PRODUCT MONOGRAPH

PACLITAXEL FOR INJECTION
(PACLITAXEL)
6MG/ML

BIOLYSE PHARMA STANDARD

ANTINEOPLASTIC AGENT

MANUFACTURER'S STANDARD CLAIM

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DATE OF PREPARATION: SEPTEMBER 2001
DATE OF REVISION: DECEMBER 2014

PRODUCT MONOGRAPH

PACLITAXEL FOR INJECTION
(Paclitaxel)
6mg/mL

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

PACLITAXEL FOR INJECTION (PACLITAXEL) SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPY AGENTS.

PATIENTS RECEIVING PACLITAXEL FOR INJECTION MUST BE PRE-TREATED WITH CORTICOSTEROIDS, ANTIHISTAMINES, AND H_2 ANTAGONISTS (SUCH AS DEXAMETHASONE, DIPHENHYDRAMINE AND CIMETIDINE OR RANITIDINE) TO MINIMIZE HYPERSENSITIVITY REACTIONS (SEE DOSAGE AND ADMINISTRATION). SEVERE HYPERSENSITIVITY REACTIONS CHARACTERIZED BY DYSPNEA AND HYPOTENSION REQUIRING TREATMENT, ANGIOEDEMA, AND GENERALIZED URTICARIA HAVE OCCURRED IN PATIENTS RECEIVING PACLITAXEL. THESE REACTIONS ARE PROBABLY HISTAMINE MEDIATED. RARE FATAL REACTIONS HAVE OCCURRED IN PATIENTS DESPITE PRE-TREATMENT. PATIENTS WHO EXPERIENCE SEVERE HYPERSENSITIVITY REACTIONS TO PACLITAXEL SHOULD NOT BE RECHALLENGED WITH THE DRUG.

ACTION AND CLINICAL PHARMACOLOGY

PACLITAXEL FOR INJECTION (paclitaxel) is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganization of the microtubules network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

In vitro, paclitaxel exhibits cytotoxic activity against a wide variety of both human and rodent tumour cell lines.

Pharmacokinetics

The pharmacokinetics of paclitaxel have been evaluated over a wide range of doses, up to 300 mg/m^2, and infusion schedules ranging from 3 to 24 hours. Following intravenous administration of paclitaxel the drug exhibited a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The latter phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3.0 to 52.7 hours, and total body clearance has ranged from 11.6 to 24.0 L/h/m^2. Mean steady state volume of distribution has ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding.

Following 3 hour infusion of 175 mg/m^2, mean terminal half-life was estimated to be 9.9 hours; mean total body clearance was 12.4 L/h/m^2.

Variability in systemic paclitaxel exposure, as measured by AUC (0-∞) for successive treatment courses was minimal; there was no evidence of accumulation of paclitaxel with multiple treatment courses.

The pharmacokinetics of paclitaxel have been shown to be non-linear. There is a disproportionately large increase in C_{max} and AUC with increasing dose, accompanied by an apparent dose-related decrease in total body clearance. These findings are most readily observed in patients in whom high plasma concentrations of paclitaxel are achieved. Saturable processes in distribution and elimination/metabolism may account for these findings.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicated that on average 89% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

The distribution and metabolism of paclitaxel *in vivo* has not been fully elucidated. High concentrations of paclitaxel and its metabolites have been reported in the bile of patients treated with the drug. Mean (standard deviation) values for urinary recovery of unchanged drug following 11-,6-, and 24-hour infusions at doses of 15 to 275 mg per square meter of body surface ranged from 1.3% (±0.5%) to 12.6% (±16.2%) of the dose, indicating extensive nonrenal clearance. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been fully elucidated.

Clinical Studies

Breast carcinoma

The safety and efficacy of PACLITAXEL FOR INJECTION in patients with advanced breast cancer unresponsive to usual treatments were evaluated in a Phase II, multi-center, non-randomized open- label trial. PACLITAXEL FOR INJECTION was infused continuously for a minimum of 3 hours every three weeks at a dose of 175 mg/m^2. Doses were reduced from 175 mg/m^2 to 135 mg/m^2 and 100 mg/m^2 in the event of toxicity. Dose escalation to 200 mg/m^2 was used in the absence of toxicity. A total of 36 patients were evaluated for safety and 27 for efficacy. The overall response rate was 27%, with a complete response reported at 4%, partial response at 19%, stable disease was seen in 51%, and disease progression was reported in 26%. Time-to-progression was assessed in 22 patients, with a median progression free survival of 83 days. The median survival for all registered and assessable patients was 102 days and 231 days, respectively.

