TAXOL® Injection
(Paclitaxel)

NAME OF THE MEDICINE

TAXOL contains paclitaxel, a natural product with antitumour activity. TAXOL is the first of a new class of anticancer agents known as taxanes.

The CAS number for paclitaxel is 33069-62-4 (USAN).

Paclitaxel has the following structural formula:

![Structural formula of paclitaxel]

Molecular Formula: C_{47}H_{51}NO_{14}

Molecular Weight: 853.929

DESCRIPTION

Paclitaxel is a white to off-white crystalline powder that is highly lipophilic and insoluble in water.

PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of paclitaxel have been evaluated over a wide range of 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. Maximum plasma concentrations are related to dose. 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.

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.

Some studies indicate that the pharmacokinetics of paclitaxel may be non-linear. There is evidence of a disproportionately large increase in Cmax and AUC with increasing dose, and total body clearance appears to decrease with higher plasma concentrations of paclitaxel. These findings were most readily observed in patients in whom high plasma concentrations of paclitaxel were achieved. Saturable processes in elimination/metabolism may account for these findings.

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. Preliminary animal/ex vivo data indicate that ketoconazole may inhibit the metabolism of paclitaxel. Likewise, preliminary reports suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination. The mechanism for this interaction is unknown. The pharmacodynamic consequences of this interaction are unclear. (see PRECAUTIONS, Drug Interactions).

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.

PHARMACODYNAMICS

Paclitaxel is a novel 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 or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. This can result in arrest of cell division and impaired function of nervous tissue.

CLINICAL TRIALS

Ovarian Carcinoma:

The safety and efficacy of TAXOL in the first-line treatment of ovarian cancer was investigated in two major, randomised, controlled trials. The first was a prospective, randomised trial in first line ovarian cancer, Protocol (CA 139-022 or GOG-111) compared the use of TAXOL (135mg/m² over 24 hours)/cisplatin (75mg/m²) to cyclophosphamide/cisplatin (standard therapy) in 410 patients with suboptimal stage III and
stage IV epithelial ovarian carcinoma. Known prognostic factors were similar in the two treatment groups. Among 219 women with measurable disease, 67% in the TAXOL/cisplatin group responded to therapy, as compared with 55% in the cyclophosphamide/cisplatin group (p= 0.074). The frequency of surgically verified complete response was similar in the two groups. Progression-free survival was significantly longer (P=0.0008) in the TAXOL/cisplatin group than the cyclophosphamide/cisplatin group (median 16.6 vs 13 months). Survival was also significantly longer (P=0.0002) in the TAXOL/cisplatin group (median 35.5 vs 24.2 months).

The second was a multicentre randomised, controlled trial in which 342 patients received TAXOL (175mg/m² over 3 hours) in combination with cisplatin (75mg/m²) every 3 weeks and 338 received cyclophosphamide plus cisplatin, demonstrated significantly increased time to progression (15.3 vs 11.5 months) and significantly increased overall survival (35.6 vs 25.9 months) in favour of the TAXOL/cisplatin combination.

Although both dosage regimens have not been studied in a direct comparison, they have both been compared to cyclophosphamide/cisplatin regimen and demonstrate comparable efficacy results.

Although the 175mg/m²/3hr regimen may be associated with greater neurotoxicity compared to the 135mg/m²/24hr regimen, this is offset by reduced haematological toxicity.

Non-Small Cell Lung Carcinoma:

Four open label phase 2 studies were conducted in 224 patients with advanced NSCLC and no prior chemotherapy; 131 received TAXOL and 93 received investigational agents in a randomised Phase 2 trial. In the earliest two trials (CA139-027 and CA139-029), TAXOL was administered as a 24-hour infusion at initial doses of 200mg/m² and 250mg/m² respectively. The response rates in both trials were 19% and 17%, respectively, with one-year survival of 33% and 40% respectively. The median survival was 8.1 months (95% CI 4.8-13.0 months) and 4.4 months (95% CI 3.0-16.2 months). In the later two trials (CA139-127 and CA139-201), TAXOL was administered as a 3-hour infusion at initial doses of 200mg/m² and 225mg/m², respectively. The response rates were 20% and 19%, with one-year survival of 43% and 35%, respectively. The median survival was 11.7 months (95% CI 7.3-16.8 months) and 9.0 months (95%CI 5.9-11.4 months), respectively. The response rates were similar to those for other single agent therapies.

