

New Zealand Data Sheet

Name of Medicine

Taxol (**Paclitaxel**) Concentrate for Injection 6mg/mL.

Presentation

Taxol (**paclitaxel**) Injection for Dilution is supplied as a nonaqueous clear, colourless to slightly yellow viscous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion.

Taxol is available in 300mg (50mL) vials.

Each mL of sterile nonpyrogenic solution contains 6mg **paclitaxel**, 527mg of Cremophor¹ EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol.

Uses

Actions

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers. It stabilises microtubules by preventing depolymerisation resulting in the inhibition of the normal dynamic reorganisation of the microtubule network essential for cellular functions. **Paclitaxel** also induces abnormal arrays of "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Pharmacokinetics

The pharmacokinetics of **paclitaxel** have been evaluated over a wide range doses, up to 300 mg/m², and infusion schedules, ranging from 3 to 24 hours. Following intravenous administration, **paclitaxel** exhibits a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination; the later 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/m² 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/m². Mean steady state volume of distribution following single dose infusion of 135 and 175 mg/m² has ranged from 198 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding. The volume of distribution is reduced in female subjects. Following 3 hour infusions of 175 mg/m², mean terminal half-life was estimated to be 9.9 hours; mean total body clearance was 12.4 L/h/m².

The pharmacokinetics of **paclitaxel** have been shown to be nonlinear. There is a disproportionately large increase in C_{max} and AUC with increasing dose, accompanied by an apparent dose related decrease in 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.

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

On average, 89% of drug is bound to serum proteins; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine does not affect protein binding of **paclitaxel**. Premedication with this combination of drugs reduces the total body clearance from 14.2 L/hr/m² to 8.6 L/hr/m².

The disposition of **paclitaxel** has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.8 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism has been demonstrated in animals. Hydroxylated metabolites isolated in bile have been demonstrated to be the principal metabolites. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of **paclitaxel**. The effect of renal or hepatic dysfunction on the disposition of **paclitaxel** has not been investigated.

Indications

Taxol is indicated for the primary treatment of ovarian cancer in combination with other chemotherapeutic agents.

Taxol is indicated for the treatment of metastatic carcinoma of the ovary after failure of standard therapy.

Taxol is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline containing therapy or where anthracycline therapy is contraindicated.

Taxol is indicated for the treatment of non-small cell lung cancer (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Taxol is indicated for the second-line treatment of AIDS-related Kaposi's Sarcoma (KS).

Taxol is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy.

Dosage and Administration

All patients must be premedicated prior to TAXOL administration to reduce the risk of severe hypersensitivity reactions. Such premedication may consist of dexamethosone 20mg orally* (or its equivalent), approximately 12 and 6 hours before TAXOL, promethazine 25mg or 50mg IV 30 to 60 minutes prior to TAXOL, and cimetidine (300mg) or ranitidine (50mg) IV 30 to 60 minutes before TAXOL.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. (See **Preparation for Intravenous Administration** and **Note** below).

*10mg for KS patients.

Primary treatment of Ovarian Cancer

The recommended dose of TAXOL for the primary treatment of ovarian cancer is:

- (a) 175mg/m² administered over 3 hours, followed by cisplatin 75mg/m², with a 3 week interval between courses.
- (b) 135mg/m² administered intravenously over 24 hours, followed by cisplatin 75mg/m², with a 3 week interval between courses.

Secondary treatment of Ovarian Cancer and Breast Cancer

The recommended dose of TAXOL is 175mg/m² administered intravenously over 3 hours every three weeks. TAXOL should not be readministered until the neutrophil count is at least 1,500 cells/mm³ and the platelet count is at least 100,000 cells/mm³. Patients who experience severe neutropenia (neutrophil < 500 cells/mm³) or severe peripheral neuropathy should receive a dosage reduced by 20% for subsequent courses.

AIDS-related Kaposi's Sarcoma

The recommended dose of TAXOL for secondary treatment of AIDS-related KS is 135mg/m² administered over a period of 3 hours, with a 3 week interval between courses, or, 100mg/m² administered over a period of 3 hours with a 2 week interval between courses. Both regimens result in comparable dosing intensity (45-50mg/m²/week).

Primary treatment of NSCLC

The recommended dose of TAXOL is 175mg/m² administered intravenously over 3 hours, followed by a platinum compound, with a 3 week interval between courses.