Lung carcinoma

The safety and efficacy of PACLITAXEL FOR INJECTION in patients with metastatic or locally advanced non-small-cell lung cancer not subject to curative treatment were evaluated in a Phase II, multi-centre, non-randomized, open-label-trial. PACLITAXEL FOR INJECTION was infused continuously for a minimum of 3 hours every three weeks at a dose of 175 mg/m^2 to 200 mg/m^2. Dose escalation to 200 mg/m^2 and 225 mg/m^2 was used in the absence of toxicities. A total of 60 patients with advanced or metastatic non-small cell lung cancer were enrolled in this study. The overall response rate for registered patients was 25%. Time-to-progression was assessed in 52 patients at 125 days. Median survival was reported for all registered and assessable patients at 204 and 237 days, respectively.

INDICATIONS AND CLINICAL USE

PACLITAXEL FOR INJECTION (paclitaxel) is indicated for the treatment of carcinoma of the breast or lung, as follows:

Breast Carcinoma

Second-line treatment of advanced metastatic breast cancer resistant to the usual treatments

Lung Carcinoma

First-line treatment of metastatic or locally advanced non-small cell lung cancer not subject to curative treatment by radiotherapy.

CONTRAINDICATIONS

PACLITAXEL FOR INJECTION (paclitaxel) is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in polyethoxylated castor oil.

PACLITAXEL FOR INJECTION should not be used in patients with severe baseline neutropenia (<1 500 cells/mm^3)

WARNINGS

PACLITAXEL FOR INJECTION (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapy agents.

PACLITAXEL FOR INJECTION should be administered as a diluted infusion. Patients receiving PACLITAXEL FOR INJECTION should be pretreated with corticosteroids, antihistamines, and H_2 antagonists (such as dexamethasone, diphenhydramine and cimetidine or ranitidine) to minimize hypersensitivity reactions (see DOSAGE AND ADMINISTRATION). Anaphylaxis, and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in patients receiving paclitaxel. These reactions are probably histamine-mediated. Literature reports indicate that rare fatal reactions have occurred in patients despite pre-treatment. In case of a severe hypersensitivity reaction, PACLITAXEL FOR INJECTION infusion should be discontinued immediately and the patient should not be rechallenged with the drug (see ADVERSE REACTIONS).

PACLITAXEL FOR INJECTION should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. Bone marrow suppression (primarily neutropenia) is dose and schedule dependent and is the dose-limiting toxicity within a regimen. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted during PACLITAXEL FOR INJECTION treatment. Patients should not be retreated with subsequent cycles of PACLITAXEL FOR INJECTION until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3 (see DOSAGE AND ADMINISTRATION).

Severe cardiac conduction abnormalities have rarely been reported during paclitaxel therapy. If patients develop significant conduction abnormalities during administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with PACLITAXEL FOR INJECTION (see ADVERSE REACTIONS).

Use in Pregnancy

PACLITAXEL FOR INJECTION may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryotoxic and fetotoxic in rabbits and to decrease fertility in rats. There are no studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with PACLITAXEL FOR INJECTION.

Nursing Mothers

It is not known whether PACLITAXEL FOR INJECTION is excreted in human milk. Breast feeding should be discontinued for the duration of PACLITAXEL FOR INJECTION therapy.

Use in Children

The safety and effectiveness of PACLITAXEL FOR INJECTION in pediatric patients have not been established.

PRECAUTIONS

Undiluted concentrate should not come in contact with plasticized polyvinyl chloride (PVC) equipment. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate)], which may leach from PVC infusion bags or sets, diluted PACLITAXEL FOR INJECTION (paclitaxel) solutions should preferably be stored in glass bottles and administered through polyethylene-lined administration sets.

