PCH Pharmachemie b.v.
Postbus 552
2003RN Haarlem
The Netherlands
Tel: ++ 31-(0) 23-5147147

MATERIAL SAFETY DATA SHEET

SECTION 1. CHEMICAL IDENTIFICATION

Product Name: PACLITAXEL 6mg/ml, Solution Concentrate for Infusion	**Chemical Family:** Diterpenoid taxane
On the market in different strengths and concentrations. Distributed in several volumes and package sizes. **PCH Presentations:** 6mg/ml in 5ml vials; 20ml vials and 50 ml vials	**Therapeutic Category:** Antineoplastic
Common Used Brand Names: Taxol, Paclitaxel, Paclitaxin, Paxene	**Product Use:** Paclitaxel is used as a medicinal drug. Cytotoxic antineoplastic, antileukaemic and antitumor agent.
Company: PCH Pharmachemie b.v. Postbus 552 2003RN Haarlem The Netherlands ++ 31-(0) 23-5147147	**Contain the following ingredients:** Paclitaxel, Anhydrous Citric acid, Cremophor EL, Anhydrous ethanol.
Emergency Telephone number: *In The Netherlands:* Contact the National Poisoning Information Centre Tel. 030 – 2748888 (Only attainable by accidental poisoning for an attendant physician). Or Contact an emergency room of a local hospital. *In other Countries:* In case of emergency contact an emergency room of a local hospital	

SECTION 2. COMPOSITION & INFORMATION ON INGREDIENTS

Chemical Name	CAS #	EC #	RTECS #	Concentration %	Empirical Formula	Molecular weight	Symbol & R-Phrases	Exposure Guideline
Paclitaxel (Baccatin III N-Benzyl-beta-phenylisoserine Esther)	33069-62-4	Not Available	DA8340700	0.6	$C_{47}H_{51}NO_{14}$	853.9182	T Symbol R48/23/24/25 R46, R60	None
Anhydrous Citric acid EP	77-92-9	201-069-9	GE7350000	0.2	$C_6H_8O_7$	192.12	Xi R 36	None
Cremophor EL EP (ricinusolieethoxylaat)	61791-12-6	500-151-7 NLP	GO5661000	30-60				None
Anhydrous ethanol BP/EP (Ethyl alcohol)	64-17-5	603-002-00-5	KQ6300000	30-60	C_2H_6O	46.07	F Symbol R11	500 ppm (1), 1000 ppm (2)

(1) MAC-TGG Occupational Exposure Limit - THE NETHERLANDS, JAN1999
(2). Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (General Industry) 8 hour time-weighted average, and Occupational Exposure Limit - UNITED KINGDOM, SEP2000

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MATERIAL SAFETY DATA SHEET

SECTION 3. HAZARD IDENTIFICATION

Route of Entry:
Inhalation, Skin, Eyes, and Ingestion:
Under normal conditions, this product is contained within vials and inhalation, skin and eyes contact and ingestion of large quantities would not be expected to occur.
However there is a potential for the outside of the drug vials to be contaminated with the drugs and if vials break or spill, exposure to paclitaxel solution may occur. The extent of systemic absorption of paclitaxel after inhalation, skin and eyes contact or gastrointestinal tract is unknown.

Potential Health Hazards Acute & Chronic:
This product is a concentrate for infusion and contains paclitaxel dissolved in a mixture of ethanol and cremophor EL. It is further diluted with other solutions for intravenous administration to patients.
Repeated exposure to paclitaxel in sufficient dose may affect the bone marrow, the peripherical nervous system, gastrointestinal tract and reproductive systems
Inhalation: Irritating to respiratory system.
Skin: Irritating to skin
Eyes: Risk of serious damage to eyes.
Ingestion: Nausea, abdominal irritation, pain and vomiting.

Possible Signs & Symptoms of Overexposure:
Irritation, dizziness, nausea, throat swelling, burning sensation, wheezing, dry cough, shortness of breath, headaches, rash, photo-sensibility, chest pain, tingling.

Medical Conditions Aggravated by Exposure:
Pre-existing asthma, anaemia/other forms of bone marrow suppression, cardiac arrhythmias.

Carcenogenicity:
Paclitaxel is a potent cytotoxic drug and potential carcinogen.

SECTION 4. FIRST-AID MEASURES

Obtain Medical Attention in All Cases.
Remove or cover gross contamination to avoid exposure to rescuers.