Two prospective multicentre trials were conducted in patients with advanced NSCLC and no prior chemotherapy. Five hundred and sixty-five patients were randomised to receive TAXOL followed by cisplatin in these studies. The majority of patients had stage IV NSCLC and approximately two thirds had an impaired performance status (ECOG PS 1 or 2). In a study conducted by the European Organization for Research and Treatment of Cancer (EORTC), patients were randomised to either TAXOL (T) 175mg/m² as a 3 hour infusion followed by cisplatin (c) 80mg/m² or cisplatin (c) 80mg/m² on day 1 followed by teniposide (VM) 100mg/m³ on day 1, 3 and 5 (control). In a study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomised to either TAXOL (T) 135 mg/m² as a 24-hour infusion followed by cisplatin (c) 75mg/m² , TAXOL (T) 250mg/m² as a 24 hour infusion followed by cisplatin (c) 75mg/m² with G-CSF support , or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100mg/m² on days 1, 2 and 3 (control). Response rates, median time to progression, median survival and one-year survival rates for the two studies and respective treatment arms are given in the following table (Table 1). The TAXOL combinations showed improvement in response rates (>20%) and median time to progression.
(>4 months), but no significant increase in survival.

<table>
<thead>
<tr>
<th>Table 1: Key Efficacy Parameters in the Phase 3 NSCLC Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC Study</td>
</tr>
<tr>
<td>T175/3</td>
</tr>
<tr>
<td>c80</td>
</tr>
<tr>
<td>(n=166)</td>
</tr>
</tbody>
</table>

\begin{itemize}
  \item Response Rate (evaluable Pts.)
    \begin{itemize}
      \item Rate(percent)
      \item 95% Confidence Interval
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item Time to Progression
    \begin{itemize}
      \item Median (months)
      \item 95% Confidence Interval
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item Survival
    \begin{itemize}
      \item Median (months)
      \item 95% Confidence Interval
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item One-Year Survival
    \begin{itemize}
      \item Percent of patients
      \item 95% Confidence Interval
    \end{itemize}
  \end{itemize}

\begin{tabular}{|c|c|c|c|c|}
\hline
  & EORTC Study & ECOG Study & EORTC Study & ECOG Study \\
\hline
  & T175/3 | VM100\textsuperscript{a} | T135/24 | T250/24 | VP100\textsuperscript{b} \\
\hline
  & c80 | c80 | c75 | c75 | c75 \\
\hline
  & (n=166) | (n=166) | (n=198) | (n=201) | (n=200) \\
\hline
  Response Rate (evaluable Pts.) & 36 & 25 & 26 & 30 & 14 \\
    Rate(percent) & (29-44) & (19-33) & (20-34) & (23-38) & (9-20) \\
  95% Confidence Interval & & & & & \\
\hline
  Time to Progression (median (months)) & 5.1 & 5.0 & 4.3 & 4.9 & 2.7 \\
    95% Confidence Interval & (4.3-5.9) & (3.7-5.8) & (3.3-5.1) & (4.0-5.8) & (2.2-3.2) \\
\hline
  Survival (median (months)) & 9.5 & 9.9 & 9.3 & 10.0 & 7.4 \\
    95% Confidence Interval & (8.2-11.7) & (8.2-12.0) & (8.0-10.4) & (8.9-11.7) & (6.5-8.6) \\
\hline
  One-Year Survival & 41 & 41 & 36 & 40 & 32 \\
    Percent of patients & (33-49) & (33-49) & (30-43) & (34-47) & (26-39) \\
  95% Confidence Interval & & & & & \\
\hline
\end{tabular}

