: None

Drug Abuse and Dependence: None

Pregnancy Comments: Paclitaxel Injection, USP can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality. There are no adequate and well-controlled studies in pregnant women. If Paclitaxel Injection, USP is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Pregnancy Category: D

Section Four: First Aid Measures

General: Contact with skin: Immediately take off all contaminated clothing.
Areas of the body that have – or are only even suspected of having – come into contact with the product must be rinsed immediately with plenty of running water and possibly with soap.
WARNING! This product is toxic through skin contact. OBTAIN IMMEDIATE MEDICAL ATTENTION.
Contact with eyes: Do not use eyewash or ointment of any kind (before obtaining an examination or advice from an eye specialist).
Swallowing: Induce vomiting. SEEK A MEDICAL EXAMINATION IMMEDIATELY and present the safety-data sheet.
Give liquid paraffin to drink; do not give milk or animal or vegetables fats of any kind.
Inhalation: Ventilate the premises. The patient is to be removed immediately from the contaminated premises to rest in a well ventilated area. OBTAIN MEDICAL ATTENTION. If breathing stops, apply artificial respiration.

Overdose Treatment: There is no known antidote for paclitaxel overdosage. Treatment consists of drug discontinuation and supportive therapy.

Section Five: Firefighting Measures

Flash Point: NA **Upper Flammable Limit:** NA
Auto-Ignition Temperature: NA **Lower Flammable Limit:** NA
Extinguisher Media: Water, CO2, Foam, Chemical powders, according to the materials involved in the fire.
Fire and Explosion Hazards: None are expected.
Firefighting Procedures: Put on breathing apparatus. Wear full protective suit.

Section Six: Accidental Release Measures

Personal Precautions: Use a mask, gloves and protective clothing.
Environmental Precautions: Limit leakages with earth or sand.
If the product has escaped into a water course, into the drainage system, or has contaminated the ground or vegetation, notify the competent authorities.
Clean-Up Methods: Rapidly recover the product. To do so, wear a mask and protective clothing.
If the product is in a liquid form, stop it from entering the drainage system.
Recover the product for re-use if possible, or for elimination. The product might, where appropriate, be absorbed by inert material.
After the product has been recovered, rinse the area and material involved with water.
Decontamination Procedure: Ensure adequate ventilation

Section Seven: Handling and Storage

Handling: Avoid contact and inhalation of the vapors.
Do not eat or drink while working.
Waste Disposal Method: Refer to local, state, and federal rules.
Storage: Do not store together with incompatible materials. Keep container tightly sealed.
Other Precautions: None

Section Eight: Exposure Controls/ Personal Protection

PACLITAXEL INJECTION, USP IS A CYTOTOXIC AGENT. ALL WORK PRACTICES MUST BE DESIGNED TO REDUCE HUMAN EXPOSURE TO THE LOWEST LEVEL.

Respiratory Protection: Use adequate protective respiratory equipment, e.g. CEN/FFP-2(S) or CEN/FFP-3(S)
Ventilation: Local exhaust.

Gloves:	Use protective gloves that provide comprehensive protection, e.g. P.V.C., neoprene or rubber.
Eye Protection:	Use close fitting safety goggles and/or visor conforming to BS 2092 GRADE 1).
Protective Clothing:	Use clothing that provides comprehensive protection to the skin, e.g. cotton, rubber, PVC or viton.
Work/Hygienic Practices:	Keep away from food stuff, beverages and food. Take off immediately all contaminated clothing. Wash hands during breaks and at the end of the work. Store protective clothing separately. Avoid contact with eyes and skin. Do not eat or drink while working. Ensure that washing facilities are available in the work place.

Section Nine: Physical and Chemical Properties

Appearance and Odor:	Clear colorless to slightly yellow viscous sterile solution	**pH:**	3.0 to 7.0
Melting Point:	NA	**Vapor Pressure:**	NF
Solubility:	Soluble	**Vapor Density:**	NF
Boiling Point:	Not determined	**Evaporation Rate:**	NF
Specific Gravity:	NF	**Reactivity in Water:**	NF

Section Ten: Stability and Reactivity

Stability:	Stable under normal conditions of storage and handling.
Materials to Avoid:	NF
Hazardous Decomposition or Byproducts:	No decomposition if used according to specifications.
Hazardous Polymerization:	NF
Conditions to Avoid:	Freezing, refrigerating, extreme heat, mixing with incompatible chemicals.

Section Eleven: Toxicological Properties

Ip-rat LD50: 32mg/Kg (NIOSH-RTECS, 2002); oral and dermal rat LD50: >2000 mg/Kg (RBM, 2000).
Human side effects (iv): hypersensitivity, damage to the bone marrow, anemia, gastrointestinal effects (NCI, Cancer Facts, 2001).
The product is used as anti-cancer agent because of its cytotoxic activity and it is very toxic after acute iv administration.
It is a potential carcinogen and possibly a reproductive toxin.
The product is TOXIC.

Intravenous Rat:	NF
Intravenous Mouse:	NF
Intravenous Guinea Pig:	NF
Intravenous Dog:	NF
Irritancy Data:	NF
Target Organ(s):	Exposure to the material has not demonstrated classical target organ effects.
Listed as a Carcinogen?	NTP- NF IARC- NF OSHA- NF Other- NF

Section Twelve: Ecological Information

Summary: Adopt sound working practices, so that the product is not released into the environment.
Paclitaxel is a natural product, biodegradable.
Based on this and on its low water solubility it is unlikely to persist in the aquatic compartment.
Because of its high lipid solubility it is expected to deposit in the terrestrial compartment, but its biodegradability will prevent it to be persistent.

Section Thirteen: Disposal Consideration

Disposal Recommendations: Recover, if possible. Send to authorized disposal plants or for incineration under controlled conditions. In so doing, comply with the local and national regulations currently in force.

Regulatory Requirements: Observe all federal, state and local environmental regulations.

Section Fourteen: Transport Information

IATA – NF
IMDG - NF
ADR – NF
RID – NF
ADNR – NF

Section Fifteen: Regulatory Information

SARA 313 Listed: NF
CERCLA Listed: NF
RCRA Listed: NF

Section Sixteen: Other Information

Main bibliographie sources:
NIOSH – Registry of toxic effects of chemical substances (1893)
I.N.R.S. – Fiche Toxicologique
CESIO – Classification and labeling of anionic, nonionic surfactants (1990)
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It is the duty of the user to ensure that this information is appropriate and complete with respect to the specific use intended.