Inhalation:
Remove exposed person to fresh air.
Loosen tight clothing such as a collar, tie, belt or waistband.
Persons developing serious hypersensitivity (anaphylactic) reactions must receive immediate medical attention.
If person is not breathing give artificial respiration.
If breathing is difficult administer oxygen.

Skin:
Remove contaminated clothing and shoes.
Immediately wash the affected area with soap and water and flush with running water for at least 15 minutes.

Eyes:
Check for and remove any contact lenses.
Flush with running water at least for 15 minutes.
Assure adequate flushing by separating the eyelids with fingers.

Ingestion:
Rinse mouth and call a physician or Poison Center immediately.
Loosen tight clothing such as a collar, tie, belt or waistband.
Only induce vomiting at instructions of a physician.
Never give anything by mouth to an unconscious person.

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SECTION 5. FIRE-FIGHTING MEASURES

Product is a Flammable Liquid.
The size and nature of this product is such that it will not contribute to the intensity of a fire.
Fire fighting should be aimed at surrounding materials.

Extinguishing Media:
Water spray, Dry chemical {Carbon Dioxide (CO_2)}, Alcohol Foam

Special Fire Fighting Procedure:

- First stage fire responders should wear eye protection.
- Structural fire fighters must wear self-contained breathing apparatus and full protective equipment (i.e. flame and chemical resistant clothing, boots and gloves).
- Evacuate personnel to upwind direction.
- Safely remove unneeded material and cool container(s) with water from maximum distance.

Unusual Fire and Explosion Hazard:
Product is assumed to be Flammable.
When heated to decomposition, this product may emit toxic fumes; oxides of carbon and nitrogen and possibly compounds with carcinogenic potential.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Spill and Leak Procedures:
Remove all ignition sources. Provision for sufficient ventilation. Collect leaking and spilled liquid in seal able containers as far as possible. Wash away remainder with plenty of water

Small Releases:
Wear latex or nitrite gloves and safety glasses.

Large Releases:

- Trained personnel using pre-planned procedures should respond to large or uncontrolled releases.
- Wear suitable protective clothing and equipment.
- Place collected material into a double plastic bag and a suitable container for disposal.
- Decontaminate area thoroughly with sodium carbonate solution (1% for trace material remaining on surfaces, 10% for larger quantities or for solutions containing paclitaxel) for 30 minutes.
- After procedure wash twice with detergent and water.
- Wipe up with absorbent material and avoid splashing or spraying liquid.

Waste:
Product is classified as Hazardous Waste due to the alcohol content. Due to its Paclitaxel content, it is recommended that the diluted solutions and contaminated material also be treated as a hazardous cytotoxic material.

SECTION 7. HANDLING & STORAGE

Handling Precautions:
Proper precautions should be taken while unpacking, transporting and manipulation. See relevant guidance for handling of cytotoxic materials.
Do not break vials or spill contents.
Avoid inhalation, skin or eye contact with this material.
Keep away from sources of ignition -- No smoking.

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Container Requirements: Comply with international transportation regulations. Packaging & Labelling see section 14.
Storage Conditions: Recommended storage is 20-25 degree C. Product may be refrigerated or frozen. Store in original containers in approved flammable liquid storage area. Keep away from sources of ignition -- No smoking.

SECTION 8. EXPOSURE CONTROLS – PERSONAL PROTECTION

Exposure Limit Values: See Section 2. Composition & Information on Ingredients
Occupational Exposure Controls Use with adequate ventilation. Follow standard medical product handling procedures. Local mechanical exhaust ventilation is recommended to minimize employee exposure. Control exposure by enclosure of processes whenever possible. A biological safety cabinet should be used for preparation of this drug.
Respiratory Protection: ▪ Insufficient engineering control i.e. building system control is not sufficient to control exposure*:* Wear approved respirator with HEPA filters or powered air-purifying respirator with HEPA cartridges. Always use a NIOSH or European Standard EN 149 approved respirator when necessary. ▪ Handling large quantities: Wear a positive air pressure respirator with an organic vapour cartridge and HEPA filter. Always use a NIOSH or European Standard EN 149 approved respirator when necessary. Self-containing breathing apparatus should be available for emergency use.
Hand Protection: Chemically impervious gloves appropriate for highly toxic material. (i.e. butyl, other gloves suitable for use with alcohol). Gloves should be changed regularly and removed immediately after overt contamination. Double gloving is recommended.
Eye Protection: Chemical safety goggles with side shields. Contact lenses pose a special hazard; soft lenses may absorb irritants an all lenses concentrate them.
Skin Protection: Protective lab coat and/or face shield. If the potential exists for significant dermal contact, wear impervious disposable coveralls with closed front, long sleeves with elastic cuffs and boots.
Environmental Exposure Controls & Work Hygienic Practices: Remove and laundry contaminated clothing before reuse. Place used disposable material in a disposal bag. Wash hands, forearms and face thoroughly after handling compounds and before eating, smoking, using lavatory, and at the end of the working day.

