For the use of cancer specialist of a hospital or a laboratory only

Paclitaxel 300mg/50ml,260mg/43.4ml,100mg/16.7ml,30mg/5ml

ZAXOL

COMPOSITION

Each ml contains:

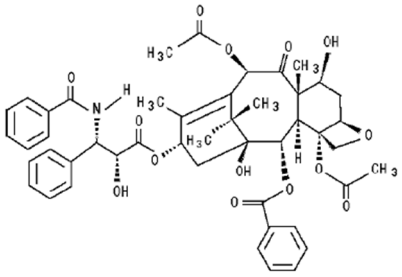
Paclitaxel IP……..6mg

Absolute alcohol I.P 49.7% v/v

DESCRIPTION

Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via a semisynthetic process from Taxus baccata. The chemical name for paclitaxel is 5B, 20-Epoxy 1,2 a, 4,7B, 10 B, 13 a-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benoate 13-ester with (2R,. 3S)-N-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula C47H51 NO14 and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217°C.

Parmacological Information/Pharmocodynamics

Paclitaxel is a novel anti-microtubule agent, which promotes the assembly for microtubule from tubulin dimmers and stabilizes microtubules by preventing

depolymerization. Because of this stability the normal dynamic reorganization of the microtubule network (which is essential for vital interphase and mitotic cellular functions) is inhibited. Besides, Paclitaxel induces abnormal arrays or bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. These effects occur in G2 and M phases of the cell cycle.

Paclitaxel in several clinical studies demonstrated substantial anti-tumor activity in carcinoma of the breast, ovary, and lung (both non-small cell and small cell) and was effective in patients with advanced carcinomas of the head and neck, bladder, testes, esophagus and endometrium, additionally, modest activity has been reported in Kaposi's sarcoma, lymphoma and carcinoma of the stomach and cervix.

Pharmacokinetic Profile

Following intravenous administration Paclitaxel exhibits a biphasic decline in plasma concentrations, the initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The latest phase is due in part to a relatively slow efflux of paclitaxel from the peripheral compartment The pharmacokinetics are non-linear. The steady-state volume of distribution is reported to range from about 67 to 182 L/m2, indicating extensive extravascular distribution, tissue binding, or both. Paclitaxel is 89% to 98% bound to plasma protein in Vitro. Paclitaxel is metabolized in liver, by the cytochrome P450 isozymes CYP2C8 and CYP3A4 and high paclitaxel concentrations have been reported in bile. Hence its use is not recommended in patients with severe hepatic impairment. The elimination of paclitaxel has not been fully elucidated; only about 1.3% to 12.6% of a dose is reported to be excreted in urine, as unchanged drug, indicating extensive non renal clearance. Total Body clearance: 12.2 to 23.8 I/H/m2. The elimination half-life of the parent compound is 13.1 to 52.7 hours.

PHARMACEUTICAL INFORMATION

Incompatibilities

The Vehicle for paclitaxel Injection which contains alcohol and polyethoxylated castor oil was found to leach the plasticizer diethylhexyl phthalate from some plastic administration sets. Hence contact of paclitaxel with plasticized polyvinyl chloride (PVC) equipment or devices must be avoided and paclitaxel solution should be diluted and stored in glass or polypropylene bottles or in plastic bags (Pollypropylene, polyolefin) and administered through polyethylenelined administration sets.

INDICATION

ZAXOL (Paclitaxel) is indicated for the treatment of metastatic carcinoma of the ovary or breast after failure of standard therapy. The standard therapy means anthracycline containing regimen for ovarian cancer unless clinically contraindicated.

DOSAGE AND ADMINISTRATION

All patients should be per medicated prior to ZAXOL administration in order to minimize severe hypersensitivity reaction Such pre medication may consist of dexamethasone 20mg orally approximately 12 and 6 hours before ZAXOL, diphenhydramine (or its equivalent) 50mg IV 30 to 60 minutes prior to ZAXOL and cimetidine (300mg) or rantidine (50mg) IV 30 to 60 minutes before ZAXOL

ZAXOL at a dose of 175mg/m^2 administration intravenously. Over 3 hours every three week has been to the effective in patients with metastatic carcinoma of the ovary or breast who have failed standard therapy. Single course of ZAXOL should not be repeated until the neutrophil count is at least 1500 cells/mm^2 and platelet count is at least 100,000 cells/mm^2 patient who experience who experience severe neutropenia (neutrophil <500 cells/mm^2) or severe peripheral neutropenia during ZAXOL therapy should have the dosage reduced by 20% for subsequent course of ZAXOL

Preparation for Intravenous Administration

ZAXOL for injection must be diluted prior to infusion. ZAXOL should be diluted in 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9%

sodium chloride injection, or 5 % dextrose in Ringer's injection to a final concentration of 0.3 to 1.2mg/ml. The solution are physically and chemically stable for up to 27 hours at ambient temperature (15 - 30º). Upon preparation solution may show haziness, which is attributed to the formulation vehicle.