\textsuperscript{a}Teniposide (VM) 100mg/m\textsuperscript{2} was administered IV on days 1, 3 and 5

\textsuperscript{b} Etoposide (VP) 100mg/m\textsuperscript{2} was administered IV on days 1, 2 and 3

**Breast Carcinoma:**

A randomised Phase 3 intergroup multicenter, 3 x 2 factorial study of the adjuvant use of TAXOL was conducted in 3170 women with histologically positive lymph nodes following either a mastectomy or segmental mastectomy and nodal dissections. The 3 x 2 factorial study was designed to assess the efficacy and safety of three different dose levels of doxorubicin and to evaluate the effect of the addition of TAXOL administered following the completion of doxorubicin and cyclophosphamide (AC) therapy. Patients were randomised, after stratification for the number of positive lymph nodes, to receive cyclophosphamide at a dose of 600 mg/m\textsuperscript{2} and doxorubicin at doses of either 60 mg/m\textsuperscript{2} (on day 1), 75 mg/m\textsuperscript{2} (in two divided doses on days 1 and 2), or 90 mg/m\textsuperscript{2} (in two divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for four courses and either TAXOL 175 mg/m\textsuperscript{2} as a 3-hour infusion every 3 weeks for four additional courses or no additional chemotherapy. Patients whose tumours were positive or of unknown hormone receptor status were to receive subsequent tamoxifen treatment (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.

The primary analyses of disease-free survival and overall survival used multivariate Cox models which included TAXOL administration, doxorubicin dose, number of positive lymph nodes, tumour size, menopausal status, and oestrogen receptor status as factors. Based on the model for disease-free survival, patients receiving AC followed by TAXOL had a 22% reduction in the risk of disease recurrence compared to patients randomised to AC alone (Hazard Ratio=0.78 with 95% CI: 0.67-0.91, p=0.0022). They also had a 26% reduction in
the risk of death (Hazard Ratio=0.74 with 95% CI: 0.60-0.92, p=0.0065). The absolute increases in disease-free survival and overall survival were 4% and 2% respectively. Doxorubicin dose had no effect on either disease-free survival or overall survival. The overall median follow-up was 30.1 months.

Subset analysis revealed that adjunctive treatment with paclitaxel is most beneficial in patients with hormone receptor-negative disease (see Table 2).

### TABLE 2
**SUBSET ANALYSES - ADJUVANT BREAST CARCINOMA STUDY**

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Disease-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of Patients</td>
<td>No of Recurrences</td>
</tr>
<tr>
<td><strong>No of Positive Nodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>1449</td>
<td>221</td>
</tr>
<tr>
<td>4-9</td>
<td>1310</td>
<td>274</td>
</tr>
<tr>
<td>10+</td>
<td>360</td>
<td>129</td>
</tr>
<tr>
<td><strong>Tumour Size (cm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>1096</td>
<td>153</td>
</tr>
<tr>
<td>&gt;2 and ≤5</td>
<td>1611</td>
<td>358</td>
</tr>
<tr>
<td>&gt;5</td>
<td>397</td>
<td>111</td>
</tr>
<tr>
<td><strong>Menopausal Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1929</td>
<td>374</td>
</tr>
<tr>
<td>Post</td>
<td>1183</td>
<td>250</td>
</tr>
<tr>
<td><strong>Receptor Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2066</td>
<td>293</td>
</tr>
<tr>
<td>Negative/Unknown&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1055</td>
<td>331</td>
</tr>
</tbody>
</table>

<sup>a</sup> Positive for either oestrogen or progesterone receptors

<sup>b</sup> Negative or missing for both oestrogen and progesterone receptors (both missing:n=15)