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MATERIAL SAFETY DATA SHEET

SECTION 9. PHYSICAL & CHEMICAL PROPERTIES

Drug Product Appearance, Physical State and Colour: 5ml, 16,7ml and 50ml of liquid drug product, containing 30 mg, 100mg and 300mg of active ingredient, respectively, are packaged in glass vials. The drug product may appear cloudy when refrigerated or frozen.	
Appearance: Clear to pale-yellow flammable solution	Odour: Alcohol
Important Health, Safety & Environmental Information	
pH: 3,5	Relative density: (Bulk paclitaxel) 0.933 (Ethanol = 0,8)
Boiling point: 78.5°C (anhydrous ethanol)	Solubility in Water: Miscible
Flash point: Approximately 16°C (anhydrous ethanol = 12°C)	Freezing Point: Not determined
Flammability (solid, gas): Not available	Partition coefficient: n-octanol/water: *(Bulk paclitaxel)* log K_{ow} = 3.5 at pH 5, pH 7, and pH 9
Explosive properties: Not available	Viscosity: Not available
Oxidising properties: Not available	Relative vapour density: 1.6 (anhydrous ethanol) If adequate temperatures caused the Paclitaxel for infusion to volatilise, its vapour density would be greater than 1 (heavier than air)
Vapour pressure: 5.8 Pa at 20^0 C (anhydrous ethanol)	Evaporation rate: Not determined
Other Information	
Specific gravity: 0,926	Melting point: Not available

SECTION 10. STABILITY & REACTIVITY

Stability: Stable Recommended storage is 20-25°C in original container, material is stable to expiration date shown on product label.
Conditions to avoid: Avoid exposure to heat, oxidizers or open flame.
Materials to avoid: Product is assumed to be flammable. Incompatible with strong oxidizers, acids, and bases.
Hazardous Decomposition Products: CO, CO_2, NOx (oxides of Nitrogen) and possibly other compounds with carcinogenic potential. **Hazardous Polymerisation:** Will not occur. **Explosion data relative to mechanical impact:** No information. **Explosion data relative to static discharge:** Approximately 50% of the material consists of ethanol, which is flammable. Care should be taken to reduce the possibility of static charge build-up and accidental release when handling large quantities of the material. Particular care is essential in a work area with large volumes of the material released to the air and inadequate ventilation present in work area.

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MATERIAL SAFETY DATA SHEET

SECTION 11. TOXICOLOGICAL INFORMATION

Toxicity information is for the Active Pharmaceutical Ingredient: PACLITAXEL	
Acute Effects: Hazardous in case of skin contact (irritant), of inhalation (lung irritant) May cause congenital malformations in the foetus. Laboratory experiments have shown mutagenic effects. May cause serious damage to the eyes. Material is irritating to mucous membranes and upper respiratory tract.	
Chronic Effects: Repeated exposure to a highly toxic material may produce general deterioration of health by an accumulation in one or many human organs.	
Specific Effects.	Carcinogenic effects: Studies not performed to date. However, because of its mechanism of action, the drug should be considered a POTENTIAL carcinogen.
	Mutagenic effects: Classified POSSIBLE for human.
	Teratogenic effects: Classified POSSIBLE for human.
	Toxicity for Reproduction Fertility: Classified Reproductive system/toxin/female & Reproductive system/toxin/male {PROVEN}
Toxicity Data:	LD50: Intraperitoneal, (rat): 33 mg/kg Intraperitoneal, (rat; 5day dosing): 9 mg/kg Intraperitoneal, (mouse): 128mg/kg Intraperitoneal, (mouse; 5day dosing): 27 mg/kg Intravenous, (mouse): 12 mg/kg
	LD Low: Intravenous, (dog): 2,25 mg/kg (toxic effects-myelosuppression and 18 mg/kg was lethal)
	LC50: Not available

SECTION 12. ECOLOGICAL INFORMATION

This product is a concentrate for infusion and contains paclitaxel dissolved in a mixture of ethanol and cremophor EL. Approximately 49% of the preparation consist of Ethanol and 49% of Cremophor EL.

Data for ingredients:

Ecotoxicity:

Paclitaxel:
Acute toxicity Daphnia: > 0,74 mg/l.

