

New Zealand Data Sheet

PACLITAXEL ACTAVIS

Paclitaxel Actavis, concentrate for injection 6mg/mL

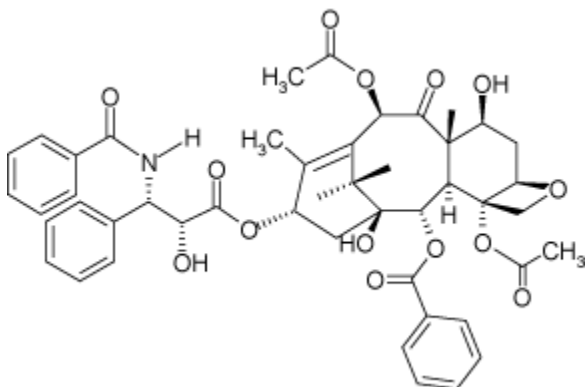
NAME OF THE DRUG

Paclitaxel

Composition

Active: Paclitaxel

Inactive: Each mL contains absolute ethanol 402mg, PEG-35 castor oil 522mg.



Molecular formula: C₄₇H₅₁NO₁₄

Molecular weight: 853.9

CAS: 33069-62-4

DESCRIPTION

Paclitaxel is a natural product with antitumour activity. It is a white to off-white crystalline powder that is extremely highly lipophilic and practically insoluble in water. Paclitaxel is partially soluble in ethanol and is therefore formulated with PEG-35 castor oil and absolute ethanol.

PHARMACOLOGY

Paclitaxel is an antimicrotubule antineoplastic agent. It promotes microtubule assembly by enhancing the polymerisation of tubulin, the protein subunit of spindle microtubules, even in the absence of the mediators normally required for microtubule assembly (e.g. guanosine triphosphate (GTP)), thereby inducing the formation of stable, nonfunctional microtubules. While the precise mechanism of action of the drug is not completely known, paclitaxel disrupts the dynamic equilibrium within the microtubule system and blocks cells in the late G2 phase and M phase of the cell cycle, inhibiting cell replication and impairing function of nervous tissue.

Pharmacokinetics

After paclitaxel is administered intravenously, its plasma concentration declines biphasically. The first phase shows rapid decline, representing distribution of paclitaxel to the peripheral compartment and elimination. This initial phase is followed by a relatively slow elimination of paclitaxel from the peripheral compartment.

The following ranges for the pharmacokinetic parameters have been determined in patients given doses of 135 and 175 mg/m² as 3 and 24 hour infusions of paclitaxel. Mean terminal half-life: 3.0 to 52.7 hours; total body clearance: 11.6 to 24.0 L/hour/ m²; mean steady-state volume of distribution: 198 to 688 L/ m². These indicate extensive distribution of paclitaxel outside the vascular system and/or tissue binding. The volume of distribution is reduced in female subjects. The following mean values for the pharmacokinetic parameters have been reported following a three hour infusion of 175 mg/ m² paclitaxel. Mean terminal half-life: 9.9 hours; mean total body clearance: 12.4 L/hour/ m². The serum protein binding of paclitaxel is 89%. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine does not affect protein binding of paclitaxel. The liver is thought to be the primary site of metabolism for paclitaxel. The mean cumulative urinary recovery of unchanged paclitaxel has been reported to be 1.8 to 12.6% of the dose, indicating extensive non-renal clearance.

INDICATIONS

Primary treatment of ovarian cancer in combination with a platinum agent.

Treatment of metastatic ovarian cancer and metastatic breast cancer, after failure of standard therapy.

Treatment of non-small cell lung cancer (NSCLC).

Adjuvant treatment of node positive breast cancer administered sequentially to doxorubicin and cyclophosphamide.

Treatment of metastatic cancer of the breast, in combination with trastuzumab (Herceptin), in patients who have tumours that overexpress HER-2 and who have not received previous chemotherapy for their metastatic disease.

CONTRAINDICATIONS

Patients who have exhibited hypersensitivity reactions to paclitaxel. Patients who have a history of hypersensitivity reactions to PEG-35 castor oil (Cremophor EL) or drugs formulated in PEG-35 castor oil (e.g. cyclosporin for injection concentrate, teniposide for injection concentrate).