Cardiovascular

Hypotension, hypertension and bradycardia have been observed during PACLITAXEL FOR INJECTION (paclitaxel) administration; patients are usually asymptomatic and generally do not require treatment. In severe cases paclitaxel infusions may need to be interrupted or discontinued at the discretion of the treating physician. Frequent monitoring of vital signs, particularly during the first hour of PACLITAXEL FOR INJECTION infusion is recommended. Continuous cardiac monitoring is not required except for patients who develop serious conduction abnormalities (see WARNINGS, ADVERSE REACTIONS).

Nervous System

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual. A dose reduction of 20% is recommended for all subsequent courses of PACLITAXEL FOR INJECTION for moderate to severe neuropathy (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION).

Hepatic

There is evidence that the toxicity of PACLITAXEL FOR INJECTION is enhanced in patients with increased liver enzymes. Caution should be exercised when administering PACLITAXEL FOR INJECTION to patients with moderate to severe hepatic impairment and dose adjustments should be considered (see ADVERSE REACTIONS).

Drug Interactions

The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP 3A4 and CYP 2C8. Caution should be exercised when administering paclitaxel concomitantly with known substrates, inducers or inhibitors of these isoenzymes.

Montelukast should not be taken with Paclitaxel since it is known to be a potent in vitro inhibitor of the P450 2C8 enzyme, as well it may decrease the metabolic clearance of drugs that are primarily metabolized by the 2C8 pathway.

Driving/Operating Machinery

Since PACLITAXEL FOR INJECTION contains ethanol, consideration should be given to the possibility of CNS and other effects.

ADVERSE REACTIONS

The incidence of adverse reactions in the table that follows are derived from ten clinical trials in carcinoma of the ovary and of the breast involving 812 patients treated with paclitaxel at doses ranging from 135-300 mg/m^2/day and schedules of three or twenty-four hours. Data from a subset of 181 patients treated with 175 mg/m^2 and a three-hour infusion schedule are also included in the table.

SUMMARY OF ADVERSE REACTIONS			
		135 to 300 mg/m^2 % of Patients (N=812)	175 mg/m^2 % of Patients (N=181)
Bone Marrow			
Neutropenia	< 2 000/mm^3	90	87

Leukopenia	< 500/mm^3	52	27
	< 4 000/mm^3	90	86
	< 1 000/mm^3	17	4
Thrombocytopenia	< 100 000 mm^3	20	6
	< 50 000 mm^3	7	1
Anemia	< 11 g/dL	78	62
	< 8 g/dL	16	6
Infections		30	18
Bleeding		14	9
Red Cell Transfusions		25	13
Red Cell Transfusions (normal baseline)		12	6
Platelet Transfusions		2	0
<u>Hypersensitivity Reactions</u>			
All		41	40
Severe		2	1
<u>Cardiovascular</u>			
Bradycardia during first 3 hours of infusion		3	3
Hypotension during first 3 hours of infusion		12	11
Severe cardiovascular events		1	2
<u>Abnormal ECG</u>			
All patients		23	13
Patients with normal baseline		14	8
<u>Peripheral Neuropathy</u>			
Any symptoms		60	64
Severe symptoms		3	4
<u>Myalgia/Arthralgia</u>			
Any symptoms		60	54
Severe symptoms		8	12
<u>Gastrointestinal</u>			
Nausea and vomiting		52	44
Diarhhea		38	25
Mucositis		31	20
<u>Alopecia</u>		87	93
<u>Hepatic</u> (patients with normal baseline)			
Bilirubin elevations		7	4
Alkaline phosphatase elevations		22	18

AST elevations	19	18
Injection site reactions	13	4

The safety profile has been evaluated from a large randomized trial (paclitaxel 135 mg/m^2 over 24 hours with cisplatin 75 mg/m^2 versus cyclophosphamide/cisplatin) which included 410 patients, 196 of whom received paclitaxel. Use of paclitaxel with platinum agents has not resulted in any clinically significant changes to the safety profile of the product when used at the recommended dosage.