Adjuvant therapy of breast cancer

Taxol 175 mg/m² administered intravenously over 3 hours every 3 weeks for 4 courses sequentially to standard combination therapy.

Note:

Contact of the undiluted concentrate with plasticised PVC (polyvinyl chloride) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted TAXOL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and be administered through polyethylene-lined administration sets. See **Preparation for Intravenous Administration**. Use of filter devices such as IVEX-27 filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in a significant leaching of DEHP.

Preparation and Administration Precautions

Taxol is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling TAXOL. The use of gloves is recommended. Following topical exposure, tingling, burning, redness have been observed. If TAXOL solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If TAXOL 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. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Preparation for Intravenous Administration

Taxol Injection for Dilution must be diluted prior to infusion. TAXOL 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. These solutions are physically and chemically stable for up to 72 hours at ambient temperature (approximately 25°C) and room lighting conditions.

The shelf life of paclitaxel solutions reconstituted with 5% glucose, under controlled aseptic conditions for IV infusion, and stored in glass bottles, is 7 days at 2-8°C (refrigerate, do not freeze), or 25°C.

The shelf life of paclitaxel solutions reconstituted with 0.9% sodium chloride under controlled aseptic conditions for IV infusion, and stored in glass bottles, is 14 days at both 2-8°C (refrigerate: do not freeze) and room temperature (25°C).

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through i.v. tubing containing an in-line 0.22 micron filter.

When dilutions of TAXOL are prepared in PVC containers, extractable plasticiser DEHP [di-(2-

ethylhexyl)phthalate] levels increase with time and Taxol concentration. Consequently, the use of plasticised PVC containers and administration sets is not recommended. Taxol solutions 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.

Devices with spikes should not be used with vials of Taxol since they can cause the stopper to collapse, resulting in loss of sterile integrity of the Taxol solution.

Contraindications

Taxol is contraindicated in patients who have a history of severe hypersensitivity reactions to Taxol or other drugs formulated with polyoxyethylated castor oil (Cremophor EL).

Taxol should not be administered to patients with baseline neutropenia ($< 1,500$ cells/mm³) or patients with AIDS-related Kaposi's sarcoma with baseline or subsequent neutrophil counts of < 1000 cells/mm³.

Warnings and Precautions

Taxol (**paclitaxel**) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Taxol should be administered as a diluted infusion. Patients must be pretreated with corticosteroids, antihistamines and H₂ antagonists (such as dexamethasone, diphenhydramine, and cimetidine and ranitidine) before receiving Taxol.

Taxol should be given before a platinum compound when it is given in combination with a platinum compound.

Severe hypersensitivity (anaphylactoid) reactions characterised by dyspnea flushing, chest pain and tachycardia occur in approximately 2% of patients receiving Taxol. Angioedema, and generalised urticaria have occurred uncommonly in patients receiving Taxol. Rare fatal reactions have occurred in patients despite pretreatment. These reactions are probably histamine-mediated. In case of a severe hypersensitivity reaction, Taxol infusion should be discontinued immediately and the patient should not be rechallenged with the drug. Minor hypersensitivity reactions such as flushing, skin reactions, etc, do not require interruption of therapy (See also **Adverse Effects**)

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during Taxol treatment. Taxol should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³ ($< 1,000$ cells/mm³ in KS patients). In the case of severe neutropenia (< 500 cells/mm³) during a course of

Taxol, a 20% reduction in dose for subsequent courses of therapy is recommended. (See also **Adverse Effects**). Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian cancer.

Severe cardiac conduction abnormalities have been reported uncommonly during Taxol therapy. If patients develop significant conduction abnormalities during Taxol administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with Taxol. (See also **Adverse Effects**).

Pseudomembranous colitis has been reported in patients who have not received concurrent antibiotic treatment and should be considered in patients with severe or persistent cases of diarrhoea.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Taxol has not been studied. Taxol has been shown to be mutagenic in both in vitro and in vivo mammalian test systems. Decreased fertility and decreased numbers of implantations and live fetuses occurred in rats receiving Taxol. Taxol has also been shown to be embryotoxic and fetotoxic in rabbits receiving the drug during organogenesis (see **Warnings**, Use in Pregnancy and Use in Lactation).