PRECAUTIONS

Paclitaxel should be administered under the supervision of medical staff experienced in the use of cancer chemotherapeutic agents.

Premedication

In order to minimise the possibility of hypersensitivity reactions due to histamine release, patients should be premedicated before every treatment cycle of paclitaxel. Premedication

should include corticosteroids (e.g. dexamethasone), antihistamines (e.g. diphenhydramine or promethazine) and an H₂-receptor antagonist (e.g. cimetidine or ranitidine). (See Dosage and Administration.) The characteristic symptoms of hypersensitivity reactions are dyspnoea and hypotension (both requiring treatment), angioedema and widespread urticaria. In clinical trials, 2% of patients treated with paclitaxel experienced severe hypersensitivity. One of these reactions was fatal in a patient treated without premedication.

Paclitaxel Injection Concentrate must not be used in patients who have exhibited hypersensitivity reactions to paclitaxel.

Neutropenia

Neutropenia. (See Adverse Reactions.) Bone marrow suppression (primarily neutropenia) is the dose limiting toxicity. Blood counts should be frequently monitored during treatment with paclitaxel. Extreme care should be taken when paclitaxel is given to patients with a pretreatment neutrophil count of less than 1.5×10^9 cells/L (1,500 cells/mm³). Pretreatment with paclitaxel should not be administered until the patient's neutrophil count is greater than 1.5×10^9 cells/L (1,500 cells/mm³) and the platelet count is greater than 100×10^9 cells/L (100,000 cells/mm³). If there is severe neutropenia during a course of paclitaxel (i.e. neutrophil count less than 0.5×10^9 cells/L (500 cells/mm³) for seven or more days), the dose of paclitaxel in subsequent cycles should be reduced by 20%. Previous radiation therapy may induce more severe myelosuppression. There is little information available from such patients at doses above 135 mg/m².

Conduction abnormalities

Severe conduction abnormalities have occurred rarely in patients receiving paclitaxel. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered. Any subsequent treatment of the patient with paclitaxel should be accompanied by continuous cardiac monitoring. Severe cardiovascular events have been observed more frequently in patients with non-small cell lung cancer (NSCLC) than breast or ovarian cancer.

Gastrointestinal

In patients receiving Paclitaxel who complain of abdominal pain with other signs and symptoms, bowel perforation should be excluded.

Renal and hepatic impairment

The effect of renal and/or hepatic impairment on the pharmacokinetics of paclitaxel has not been established. However, as the liver is thought to be the primary site for metabolism of the drug, paclitaxel should be given cautiously to patients with decreased liver function. Paclitaxel has been shown to cause a dose related elevation of liver enzymes.

When paclitaxel is given as a 24 hour infusion to patients with moderate to severe hepatic impairment, increased myelosuppression may be seen as compared to patients with mildly elevated liver function tests given 24 hour infusions.

Hypotension and bradycardia

Patients may develop hypotension and bradycardia during paclitaxel treatment, but generally not to a level requiring treatment. Vital signs should be monitored frequently, particularly during the first hour of paclitaxel infusion. Only patients with serious conduction abnormalities require continuous cardiac monitoring (see Conduction abnormalities (above) and Adverse Reactions).

Nervous system

The occurrence of peripheral neuropathy is frequent and the severity is dose dependent. Patients with pre-existing neuropathy should be carefully monitored. In severe cases, all subsequent doses of paclitaxel should be reduced by 20% (See Adverse Reactions). In NSCLC patients, the administration of paclitaxel in combination with cisplatin resulted in a greater incidence of neurotoxicity than usually seen in patients receiving single agent paclitaxel. Paclitaxel contains absolute ethanol, 402mg/mL and consideration should be given to possible central nervous system and other effects of absolute ethanol. For instance, children may be more sensitive than adults to the effects of absolute ethanol.

Carcinogenesis, mutagenesis, impairment of fertility

No studies have examined the carcinogenic potential of paclitaxel however, drugs similar to paclitaxel are carcinogens. In vitro studies (chromosome abnormalities in human lymphocytes) and in vivo (micronucleus test using mice) mammalian test systems have shown paclitaxel to be mutagenic. When tested using the Ames test or the CHO/HGPRT (Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase) gene mutation assay, paclitaxel did not induce mutagenicity. Following treatment with intravenous paclitaxel at a dose of 1 mg/kg (6 mg/m²), rats showed decreased fertility and toxicity in unborn offspring. Paclitaxel administered intravenously to rabbits during organogenesis at a dose of 3 mg/kg (33 mg/m²) was toxic to both mother and fetus.