Cremophor EL:
Toxicity to fish: Leucidus idus: LC50 (24hrs): 713 mg/l; LC50 (48h): 448mg/l
Toxicity to Daphnia magna/EC50 (48hrs): > 100mg/l

Ethanol:
Toxicity to fish: Rainbow trout: LC50 (24hrs): 11200 mg/l; Rainbow trout: LC50 (96hrs): 12900 mg/l –15300mg/l
Toxicity to Daphnia magna/EC50 (24hrs): 10800 mg/l
Ethanol presents no appreciable risk to aquatic flora or fauna. It is readily biodegradable and evaporates.

Mobility:

Paclitaxel:
Paclitaxel's low vapour pressure precludes the air compartment from being affected by volatilisation of this material. Based on paclitaxel's low water solubility and its aerobic biodegradation of 3.8 days, it is not expected 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.

Cremophor EL:

Ethanol:
Its low octanol/water partition coefficient indicates that its absorption to soil will be low.

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MATERIAL SAFETY DATA SHEET

Persistence and degradability:
Paclitaxel:
Paclitaxel is a natural product, biodegradable. Paclitaxel's partition coefficient will tend to cause it to deposit in the terrestrial environmental compartment. It is anticipated that paclitaxel will continue to biodegrade in this compartment because of both its short half-life (3.8 days) and lack of sludge respiration inhibition.
Cremophor EL:
Test method: OECD 302B/ ISO 9888/ EEC88/302,C; Method of analysis: DOC reduction;
Degree of elimination: >70%; Evaluation: Easy to eliminate
Inhibition of degradation activity in activated sludge is not to be anticipated during correct introduction of low concentrations.
Ethanol:
Ethanol dissolves quite quickly in water and is biodegradable. Ethanol does not bio-accumulate to an appreciable extent. Indirect photo degradation is about 50% in 6 hours. Aerobic degradation with adapted sludge is 74% after 5 days. Release into air will result in photo-degradation and wet deposition.

Bioaccumulative potential:
Paclitaxel: No data found
Cremophor EL: No data found
Ethanol: Ethanol is not bioaccumulative

Other adverse effects:
Ozone depletion potential: No data found
Photochemical ozone creation potential: No data found
Global warning Potential: No data found

SECTION 13. DISPOSAL CONSIDERATIONS

Treat and dispose as dangerous material in accordance with all applicable national and local laws, by a licensed professional waste disposal service.

Methods of disposal; Waste of residues; Contaminated packaging:
Product is classified as Hazardous Waste due to the alcohol content.
Due to its Paclitaxel content, it is recommended that the diluted solutions and contaminated material also be treated as a hazardous cytotoxic material.
Incineration at an approved facility is recommended
Waste must be disposed of in accordance with local environmental control regulations.

SECTION 14. TRANSPORT INFORMATION

The International Transport Regulations for Sea transport IMD, Road transport ADR/RID & air transport ICAO-TI and IATA-DGR do not apply for Pharmaceutical drugs, ready for use, prepared and packaged in packing destined for retail or distribution, personal or household purposes

Transport information according to EU Guidelines	
Hazard class:	3
Identification number:	UN1170
Packing group:	II
Proper shipping name (technical name):	Ethanol, mixture
Packaging & Labelling Symbols:	F; R11; S16; UN Hazard Class 3

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SECTION 15. REGULATORY INFORMATION

Labelling Directive 1999/45/EG does not apply to medicinal products for human use.

Labelling according to EU guidelines:
Labelling of the component Paclitaxel Solution Concentrate for Infusion according to the EU directives.

Hazard Symbols:  

Classification: F T

Risks Phrases:
R11 Highly Flammable. R48/23/24/25 Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed. R46 May cause heritable genetic damage. R60 May impair fertility.

S-phrases:
S16 Keep away from sources of ignition—No smoking. S36/37/39 Wear suitable protective clothing, gloves and eyes/face protection. S53: Avoid exposure - obtain special instructions before use.

SECTION 16. OTHER INFORMATION

Conform to 67/548/EEC, 1999/45/EC and 2001/58/EC
MSDS Creation Date: 04/10/2004
Revision #
Revision Date:

SECTION 17. DISCLAIMER

The above information is based on MSDS's from suppliers and is believed to be correct but does not claim to be all-inclusive and shall be used only as a guide.
It is hereby expressly stated that the use of this information shall be solely at user's own risk, and that such users shall have no claim(s) against Pharmachemie B.V. for any damage resulting from the use of this information and / or the handling and / or contact with the above product.