Cardiovascular

Hypotension, hypertension and bradycardia have been observed during Taxol administration, but generally do not require treatment. In severe cases, Taxol 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 Taxol infusion is recommended. Continuous electrocardiographic monitoring is not required except for patients with serious conduction abnormalities. (See also **Adverse Effects**).

Nervous System

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual. A dose reduction of 20% for all subsequent courses of Taxol is recommended in such cases. (See also **Adverse Effects**). In NSCLC patients, the administration of Taxol in combination with cisplatin, resulted in a greater incidence of neurotoxicity than usually seen in patients receiving single agent Taxol.

Taxol contains dehydrated alcohol 396mg/mL; consideration should be given to possible CNS and other effects of alcohol. Children may be more sensitive than adults to the effects of ethanol.

Hepatic

There is evidence that the toxicity of Taxol is enhanced in patients with abnormal liver function. Caution should be exercised when administering Taxol to patients with moderate to

severe hepatic impairment and dose adjustments should be considered. Patients should be monitored closely for the development of profound myelosuppression. No data is available for patients with severe baseline cholestasis.

When Taxol 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 mild hepatic impairment. Therefore, Liver Function Tests should be given to the patient prior to commencement of therapy.

Use in Pregnancy

Pregnancy Category "D": Taxol may cause foetal harm when administered to a pregnant woman. Taxol has been shown to be embryotoxic and foetotoxic in rabbits and to decrease fertility in rats. There are no studies in pregnant women. If Taxol is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Taxol.

Use in Lactation

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

Paediatric Use

The safety and effectiveness of Taxol in paediatric patients has not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in paediatric patients in which Taxol was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the Taxol vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the **paclitaxel** itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of Taxol for use in this population.

Effect on Ability to Drive and Use Machines

Since Taxol contains ethanol, consideration should be given to the possibility of CNS and other effects. Consideration should also be given to possible CNS effects of premedications given to reduce the risk of severe hypersensitivity reactions.

Adverse Effects

The frequency and severity of adverse effects are generally similar between patients receiving Taxol for the treatment of ovarian, breast or lung cancer. Taxol when given at the recommended dose and schedule, is well tolerated.

Safety of the TAXOL/platinum combination has been evaluated in a large randomised trial in ovarian cancer and in two phase III trials in NSCLC. Unless otherwise mentioned, the combination of TAXOL with platinum agents did not result in any clinically relevant changes to the safety profile of single agent TAXOL.

The frequency and severity of adverse events are generally similar between patients with solid tumors and AIDS-related KS patients. AIDS-related KS patients may present with more frequent and more severe haematologic toxicities, infections (including opportunistic infections*), and febrile neutropenia than patients with solid tumors. These patients require a lower dose intensity and supportive care.

*Opportunistic infections include cytomegalovirus, herpes simplex, *pneumocystis carinii*, *M. avium intracellulare*, esophageal candidiasis, cryptosporidiosis, cryptococcal meningitis, and leukoencephalopathy.

Haematologic

Bone marrow suppression is the major dose limiting toxicity of TAXOL. Neutropenia, the most important haematologic toxicity, was dose and schedule dependent and generally rapidly reversible with only 7% of patients having severe neutropenia (< 500 cells/mm³) for 7 days or more. Overall, 52% of the patients experienced severe neutropenia. Neutrophil nadirs occurred at a median of 11 days after TAXOL administration. Severe neutropenia was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Infectious episodes occurred very commonly and were fatal in 1% of all patients. Febrile neutropenia occurred in 5% of all courses and 30% of all courses were associated with an infectious episode, including peritonitis, urinary tract infections, pneumonia, upper respiratory tract infections, sepsis and septic shock. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. Five septic episodes, which were associated with severe neutropenia attributable to TAXOL administration had a fatal outcome. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, sixty-one percent of KS patients reported at least one opportunistic infection. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

Thrombocytopenia is less frequent and less pronounced than neutropenia. Overall, 7% of patients had a platelet nadir count below 50,000 cells/mm³, and 20% of patients experienced a drop in their platelet count below 100 000 cells/mm³. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the haemorrhagic episodes were localized and the frequency of these events was unrelated to the TAXOL dose and schedule. Leukopenia, fever, acute myeloid leukaemia and myelodysplastic syndrome have also been reported.

Median day of nadir for platelets occurred in days 8 and 9. Two percent of patients received platelet transfusions.