The safety and efficacy of TAXOL were studied in a randomised controlled multinational study of chemotherapy alone and in combination with Herceptin (trastuzumab). Patients with previously untreated metastatic breast cancer were treated with an anthracycline (doxorubicin 60mg/m² or epirubicin 75mg/ m²) plus cyclophosphamide (600mg/ m²) with (H+AC) or without (AC alone) Herceptin or paclitaxel(175mg/ m² infused over three hours every three
weeks) with (H+P) or without (P alone) Herceptin. Patients were treated with paclitaxel for six cycles, and could be treated with Herceptin until progression of disease. Patients who had previously received anthracycline based adjuvant therapy were treated with paclitaxel whereas those who were anthracycline naive were treated with an anthracycline plus cyclophosphamide. Patients in the Herceptin treatment groups received a 4mg/kg intravenous loading dose of Herceptin on day 0. From day 7, patients received weekly infusions of Herceptin 2mg/kg, which they could continue to receive until evidence of disease progression. Patients in both treatment groups were eligible to receive Herceptin in an open label study following disease progression.

The prospectively defined primary intent to treat analysis indicated that the combination of chemotherapy and Herceptin significantly prolonged the time to disease progression (progression free survival) compared with chemotherapy alone as first line treatment of women with metastatic breast cancer who had tumours that over-expressed HER2. The addition of Herceptin to chemotherapy extended the median time to disease progression by 2.8months representing a 61% increase (p=0.0001).

Both AC treated and paclitaxel treated patients benefited from Herceptin treatment, although the effect appeared to be greater in the paclitaxel stratum.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Efficacy outcomes in combined therapy trial H0648g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Herceptin + Chemo Chemo alone Herceptin + AC AC alone Herceptin + Paclitaxel Paclitaxel alone</td>
</tr>
<tr>
<td></td>
<td>n=235 n=234 n=143 n=138 n=92 n=96</td>
</tr>
<tr>
<td>Median time to disease progression (months, 95% CI)</td>
<td>7.4 (7.0, 9.0) 4.6 (4.4, 5.4) 7.8 (7.3, 9.4) 6.1 (4.9, 7.1) 6.9 (5.3, 9.9) 3.0 (2.1, 4.3)</td>
</tr>
<tr>
<td>p</td>
<td>0.0001 0.0004 0.0001</td>
</tr>
<tr>
<td>Response Rate n (%)</td>
<td>118 (50%) 74 (32%) 80 (56%) 58 (42%) 38 (41%) 16 (17%)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001 0.0197 0.0002</td>
</tr>
<tr>
<td>Median duration of response (months, 95% CI)</td>
<td>9.1 (7.7, 11.0) 6.1 (5.5, 7.8) 9.1 (7.4, 12.2) 6.7 (5.8, 8.2) 10.5 (7.3, 12.5) 4.5 (3.9, 6.4)</td>
</tr>
<tr>
<td>p</td>
<td>0.0002 0.0047 0.0124</td>
</tr>
<tr>
<td>One year Survival</td>
<td>79% 68% 83% 73% 73% 60%</td>
</tr>
<tr>
<td>p</td>
<td>0.0080 0.0415 0.0124</td>
</tr>
</tbody>
</table>

AC= anthracycline + cyclophosphamide; Chemo= chemotherapy

One year survival rates (the prospectively defined survival endpoint) were significantly better for chemotherapy + Herceptin versus chemotherapy arms (79 versus 68%; p=0.008). With a median follow-up of approximately two years, overall survival is improved for patients initially treated with chemotherapy and Herceptin compared with those receiving chemotherapy alone (25.4 versus 20.3 months; p=0.025) with a relative risk of death of 0.769 (95% CI 0.607 to 0.973; p=0.028).
The relative overall survival advantage with the addition of Herceptin was observed in both subgroups: AC (26.8 months (H=AC) versus 22.8 months (AC alone); p=0.052) and paclitaxel (22.1 months (H+P) versus 18.4 months (P alone); p=0.273). The analysis of overall survival was, however, greatly confounded by subsequent Herceptin treatment of each of the control arms’ patients, following disease progression, in the open label extension study, H0659g (59% of patients in the AC alone group, and 75% of patients in the paclitaxel alone group subsequently received Herceptin). Hence, the survival advantage seen above, for chemotherapy + Herceptin treatment versus chemotherapy alone (which includes patients who subsequently received Herceptin) may underestimate the benefit to patients.