No significant loss in potency has been noted following simulated delivery of the solution through I.V. tubing containing an in – line (0.22 micron) filter

Data collected for the presence of the extractable plasticizer DEPH (di(2-exthylexly phthalate) show that level increase with time and concentration when dilutions are prepared in pvc containers. Consequently the use of plasticized pvc containers and administration sets are not recommended. ZAXOL solution should be prepared and stored in glass, polypropylene, or polyolefin containers Non-PVC containing administration sets, such as those which are polyethylene- lined, should be used.

Warnings:

Patients should be pretreated with corticosteroids, diphenhydramine and histamine antagonists (such as ranitidine of cimetidine) prior to Paclitaxel therapy since hypersensitivity reactions with Dyspnea, hypotension and angioedema have been reported with Paclitaxel. Patients who experience severe hypersensitivity reactions to Paclitaxel should not be re-challenged with the drug.

Use in Patients with Impaired Kidney Function:

The pharmacokinetic parameters are not fully elucidated in patients with impaired Kidney function.

Use in elderly patients:

It is not necessary to adjust the dose of Paclitaxel in elderly patients since the safety and efficacy of Paclitaxel are not altered in these patients when compared to younger patients.

With Laboratory Tests

Treatment with Paclitaxel may cause transient increases in serum alkaline phosphatase, asparate aminotransferase and bilirubin levels. Therefore consideration should be given to these effects when laboratory determinations are interpreted.

Lactating Women

Safety and efficacy has not been established in lactating women.

Precautions:

During Paclitaxel therapy, continuous cardiac monitoring should be performed in patients with a previous history of conduction abnormalities since cardiac adverse effects (i.e. Myocardial infarction symptoms of congestive heart failure) have been reported in patients receiving Paclitaxel.

Paclitaxel produces severe dose-limiting bone marrow depression. Therefore regular blood counts should be performed on patients receiving Paclitaxel, and dosage should not be repeated until the neutrophils count is greater than 1,500 cell/mm2 and the platelet count is at least /greater the 100,000cell/mm2

Interactions

With other Drugs

Concurrent use of radiation therapy with Paclitaxel should be avoided because of additive bone marrow depression. Pretreatment with Cisplatin may reduce the clearance of Paclitaxel resulting in increased toxicity specially increased myelosuppression. Hence, when the two drugs are given in combination Paclitaxel should be given first.

The metabolism of Paclitaxel is catalyzed by CYP2C8 and CYP3A4 in the absence of drug interaction data caution should be exercised when administering Paclitaxel concomitantly with known substrates or inhibitors of Cytochrome P450 isoenzymes CYP2CB and CYP3A4.

Paclitaxel should be given with caution to those patients who are on Ketoconazole therapy due to the inhibition of Paclitaxel metabolism by Ketoconazole leading to drug accumulation.

Adverse Reactions

The incidence of adverse reaction that follows are derived from ten clinical trials in carcinoma of the ovary and of the breast involving 812 patients treated as dosage ranging from 135-300mg/mm^2 / day and schedules of 3 to 24 hours.

Summary of 3 hours infusion data of 175mg/m^2

Unless otherwise stated the following safety data realete to 62 patients with ovarian cancer and 119 patients with breast cancer treated at dose of 175mg/m^2 and a 3 hours infusion schedule, in Phase III clinical trials all patients were pre medicated to minimize hypersensitivity reaction. Data from these clinical trials demonstrates the paclitaxel given at this dose and schedule is well tolerated, mylosupperession, in particular, is less frequent and incidence of hypersensitivity reaction, peripheral neuropathy or other significant undesirable effect was not. None of the observed toxicities were influenced by age.

Hematologic

The most frequent significant undesirable effect of paclitaxel was bone marrow suppression. Severe neutropenia (<500cell/$mm)^3$ occurred in 27% of patients, but was not assossiated with febrile episodes. Only 1% o0f patients experienced severe neutropenia for 7 days or more

Eighteen percent patients had an infectious episode. Although severe septic episodes associated with severe neutropenia altribute to paclitaxel were reported in early clinical trials, no severe infection oe septic episodes were seen at recommended dose and infusion schedule. Thrombocytopenia was reported in

6% of patients. One percent of patients had a platelet nadircount 50000/mm^3 at least once white on study.