Anaemia (Hb < 11 g/dL) was observed in 78% of overall patients and severe anaemia (Hb < 8 g/dL) in 16% of patients overall. The incidence and severity of anaemia increased with increasing exposure to TAXOL and in those who at baseline were anaemic.

Hypersensitivity

Despite premedication, severe hypersensitivity reactions occurred in 2% of overall patients generally within the first hour of TAXOL infusion. Dyspnea, flushing, chest pains and tachycardia were the most frequent manifestations. Abdominal pain, pain in the extremities, diaphoresis, hypertension, hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pains, anaphylactic reactions (with fatal outcome) and anaphylactic shock were also noted. TAXOL dosage or schedule had no effect on the frequency of hypersensitivity reactions. Overall, 21% of all courses were associated with hypersensitivity reactions with first manifestations mostly in the first two courses. The most frequent minor manifestations were flushing, rash and hypotension which were observed in 28%, 14%, and 3% of patients respectively.

Cardiovascular

During TAXOL infusion, hypotension or bradycardia have been observed in 12% and 3% of patients, respectively during the first 3 hours of infusion. Bradycardia and hypotension did not usually occur during the same course and the majority of episodes were asymptomatic and did not require treatment.

Six severe cardiovascular events possibly related to TAXOL administration occurred including asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular block (2 patients), and syncopal episodes (2 patients - in one associated with severe hypotension and coronary stenosis resulting in death).

Twenty-three percent of patients overall had an abnormal ECG during clinical trials. Fourteen percent of the patients with normal ECG prior to study entry developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarisation abnormalities (20%), sinus tachycardia (19%), sinus bradycardia, and premature beats (7%). The only cases of ECG alterations requiring therapeutic intervention consisted of two patients with atrioventricular block. In most cases, no clear relationship between TAXOL administration and ECG alterations could be defined and these alterations were of no or minimal clinical relevance.

Myocardial infarction, has been reported. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Cardiomyopathy, hypertension, thrombosis, and thrombophlebitis have been reported uncommonly. Atrial fibrillation, supraventricular tachycardia and shock have been reported very rarely.

Respiratory

Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received as part of continuing safety surveillance. Respiratory distress has been reported uncommonly. Pleural effusion, dyspnoea, interstitial pneumonia, lung fibrosis, pulmonary embolism, and respiratory failure have been reported rarely. Cough has been reported very rarely.

Neurologic

Peripheral neuropathy occurs and is dose dependent with 60% of patients affected at the recommended dose versus 87% at higher doses. Severity of symptoms also increased with dose; 4% of patients experienced severe symptoms at the recommended dose. Neurologic symptoms may occur following the first course and symptoms may worsen with increasing exposure to Taxol. Peripheral neuropathy was the cause of Taxol discontinuation in 2% of patients. The frequency of peripheral neuropathy increased with cumulative dose. Parasthesia commonly occurs in the form of hyperesthesia. Sensory symptoms have usually improved or resolved within several months of Taxol discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for treatment with Taxol.

Other rare neurologic events reported after Taxol administration 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 appeared. Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, and ataxia have also been reported very rarely. Optic nerve, and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than recommended. These effects generally have been reversible. Photopsia and visual disturbances have also been reported very rarely.

Hepatic

In patients with normal baseline liver function, 7% experienced elevated bilirubin, 22% had elevated alkaline phosphatase, 19% had elevated AST (SGOT) and 33% had elevated ALT (SGPT). A dose relationship was suggested for all tests except for ALT.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported rarely from ongoing safety surveillance.

Arthralgia/Myalgia

Arthralgia/myalgia usually consisting of pain in the large joints of the arms and legs occurred in 60% of patients; severe symptoms were seen in 8% of patients. The symptoms were usually transient occurring two to three days after Taxol administration and resolving within a few days.

Injection Site Reactions

Phlebitis may occur following the intravenous administration of Taxol.

Extravasation during intravenous administration may lead to edema, pain, erythema, tenderness and induration; on occasion, extravasation can result in cellulitis. Skin discolouration, skin exfoliation, necrosis and fibrosis have been reported as part of the ongoing safety surveillance of Taxol. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of Taxol at a different site, ie, recall has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

Gastrointestinal Toxicity

Gastrointestinal side effects such as nausea/vomiting, diarrhoea and mucositis occurred in 52%, 38% and 31% of patients who received the recommended dose, respectively. These manifestations were usually mild to moderate at the recommended dose. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion. Neutropenic enterocolitis (typhlitis), bowel obstructions/perforations and ischemic colitis have been reported in patients treated with **paclitaxel**. Rare reports of pancreatitis have been received. Very rare reports of mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, and ascites have been reported.