Importantly, the efficacy described above was obtained without a significant negative impact on the quality of life. Global quality of life decreased equally in both the chemotherapy alone group and the chemotherapy + Herceptin group and was most likely related to the effects of cytotoxic chemotherapy. However, at weeks 20 and 32, the global quality of life score had returned to baseline or better than baseline in the group receiving chemotherapy plus Herceptin, while it remained low in the chemotherapy only arm.

The safety and efficacy of TAXOL were studied in a randomised controlled multinational study of chemotherapy alone and in combination with Gemzar® (gemcitabine).

A total of 529 patients with unresectable, recurrent or metastatic breast cancer were randomised to receive gemcitabine plus paclitaxel (GT) combination therapy (n=267) or paclitaxel (T) monotherapy (n=262). In the GT arm gemcitabine (1250mg/m²) was administered intravenously over 30 to 60 minutes on Days 1 and 8 of 21-day cycle and paclitaxel (175mg/m²) was administered intravenously over 3 hours before gemcitabine on Day 1 of a 21-day cycle. In the T arm paclitaxel (175mg/m²) was administered intravenously over 3 hours on Day 1 of a 21-Day cycle. Patients were included in the trial if they had relapsed after receiving either one anthracycline-based chemotherapy in the adjuvant/neoadjuvant setting or a non-anthracycline-based regimen in the adjuvant/neoadjuvant setting if use of an anthracycline was clinically contraindicated.

The primary endpoint of the planned interim analysis was time to documented progression of disease (TtDPD). Patients who died without evidence of disease progression were excluded from this analysis. Estimates of median TtDPD were 5.4 months (95% CI, 4.6 to 6.1 months) on the GT therapy arm and 3.5 months (95% CI, 2.9 to 4.0 months) on the T arm using the earlier of the dates of disease progression, derived from either the investigator’s or the independent reviewers’ assessment. The difference between the two treatment arms was statistically significant (p=0.0013). GT also significantly improved progression-free survival by a similar amount. This endpoint accounts for not only patients with documented disease progression but also patients who die without evidence of progression.

The overall response rates, according to the investigator assessment were 39.3% (95% CI, 33.5% to 45.2%) on the GT arm and 25.6% (95% CI, 20.3% to 30.9%) on the T arm, which was statistically significant (p=0.0007).

There were no significant treatment differences in the patient-assessed quality-of-life measures, Brief Pain Inventory and Rotterdam Symptom Checklist.

**INDICATIONS**

Advanced metastatic carcinoma; node-positive breast cancer combination therapy; advanced or metastatic breast cancer after relapse within 6 months of adjuvant therapy. Prior therapy
should have included an anthracycline unless clinically contraindicated.; Non Small Cell Lung Cancer; Second-line treatment of AIDS-related Kaposi’s sarcoma; First-line therapy in combination with a cisplatin for the treatment of advanced metastatic carcinoma of the ovary; in combination with Gemcitabine for patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy and unresectable; In combination with Herceptin for first-line treatment of HER2-overexpressing metastatic breast cancer

**CONTRAINdications**

TAXOL is contraindicated in patients who have a history of severe hypersensitivity reactions to TAXOL or other drugs formulated with polyoxyl 35 castor oil (purified).

TAXOL should not be administered to patients with solid tumours who have baseline neutrophil counts of \(<1.5 \times 10^9\) cells/L.