Use in pregnancy (Category D)

Studies have shown paclitaxel to be toxic to embryos and fetuses in rabbits at an intravenous dose of 3mg/kg (33mg/m²) given during organogenesis. Paclitaxel is toxic to rat fetuses at a dose of 1mg/kg (6mg/m²). Examination revealed that no gross external, soft tissue or skeletal alterations occurred.

Use in lactation

The evidence from many drugs would suggest that paclitaxel could be excreted in breast milk, though this has not been established. Because of the potential for serious adverse reactions in breastfeeding infants, it is recommended that breastfeeding be discontinued when receiving paclitaxel therapy.

Use in children

The safety and effectiveness of paclitaxel in children has not been established.

INTERACTIONS

Cisplatin

Administration of cisplatin prior to paclitaxel treatment leads to greater myelosuppression than administering it after. In patients receiving cisplatin prior to paclitaxel, there is about a 33% decrease in paclitaxel clearance.

Ketoconazole

As ketoconazole may inhibit the metabolism of paclitaxel, patients receiving paclitaxel and ketoconazole should be closely monitored or the combination of these drugs should be avoided.

Doxorubicin

Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered before doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and three hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

Drugs metabolised in the liver

Caution should be exercised during concurrent administration of drugs which are metabolised in the liver (e.g. erythromycin), as such drugs may inhibit the metabolism of paclitaxel. The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies caution should be exercised when administering Paclitaxel Injection Concentrate concomitantly with known substrates or inhibitors of these isoenzymes.

In the clinical trial of paclitaxel in combination with trastuzumab (Herceptin), mean serum trough concentration of trastuzumab were consistently elevated 1.5-fold as compared with serum concentrations of trastuzumab in combination with anthracycline plus cyclophosphamide (AC). Arthralgia or myalgia adverse events of paclitaxel appear to be of a higher incidence in patients being treated concurrently with filgrastim (granulocyte colony stimulating factor (G-CSF)).

ADVERSE REACTIONS

The following is based on the experience of 812 patients treated in phase II and III clinical trials. The frequency and severity of adverse effects are generally similar between patients receiving paclitaxel for the treatment of ovarian, breast or lung cancer. None of the observed effects were clearly influenced by age. Unless stated otherwise percent figures, where given, are based on observed incidence when using the recommended dosing regimen. If other regimens are used, the incidence of reaction may be higher.

Safety of the paclitaxel/ platinum combination has been investigated in a large randomised trial in ovarian cancer and in two phase III trials in NSCLC (non-small cell lung cancer). Unless otherwise mentioned the combination of paclitaxel with platinum agents did not result in any clinically relevant changes to the safety profile of single agent paclitaxel.

Adverse effects reported were those occurring during or following the first course of therapy, and have, where possible, been grouped by frequency according to the following criteria:

Very common: greater than or equal to 1/10; common: greater than or equal to 1/100 and < 1/10; uncommon: greater than or equal to 1/1,000 and < 1/100; rare: greater than or equal to 1/10,000 and < 1/1,000 and very rare: < 1/10,000.

Cardiovascular

Very common: hypotension.

Common: bradycardia; ECG abnormalities (nonspecific repolarisation and sinus tachycardia).

Uncommon: ECG abnormalities (premature beats).

Rare: myocardial infarction; congestive heart failure (typically in patients who have received other chemotherapy, notably anthracyclines).

Six severe cardiovascular events possibly related to paclitaxel administration occurred including asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular block (two patients), and syncopal episodes (two patients, in one associated with severe hypotension and coronary stenosis resulting in death). Severe hypotensive reactions have been associated with serious hypersensitivity reactions and have required intervention.

Haematological

Very common: anaemia; neutropenia (overall, 52% of the patients experienced severe grade IV neutropenia and 56% had grade III/IV severe neutropenia on their first course. Neutrophil nadirs occurred at a median of eleven days after paclitaxel administration).

Common: febrile neutropenia (associated with an infectious episode, including urinary tract infection (UTI) and upper respiratory tract infection (URTI)).