Summary of Three Hour Infusion Data at a Dose of 175 mg/m^2

Unless otherwise stated, the following safety data relate to sixty-two patients with ovarian cancer and 119 patients with breast cancer treated at a dose of 175 mg/m^2 and a three hour infusion schedule, in phase III clinical trials. All patients were premedicated to minimize hypersensitivity reactions. Bone marrow suppression and peripheral neuropathy were the principal dose-related adverse reactions. Further, as compared to a 24 hour infusion schedule, the incidence of neutropenia was less common when paclitaxel was administered as a three-hour infusion. Neutropenia was generally rapidly reversible and did not become worse with cumulative exposure. Repeated exposure increases the frequency of neurologic symptoms. None of the observed toxicities were influenced by age.

Hematologic

The most frequent notable undesirable effect of paclitaxel was bone marrow suppression. Severe neutropenia (< 500 cells/mm^3) occurred in 27% of patients, but was not associated with febrile episodes. Only one percent of patients experienced severe neutropenia for seven days or more. Neutropenia was not more frequent or severe in patients who received prior radiation therapy, nor did it appear to be affected by treatment duration or cumulative exposure. Eighteen percent of patients had an infectious episode, all non-fatal. Although severe septic episodes associated with severe neutropenia attributable to paclitaxel were reported in early clinical trials, no severe infections or septic episodes were seen at the recommended dose and infusion schedule. There were five fatal septic episodes associated with severe neutropenia attributable to paclitaxel in the overall 812 patient database.

Thrombocytopenia with platelet counts <100,000 cells/mm^3 was reported in six percent of patients. Thrombocytopenia with platelet counts <50,000 cells/mm^3 was reported in one percent of patients. Severe thrombocytopenia (<50,000 cells/mm^3) was observed during the first two courses only. Bleeding episodes occurred in nine percent of patients; no patient needed platelet transfusion.

Anemia was seen in 62% of patients, but was severe (Hb<8 g/dL) in only 6% of patients. Incidence and severity of anemia are associated with baseline hemoglobin status. Red cell transfusions were required in 13% of patients (6% of those with normal baseline hemoglobin levels).

Hypersensitivity Reactions

Severe hypersensitivity reactions occurred in 1% of patients even with premedication. These reactions occurred generally in early treatment courses and within the first hour of infusion. Dyspnea, flushing, chest pain and tachycardia were the most frequent signs and symptoms.

The dosage and schedule had no effect on the frequency of hypersensitivity reactions which occurred in 21% of courses where patients were given the recommended dose at the recommended schedule. The majority of reactions were minor. The most frequent were flushing (28%), rash (14%), and hypotension (3%).

Cardiovascular

During infusion of paclitaxel, hypotension and bradycardia were experienced by 24% and 4% of patients, respectively, and did not usually occur during the same course; the majority of episodes were asymptomatic and did not require treatment.

One patient experienced transient hypertension during the second paclitaxel cycle. In addition, two patients experienced severe cardiovascular events (tachycardia and thrombophlebitis), possibly related to paclitaxel. None of these patients required discontinuation of treatment. In the same studies at a lower dose or longer infusion, three severe cardiovascular events (atrioventricular (AV) block, syncope and hypotension associated with coronary stenosis resulting in death) possibly related to paclitaxel administration were reported. Ten severe cardiovascular events occurred which included cardiac rhythm disturbance and syncope among the 812 patients (see WARNINGS).

An abnormal ECG occurred in 13% of patients during the clinical trials at a dosage of 175 mg/m^2 and a three-hour infusion schedule. Some patients (8%) with a normal ECG prior to study entry developed an abnormal tracing during the study. Of the 812 patients, the most frequently reported ECG changes were non-specific repolarisation abnormalities, sinus tachycardia and premature beats. In most cases, there was no clear relationship between the administration of paclitaxel and ECG changes; these changes were of no, or minimal, clinical relevance.

Since the above summary, cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other prior chemotherapy especially anthracyclines.

Neurologic

Peripheral neuropathy, mainly manifested by paresthesia, affected 64% of patients, but was severe in only 4% of patients. Neurologic symptoms can occur following the first course and can worsen with increased exposure to paclitaxel. Peripheral neuropathy was the cause of drug discontinuation in three cases. 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. Rare neurologic events include grand mal seizures and encephalopathy. Reports of motor neuropathy with resultant minor distal weakness and autonomic neuropathy resulting in paralytic ileus and orthostatic hypotension have also been observed. Optic nerve and/or visual disturbances (scintillation scotomata) have also been reported, especially in patients who have received higher doses than recommended. These effects have generally been reversible.