Skin and Subcutaneous Tissue Disorders

Alopecia was observed in almost all patients. Transient and mild nail and skin changes have been observed. Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritis, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis, and fibrosis have been received. Very rare reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) have been received. Scleroderma, asthenia, and malaise have been reported as a component of ongoing safety surveillance.

Other

Rare reports of pyrexia, and dehydration and very rare reports of anorexia, confusional state, hearing loss, tinnitus, vertigo, and ototoxicity have been reported.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

While one third of KS patients complained of diarrhoea prior to study start, 79% of Taxol-treated KS patients reported diarrhoea, 69% reported nausea/vomiting, and 28% reported mucositis.

Edema was reported in 21% of all patients (17% of these without baseline edema); only 1% had severe edema and none of those required treatment discontinuation. Edema was most commonly focal and disease related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Renal

Five of the 85 KS patient had grade III or IV renal toxicity, including one patient with suspected HIV nephropathy who discontinued therapy and four patients with reversible elevations of serum creatinine.

Interactions

Medications concomitantly administered with Taxol (eg: corticosteroids, antihistamines, and H₂ antagonists) did not appear to interact adversely; however, possible interactions of Taxol with concomitantly administered medications have not been formally investigated.

Combination treatment with cisplatin

In a dose-finding trial using Taxol and cisplatin given as sequential infusions, myelosuppression was more profound when Taxol was given after cisplatin than when Taxol was given before cisplatin. Pharmacokinetic data demonstrated a reduction in **paclitaxel** clearance of approximately 33% when Taxol was administered following cisplatin. When administered as a 3 hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with Taxol followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with Taxol as a 3-hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

Combination treatment with trastuzumab

When Taxol was administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to Taxol or trastuzumab) were reported more frequently than with single agent Taxol: heart failure, infection, chills, fever, cough, rash, arthralgia, tachycardia, diarrhea, hypertonia, epistaxis, acne, herpes simplex, accidental injury, insomnia, rhinitis, sinusitis and injection site reaction. Some of these frequency differences may be due to the increased number and duration of treatments with Taxol /trastuzumab combination vs single agent Taxol. Severe events were reported at similar rates for Taxol /trastuzumab and single agent Taxol.

Administration of trastuzumab in combination with Taxol in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with Taxol single agent and rarely has been associated with death. In all but these rare cases, patients responded to appropriate medical treatment.

Preliminary animal/*ex vivo* data indicate that ketoconazole may inhibit the metabolism of **paclitaxel**. Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use of Taxol and doxorubicin when Taxol was administered before doxorubicin and using longer than recommended infusion times (Taxol 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 3-hour Taxol infusion found no sequence effects on the pattern of toxicity. The mechanism for this interaction is unknown. The pharmacodynamic consequences of this interaction are unclear.

The metabolism of **paclitaxel** is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering Taxol concomitantly with known substrates or inhibitors of these isoenzymes.

Potential interactions between **paclitaxel** and protease inhibitors have not been studied.

Overdosage

There is no known antidote for TAXOL overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in paediatric patients may be associated with acute ethanol toxicity (see Warnings and Precautions, Paediatric Use).

Pharmaceutical Precautions

Store the vials in original cartons at controlled room temperature (below 25°C).

Unopened vials of TAXOL (**paclitaxel**) Injection for Dilution are stable until the date indicated on the package when stored in the original package at controlled room temperature (below 25°C). (Freezing does not adversely affect the product).

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

Care must be taken whenever handling cytostatic products. Always take steps to prevent exposure. This includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

Medicine Classification

Prescription Medicine.

Package Quantities

300mg/50mL single-dose vials, 1s.

Further Information

TAXOL contains **paclitaxel**, a natural product with antitumour activity. **Paclitaxel** is a white to off-white crystalline powder that is highly lipophilic and insoluble in water.

Paclitaxel has a Molecular Formula: $C_{47}H_{51}NO_{14}$ and a Molecular Weight: 853.9.

Name and Address

Bristol-Myers Squibb (NZ) Company
Auckland
NEW ZEALAND

Date of Preparation

16 December 2011

¹ Cremophor EL is a registered trademark of BASF Aktiengesellschaft