Rare: five septic episodes, which were associated with severe neutropenia attributable to paclitaxel administration, had a fatal outcome.

Patients who have received prior radiation or cisplatin therapy exhibit more frequent myelosuppression, which is generally of greater severity (see Precautions and Interactions). Reports of thrombocytopenia after paclitaxel therapy are less frequent and less severe than neutropenia, with platelet nadir ($< 50 \times 10^9$ cells/L) observed eight or nine days after paclitaxel administration in 5% of patients. Haemorrhage has been reported in patients receiving paclitaxel but this does not appear to be related to thrombocytopenia. Patients (3%) may require platelet transfusions.

Hepatobiliary

Very common: elevated alkaline phosphatase; elevated AST; elevated ALT.

Common: elevated bilirubin.

Rare: hepatic necrosis; hepatic encephalopathy (leading to death).

Hypersensitivity

Very common: flushing; rash.

Common: dyspnoea; hypotension; chest pains; tachycardia.

Infections. Febrile neutropenia occurred in 5% of all courses and 30% of all courses were associated with an infectious episode. The most common infections involve the upper respiratory tract, urinary tract and blood (sepsis). In phase II clinical trials, five septic episodes resulted in death.

Gastrointestinal

Very common: nausea; vomiting; diarrhoea; mucositis (these manifestations were usually mild to moderate at the recommended dose).

Rare: bowel perforation (there have been several cases of bowel perforation associated with patients receiving paclitaxel. Patients receiving paclitaxel who complain of abdominal pain with other signs and symptoms should have bowel perforation excluded).

Neutropenic enterocolitis has been reported.

Musculoskeletal

Very common: arthralgia; myalgia (the symptoms were usually transient occurring two to three days after paclitaxel administration and resolving within a few days).

Neurological

Very common: peripheral neuropathy (peripheral neuropathy occurs and is dose dependent with 60% of patients experiencing grade I toxicity, 10% grade II and 2% grade III at the recommended doses. Neuropathy was present in 87% of patients at higher doses. Severity of symptoms also increased with dose; 4% of patients experienced severe symptoms at the recommended dose versus 10% at higher doses. Neurological symptoms may occur following the first course and symptoms may worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in 2% of patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation).

Rare: optic nerve and/or visual disturbances (scintillating scotomata) particularly in patients who have received higher doses than recommended; these effects generally have been reversible; motor neuropathy with resultant minor distal weakness and autonomic neuropathy resulting in paralytic ileus and orthostatic hypotension.

There is a report of a grand mal seizure in a patient receiving paclitaxel and the seizure recurred after treatment with paclitaxel was recommenced. There is also a second report of a grand mal seizure in a patient with significant hepatic impairment during infusion with paclitaxel.

Skin and appendages

Very common: alopecia.

Rare: nail and skin changes (mild and transient); radiation recall dermatitis; recall dermatitis. Local effects: phlebitis following intravenous administration has been reported. Extravasation leading to oedema, pain, erythema and induration has been reported. On occasions extravasation can lead to cellulitis. Skin discolouration may also occur.

DOSAGE AND ADMINISTRATION

Product is for single use in one patient only.

All patients should be premedicated before paclitaxel is administered to prevent severe hypersensitivity reactions (see Precautions). Before every treatment cycle patients should be premedicated with dexamethasone 20 mg orally, 12 and 6 hours prior to starting the paclitaxel infusion; promethazine 25 to 50 mg intravenously or other suitable H1-antagonist, 30 minutes prior to starting the paclitaxel infusion; and cimetidine 300 mg or ranitidine 50 mg by intravenous infusion over 15 minutes, starting 30 minutes prior to the paclitaxel infusion.

For primary treatment of ovarian cancer - it is recommended that paclitaxel be used at a dose of 135 mg/m^2 , administered intravenously over three hours, followed by cisplatin 75 mg/m^2 . The infusion should be repeated every three weeks.

For the treatment of metastatic ovarian cancer or metastatic breast cancer - it is recommended that paclitaxel be used as a single agent at a dose of 175 mg/m^2 . Paclitaxel should be administered as an intravenous infusion over three hours. The infusion should be repeated every three weeks as tolerated. Patients have tolerated treatment with up to nine cycles of paclitaxel therapy, but the optimal course of therapy remains to be established.