Arthralgia/Myalgia

Arthralgia or myalgia affected 54% of patients and was severe in 12% of patients. The symptoms usually were pain in the large joints of the arms and legs and were transient occurring two to three days after administration and resolving within a few days.

Alopecia

Alopecia was observed in nearly all patients.

Gastrointestinal

Gastrointestinal side effects were usually mild to moderate: nausea/vomiting (44%), diarrhea (25%) and mucositis (20%) were reported. Other gastrointestinal events included anorexia (25%), constipation (18%) and intestinal obstruction (4%). Neutropenic enterocolitis, bowel obstruction/perforation and ischemic colitis and pancreatitis have occurred.

Hepatic

In patients with normal baseline liver function, four percent had elevated bilirubin, 18% had elevated alkaline phosphatase, and 18% had elevated AST (SGOT). Severe elevations (>5x normal values) of bilirubin, alkaline phosphatase or AST were seen in 1%, 5%, and 5% of patients, respectively. There have been rare reports of hepatic necrosis and hepatic encephalopathy leading to death.

Injection Site Reactions

Phlebitis can occur following the intravenous administration of paclitaxel. Extravasation during intravenous infusion can lead to edema, pain, erythema and induration. Occasionally extravasation can result in cellulitis. Skin discoloration can also occur. Recurrence of skin reactions at a site of previous extravasation following administration at a different site, so called "recall", has been reported rarely. A specific treatment of extravasation reactions is unknown, however treatment with a subcutaneous injection of hyaluronidase diluted in saline has been shown to be effective in a mouse skin model.

Other

Mild and transient nail and skin changes have been observed. Radiation pneumonitis has been reported in patients who have received concurrent radiotherapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no known antidote for PACLITAXEL FOR INJECTION (paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

DOSAGE AND ADMINISTRATION

Note: Undiluted concentrate should not come in contact with plasticized PVC equipment. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl) phthalate], which may be leached from PVC infusion bags or sets, diluted PACLITAXEL FOR INJECTION (paclitaxel) solutions should preferably be stored in bottles (glass) and administered through polyethylene-lined administration sets.

PACLITAXEL FOR INJECTION should be administered through an in-line filter with a microporous membrane

not greater than 0.22 microns.

All patients should be premedicated prior to PACLITAXEL FOR INJECTION administration in order to prevent hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 to 6 hours before PACLITAXEL FOR INJECTION, diphenhydramine 50 mg I.V. (or its equivalent), 30 to 60 minutes prior to PACLITAXEL FOR INJECTION, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before PACLITAXEL FOR INJECTION.

Preparation and Administration

Note: See WARNINGS, PRECAUTIONS and PHARMACEUTICAL INFORMATION for detailed instructions on the administration of PACLITAXEL FOR INJECTION.

PACLITAXEL FOR INJECTION must be diluted prior to infusion.

PACLITAXEL FOR INJECTION is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling PACLITAXEL FOR INJECTION. The use of gloves is recommended. Following topical exposure, tingling, burning, redness has been observed. If PACLITAXEL FOR INJECTION solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PACLITAXEL FOR INJECTION solution contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.

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. It is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Breast carcinoma

For patients with advanced metastatic breast cancer, PACLITAXEL FOR INJECTION is administered intravenously by continuous infusion over 3 hours at a dose of 175 mg/m^2 at 21 day intervals. Single courses of PACLITAXEL FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3) or severe peripheral neuropathy during PACLITAXEL FOR INJECTION therapy should have the dosage reduced by 20% for subsequent courses of PACLITAXEL FOR INJECTION.

Non-small cell lung carcinoma

For patients with non-small cell lung carcinoma, PACLITAXEL FOR INJECTION is administered intravenously by continuous infusion over 3 hours at a dose of 175 mg/m^2 at 21 day intervals. Single courses of PACLITAXEL FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3) or severe peripheral neuropathy during PACLITAXEL FOR INJECTION therapy should have the dosage reduced by 20% for subsequent courses of PACLITAXEL FOR INJECTION.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name

Paclitaxel (USAN)

Chemical Name

Benezenepropanoic acid,β-(benzoylamino)-α-hydroxy-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester, [2a*R*-[2aα,4β,4aβ,6β,9α(αR*,βS*),11α,12α,12aα,12bα]]-.