**PRECAUTIONS**

**General**

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, promethazine and cimetidine or ranitidine) before receiving TAXOL (see also DOSAGE AND ADMINISTRATION). Paclitaxel is administered by intravenous infusion only; it should not be administered by intracerebral, intrapleural or intraperitoneal.

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

**Gastrointestinal (GI) Toxicity**

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

**Anaphylaxis and Severe Hypersensitivity Reactions**

Severe hypersensitivity (anaphylactoid) reactions characterized by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred uncommonly in premedicated patients receiving TAXOL. Rare fatal reactions have occurred in patients despite pretreatment.

Patients receiving TAXOL should be under continuous observation for at least the first 30 minutes following the start of the infusion and frequently thereafter. In case of a severe hypersensitivity reaction, TAXOL infusion should be discontinued immediately and appropriate treatment given as indicated for anaphylaxis. 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 REACTIONS).
Haematologic Toxicity

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 until the baseline neutrophil count is at least 1.5 x 10^9 cells/L and the platelet count is at least 100 x 10^9 cells/L. In the case of severe neutropenia (< 0.5 x 10^9 cells/L) during a course of TAXOL, a 20% reduction in dose for subsequent courses of therapy is recommended. (See also ADVERSE REACTIONS).

Cardiovascular Toxicity

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. (See also ADVERSE REACTIONS).

Electrocardiographic monitoring is recommended for patients with serious conduction abnormalities, and should be commenced for patients who develop abnormal cardiovascular symptoms or signs during monitoring of vital signs.

Severe cardiac conduction abnormalities have been reported rarely during TAXOL therapy. If patients develop significant conduction abnormalities during TAXOL administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be commenced and performed during subsequent therapy with TAXOL. (See also ADVERSE REACTIONS). Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian cancer.

When TAXOL is used in combination with trastuzumab or doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Nervous System

The occurrence of peripheral neuropathy is frequent and the severity dose-dependent. Patients with pre-existing neuropathy should be carefully monitored. In severe cases, all subsequent doses of TAXOL should be reduced by 20%. (See also ADVERSE REACTIONS).

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.

Injection Site Reaction

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.
Hepatic Impairment

There is evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes. 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.

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 mildly elevated liver function tests given 24-hour infusions.

Carcinogenicity and Mutagenicity

The carcinogenic potential of TAXOL has not been studied. TAXOL has been shown to be mutagenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). It did not induce mutagenicity in the Ames test or mammalian cells.

Effects on Fertility

At a dose of 1mg/kg (6mg/m²) TAXOL produced low fertility and foetal toxicity in rats. TAXOL has also been shown to be embryotoxic and foetotoxic in rabbits receiving the drug at an IV dose of 3mg/kg (33mg/m²) during organogenesis.

Use in Pregnancy - Pregnancy Category D

TAXOL may cause foetal harm when administered to a pregnant woman. TAXOL has also been shown to be embryotoxic and foetotoxic in rabbits receiving the drug at an IV dose of 3mg/kg (33mg/m²) during organogenesis. At a dose of 1mg/kg (6mg/m²) TAXOL produced low fertility and foetotoxicity in rats. No gross external, soft tissue or skeletal alterations occurred. There are no studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOL. 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.

Use in Lactation

It is not known whether TAXOL is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving 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.
Use in the Elderly

Of 2228 patients who received TAXOL in eight clinical studies evaluating its safety and efficacy in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive TAXOL in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older, including 49 patients (1%) 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with TAXOL had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favoured the younger group.

Interactions with Other Medicines

Effect of other drugs on TAXOL

**Cisplatin**: In a dose-finding trial in which TAXOL was administered as a 24-hour infusion and cisplatin was administered as a 1mg/min infusion, 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.

**Substrates, Inducers, Inhibitors of Cytochrome P450 2C8 and 3A4**: The metabolism of TAXOL is catalysed 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, inducers or inhibitors of these isoenzymes.

Preliminary animal/ex vivo data indicate that ketoconazole may inhibit the metabolism of paclitaxel; caution should be exercised when treating patients with TAXOL if they are receiving ketoconazole.