For primary or secondary treatment of NSCLC (non-small cell lung cancer) - the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over three hours with a three week interval between courses.

For node positive breast cancer - the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over three hours every three weeks for four courses following doxorubicin and cyclophosphamide combination therapy.

For overexpression of HER-2 breast cancer - paclitaxel 175 mg/m^2 administered intravenously over three hours with a three week interval between courses for six cycles. Herceptin 2 mg/kg administered intravenously once a week until progression of disease after an initial loading dose of 4 mg/kg bodyweight.

Repetition of a course of paclitaxel is not recommended until the patient's neutrophil count is at least $1.5 \times 10^9 \text{ cells/L}$ ($1,500 \text{ cells/mm}^3$) and the platelet count is at least $100 \times 10^9 \text{ cells/L}$ ($100,000 \text{ cells/mm}^3$). If there is severe neutropenia (neutrophil count less than $0.5 \times 10^9 \text{ cells/L}$ for seven or more days) or severe peripheral neuropathy during paclitaxel therapy, the dose of paclitaxel in subsequent courses should be reduced by 20% (see Precautions).

Preparation for intravenous administration

Paclitaxel Injection must be diluted prior to intravenous infusion. It should be diluted in glucose 5% or sodium chloride 0.9% intravenous infusion. Dilution should be made to a final concentration of 0.3 to 1.2 mg/mL .

After the final dilution of Paclitaxel Injection Concentrate, the bottle should be swirled gently to disperse the paclitaxel. Do not shake.

Avoid contact of paclitaxel solutions with plasticised polyvinyl chloride (PVC) equipment, infusion lines or devices used when preparing infusion solutions. Prepare and store diluted paclitaxel solutions in glass or polyethylene containers.. These precautions are to avoid leaching of the plasticiser DEHP (di-[2-ethylhexyl] phthalate) from PVC infusion bags or sets. Paclitaxel solutions should be administered through polyethylene lined administration sets (e.g. Gemini 20 giving set) using an IMED pump.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at $2-8^\circ\text{C}$ for not more than 24 hours after preparation. Administration should be completed within 24 hours of preparation of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs (see Handling and disposal, below).

Facilities preparing paclitaxel solutions reconstituted under controlled aseptic conditions for IV infusion, may apply a shelf life of 14 days at 2 to 8 deg. C (refrigerate; do not freeze) when diluted with glucose 5% or sodium chloride 0.9% for intravenous infusion and stored in glass or polyethylene containers. Diluted solutions prepared this way have been shown to be chemically stable for these periods. Administration should be completed within 24 hours of the start of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs.

Filtration. A microporous membrane of 0.22 microns or less in size is recommended as the in-line filter for all infusions of paclitaxel. The IMED 0.2 micron add on filter set composed of polysulfone and the IVEX II 0.2 micron filter composed of cellulose have both been found to be suitable for Paclitaxel Injection Concentrate.

Preparation and administration precautions. Paclitaxel is a cytotoxic anti-cancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Paclitaxel. The use of gloves is recommended. Following topical exposure, tingling, burning and redness have been observed. If Paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning eyes, sore throat and nausea have been reported.

Handling and disposal

The published guidelines related to procedures for the proper handling and disposal of cytotoxic drugs should be followed.

OVERDOSAGE

At present there is no specific treatment for paclitaxel overdosage. Probable consequences of an overdose are mucositis, severe bone marrow suppression and peripheral neurotoxicity and treatment should be supportive.

PRESENTATION

30mg in 5mL glass vials: 1's
100mg in 16.7mL glass vials: 1's
150mg in 25mL glass vials: 1's
300mg in 50mL glass vials: 1's

STORAGE

Store below 25 degrees C. Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF THE SPONSOR

Australian Sponsor:

Actavis Australia Pty Ltd
Upper Ground Floor
183 Melbourne Street
North Adelaide
South Australia, 5006
ABN 42122896468
Phone Number: 1300 881 893

New Zealand Sponsor:

CSL Biotherapies (NZ) Ltd
666 Great South Road, Penrose
Auckland 1544, New Zealand
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CLASSIFICATION OF MEDICINE

PRESCRIPTION ONLY MEDICINES - S4

DATE OF PREPARATION

24 May 2010