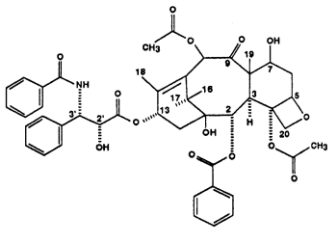
Physical Properties

Description: White to off white crystalline powder

Solubility: Paclitaxel is highly lipophilic and insoluble in water. It is slightly soluble in hexane and propylene glycol, sparingly soluble in t-butanol, and soluble in such solvents as polyethylene glycols 300 and 400, ethanol, chloroform, toluene, acetone, methylene chloride and methanol.

Melting point: 216 - 217°C

Structural Formula



Empirical Formula
$C_{47}H_{51}NO_{14}$

Molecular Weight
853.9

Composition

Each mL of sterile nonpyrogenic solution contains 6 mg of paclitaxel, 527 mg of purified polyethoxylated castor oil and 49.7% (v/v) dehydrated alcohol, USP.

Stability and Storage Recommendations

Unopened vials of Paclitaxel for Injection concentrate are stable until the date indicated on the package when stored between 2°C to 25°C in its original package. Do not freeze. The infusion must be initiated within 24 hours of reconstitution. The 50 mL bulk vial should be used within 8 hours after initial entry. The pH of Paclitaxel for Injection diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final concentration of 0.3 to 1.2 mg/mL remained within the range of 4.5 to 5.0 within a 24 hour period.

Reconstitution and Preparation of Dosage Form

NOTE: Due to the extracting effect of polyethoxylated castor oil on plastics, polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion are not recommended. Contact of paclitaxel for injection with PVC causes leaching of DEHP [di-(2-ethylhexyl) phthalate]. Paclitaxel solutions should be stored in glass bottles and administered through polyethylene lined administration sets. It is recommended to filter the solution using in-line filters of 0.22 μm.

Preparation for i.v.

Administration: Paclitaxel for Injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection or in 5% Dextrose Injection to a final concentration of 0.3 to 1.2 mg/ml. It is recommended to filter the solution using in-line filters of 0.22 microns. The solutions are physically and chemically stable for up to 24 hours at ambient temperature (15° to 30º C). The intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Special Instructions

Paclitaxel is a cytotoxic anticancer drug and is toxic in both concentrated and diluted form and must be handled and administered with care. Should accidental skin contact occur the affected part should be washed immediately with soap and water. If paclitaxel accidentally contacts eyes or mucous membranes, flush thoroughly with water.

Directions for Dispensing from Pharmacy Bulk Vial

The use of the Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture programme. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only. Dispensing from the bulk vial should be completed within 8 hours after initial entry.

AVAILABILITY OF DOSAGE FORMS

Paclitaxel for Injection is available in single dose vials of 5 mL, 16.7 mL and 25 mL and pharmacy bulk vials of 50 mL containing respectively 30 mg, 100 mg, 150 mg and 300 mg paclitaxel at a concentration of 6mg/mL. Non-medicinal ingredients: dehydrated alcohol 49.7% v/v and polyethoxylated castor oil.

PHARMACOLOGY

In vitro testing of paclitaxel on human breast carcinoma (MCF.7) and ovarian carcinoma cells (SKOV3) demonstrated the cytotoxic effect of this drug on both strains of cancerous cells. An ID_{50} of 3200 nM for MCF.7 and 15 ng/mL and 7 ng/mL for SKOV3 cells was reported in this study.

In an *in vivo* tumor model, intraperitonally administered paclitaxel from *Taxus canadensis* significantly improved the survival rate of C57 BL/6J mice bearing B16 melanoma.

TOXICOLOGY

Acute Toxicity

Acute toxicity of paclitaxel from *Taxus Canadensis* administered intraperitonally was determined in female Balb/C mice (average weight: 20g). Doses varied from 5 to 500 mg/kg. No mortality was observed 21 days after treatment in groups receiving doses less than 250 mg/kg. A 40% mortality rate was observed in the 250 mg/kg group 21 days following drug administration. Mortality was observed 5 days after drug administration in the 500 mg/kg group.