Anemia was observed in 62% of patients, but was severe (HB<8g/dl) in only 6% of patients. Incidence and severity of anemia are related to baselinehemoglobin status

Hypersensitivity Reaction

A significant Hypersensitivity reaction (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy or generalized urlicaria) occurred in 2 patients. Thirty- nine percent of patients (20% of all course) experienced minor hypersensitivity reaction. These minor reaction , mainly flushing and rash , did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Cardiovascular

Hypertension and bradycardia were experienced by 22% and 3% of patients, respectively and were asymptomatic in all case. One patients experienced transient hypertension during the second paclitaxel cycle. In addition 2 patients presented sever cardiovascular event (tachycardia and thrombophlebits), but these were considered unrelated to paclitaxel. In the same studies at lower dose or longer dose or longer infusion 3 severe cardiovascular events (antrioventicular (AV) block, syncope and hypertension associate with coronary stenosis resulting in death) possibility related to paclitaxel administration were reported. In early clinical studies , conducted with varying dosage and infusion schedule. 4(2%) patients experienced severe cardiovascular event possibility related to paclitaxel which included asymptomatic ventricular tachycardia, tachycardia with beigeminy, AV block and syncope

Neurologic:

Peripheral neutropathy, mainly manifested by paresthesia, affected 64 % of patients, but was severe in only 4% patients peripheral neutropathy can occur following the first course and can worsen with increasing exposure to paclitaxel,

sensory symptoms have usually improved or resolved within several moth of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Arthralgia/myalgia

Arthralgia or myalgia affected 54% of patients and was severe in 12% of patients

Alopecia

Aplopecia was observed in almost all patients

Gastrointestinal

Gastrointestinal side effects were usually mild to moderate:

Nausea/vomiting, diarrhea and mucositis were reported by 44%, 25% and 20% of patients, respectively. Other gastrointestinal events include anorexia (255 patients), anorexia (255 patients) constipation (18%) and intestinal obstruction (4%)

Hepatic

Severe elevation (<5x normal value) in AST (SGOT), alkaline phosphate or bilrubin were seen in 5%, 5% and 1% of patient respectively.

General precautions

Hematology

Paclitaxel should not be administered to patients with baseline neutrophil counts less than 1,500cells/mm^2 and patients recover to a level > 1,00,000 cell/mm^2. In case of severe neutropenia <500cell/mm^2) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent causes of therapy is recommended

Hypersensitivity reaction

Patients with a history of a severe hypersensitivity reaction to product containing cremaphor +EL should not be treated with paclitaxel (see WARNING

CONTRAINDICATIONS) minor symptoms such as flushing, skin reaction, dyspenea. Hypptention or lachycardia do not require interruption of therapy.

However severe reaction, such as hypotension require treatment, dyspenea requiring broncholidators, angiodema or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity should not be rechallanged with paclitaxel

Cardiovascular

Hypertension and bradycardia have been observed during administration of paclitaxel but generally do not require treatment, frequently vital sign monitoring particularly during the first hours of paclitaxel infusion, is recommended continuous cardiac monitoring is not require except for patients who develop serious conduction abnormalities.

Nervous System

Although the occurrences of peripheral neuropathy is frequent the development of severe symptomatology is unusual and require a dose reduction of 20% for all subsequent causes of paclitaxel

Hepatic

There is no evidence that the toxicity of paclitaxel is enhanced in patients with abnormal liver function. But no data are available for patients with severe baselines cholestasis.

Drug Interaction

In a phase 1 trial using escalating dose of paclitaxel (110-200mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusion, myelosupperssion was more profound when paclitaxel was given after cisplatin than with alternate sequence (i.e. paclitaxel before cisplatin) pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearances of approximately 33% when paclitaxel was administration following cisplatin

Possibility interaction of paclitaxel with concomitantly administrated medication have not been formally investigated

Use in pregnancy and nursing mothers

There are no studies in pregnant woman. Paclitaxel has been shown to be embryo and feto-toxic in rabbits and to decrease fertility in rates paclitaxel should not be administered to nursing mother

Treatment of Overdosage

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

The drugs is contraindicated in the following patients

Paclitaxel is contraindicated in patients who have history of severe hypersensitivity reaction to paclitaxel or other drugs formulated bin cremophor+EL (poleythoxylated castor oil)

Paclitaxel should not be used in patients with severe baseline Neutroperial (<1500 cells/mm)^3

Storage

Store the vials in original carton at temperature not exceeding 25°C protect from light.

Presentation

PRESENTATION:

ZAXOL - 30 mg/5ml single-dose vial individually packaged in carton.

ZAXOL- 100mg/16.7 ml. single-dose vial individually packaged in a carton.

ZAXOL -260 mg/43.4 ml single-dose vial individually packaged in a carton.

ZAXOL - 300/50 ml. single dose vial individually packed in a Carton

Manufactured in India by:

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