The toxicology of paclitaxel from *Taxus brevifolia* was studied in CD2F1 mice, Sprague-Dawley rats, and beagle dogs. In lethality studies the animals were exposed with a single dose for 1 day or for 5 consecutive days. These studies provided LD_{10}, LD50, and LD90 (dose lethal to 10%, 50%, and 90%) values of 138, 206, and 307 mg/m^2, respectively, in rats for the single dose. When administration of paclitaxel was spread over 5 days, values of LD10, LD50, and LD90, decreased to one-fourth (36, 51, and 74 mg/m^2, respectively).

Subacute toxicity

Toxic effects of paclitaxel were found in tissues with a high frequency of cell turnover, such as hematopoietic, lymphatic, gastrointestinal, and reproductive tissues; this was found in all three species. In beagle dogs, myelosuppression occurred, which was cumulative and reversible between 45 and 180 mg/m^2 in a single-dose schedule. On a 5-daily dose schedule, the dose for myelosuppression was 15-30 mg/m^2. Dogs receiving this schedule showed severe gastrointestinal effects such as weight loss, diarrhea, emesis, adipsia, and mucosal ulcerations. Diffuse inflammation and congestion of both the small and the large intestines occurred in dogs at lethal doses. Depression of the central nervous system, namely lethargy, coma, and ataxia, was also observed in dogs. All species showed a dose-related lymphoid depletion. In rats and mice, testicular lesions were observed. These lesions were characterized by necrosis of developing spermatocytes, giant cell formation in the seminiferous tubules, and oligospermia.

In vitro tests have shown that paclitaxel causes the formation of abnormal bundles of microtubules throughout the cytoplasm, leading to deregulation of normal cell functions, such as mitosis, cell proliferation, neurite initiation, and neurite branching. Direct injection of paclitaxel in rat sciatic nerve showed a sustained and local toxic effect, leading to microtubule-related abnormalities in Schwann cells and axons. The effect of paclitaxel on Schwann cells correlated with changes in myelinization and the development of the nodes of Ranvier.

Examination of ^{3}H-paclitaxel distribution in adult Spraque-Dawley rats showed no distribution of the radioactivity in the nervous system (limit of detection < 20 nM), with only a small amount detected in cerebrospinal fluid (CSF). In this study, high levels of radioactivity were observed in liver parenchyma, spleen, heart, lung, and muscles. High concentrations were seen in the portal triad, glomerulla, renal medulla, and choroid plexus. Preclinical toxicity studies showed only minor effects on nerve, hepatic, cardiovascular, and renal tissues, with no postmortem evidence of organ damage. Whole-body autoradiography with radioactive-labeled docetaxel in mice and dogs showed rapid tissue uptake, e.g., in liver, bile, intestine, stomach, spleen, myocardium, bone marrow, pancreas, and salivary glands, while no uptake was seen in the central nervous system.

Reproduction and teratology

Reproduction studies in rats and rabbits receiving i.v. paclitaxel from *Taxus brevifolia* at doses of 1 mg/kg (6 mg/m^2 or systemic exposures approximately equivalent to 0.04 times the maximum recommended human dose on a mg/m^2 basis) and 3 mg/kg (33 mg/m^2 or systemic exposures approximately equivalent to 0.2 times the maximum recommended human dose on a mg/m^2 basis), respectively, during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity. The drug resulted in intrauterine mortality, increased resorptions, and increased fetal deaths. No teratogenic effects were observed in the offspring of rats receiving daily i.v. paclitaxel from *Taxus brevifolia* doses of 1 mg/kg; however, the teratogenic potential of higher paclitaxel from *Taxus brevifolia* doses could not be assessed because of extensive fetal mortality. At an i.v. dose of 1 mg/kg (6 mg/m^2), paclitaxel from *Taxus brevifolia* produced low fertility in rat.

Mutagenicity and carcinogenicity

Paclitaxel from *Taxus brevifolia* has been shown to induce chromosome aberrations in human lymphocytes in vitro, and the drug was mutagenic in the micronucleus test in mice in vivo; however, paclitaxel from *Taxus brevifolia* was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Studies to determine the carcinogenic potential of paclitaxel have not been performed to date.

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