Medications concomitantly administered with TAXOL (eg: corticosteroids, antihistamines, and H2 antagonists) did not appear to interact adversely.

Effect of TAXOL on other drugs

**Doxorubicin**: 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.
Trastuzumab: 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).

ADVERSE EFFECTS

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 TAXOL 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 regime. If other regimes are used, the incidence of reaction may be higher.

Safety of the TAXOL/platinum combination has been investigated in a large randomised trial in ovarian cancer and in two Phase III trials in NSCLC. (see PRECAUTION, Nervous System). 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.

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.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥1/100 and &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1000 and &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10000 and &lt;1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10000</td>
</tr>
</tbody>
</table>

Infections and Infestations

Very Common: Infection

Uncommon: Septic shock

Cardiac Disorders

Common: Bradycardia; ECG abnormalities (non-specific repolarisation and sinus tachycardia)

Uncommon: ECG abnormalities (premature beats), cardiomyopathy

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

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).
Haematological Disorders

Very common: Myelosuppression, thrombocytopenia, leucopenia, fever, bleeding, 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 11 days after TAXOL administration).

Infectious episodes occurred very commonly and were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

Common: Febrile neutropenia (associated with an infectious episode, including UTI and URTI). Neutropenia, the most important haematologic toxicity, was dose and schedule dependent and was generally rapidly reversible.

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

Immune System Disorders

Very common: Minor hypersensitivity reactions (mainly flushing and rash)

Common: Hypersensitivity reactions (dyspnoea; hypotension; chest pains; tachycardia)

Uncommon: Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, oedema, back pain, chills). The most frequent symptoms observed during severe reactions were dyspnoea, flushing, chest pain and tachycardia. Abdominal pain, pain in the extremities, hyperhydrosis, and hypertension were also noted.

Rare: Anaphylactic reactions (with fatal outcome)

Very rare: Anaphylactic shock

Vascular Disorders

Very common: Hypotension

Uncommon: Hypertension, thrombosis, thrombophlebitis

Gastrointestinal Disorders

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 TAXOL. Patients receiving TAXOL who complain of abdominal pain with other signs and symptoms, should have bowel perforation excluded).

Neutropenic enterocolitis has been reported.

**Musculoskeletal, Connective Tissue and Bone Disorders**

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

**Neurological Disorders**

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. 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. Sensory symptoms have usually improved or resolved within several months of TAXOL 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.

**Hepatobiliary Disorders**

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

Common: Elevated bilirubin

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

**Skin and Subcutaneous Tissue Disorders**

Very common: Alopecia

Common: Nail and skin changes (mild and transient)

Rare: Radiation-recall dermatitis; recall dermatitis.

**General Disorders and Administration Site Conditions**
Common: Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis).

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of localised oedema, pain, erythema, tenderness, induration, skin discoloration, or swelling at the injection site. 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, i.e., ‘recall’, has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of TAXOL safety. 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.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

**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.

**Postmarketing Experience**

The following additional adverse reactions have been identified during post approval use of TAXOL. Because there reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Infections and Infestations:** Pneumonia, sepsis

**Cardiac Disorders:** Atrial fibrillation, supraventricular tachycardia, reduction of left ventricular ejection fraction, ventricular failure

**Haematological Disorders:** Acute myeloid leukaemia,
myelodysplastic syndrome

**Immune System Disorders:**
- Anaphylactic reactions (with fatal outcome); Anaphylactic shock

**Metabolism and Nutrition Disorders:**
- Anorexia

**Psychiatric Disorders:**
- Confusional state

**Vascular Disorders:**
- Shock

**Respiratory, Thoracic and Mediastinal Disorders:**
- Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough

**Gastrointestinal Disorders:**
- Bowel obstruction, bowel perforation, ischemic colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites

**Neurological Disorders:**
- Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia, paresthesia, hyperesthesia.

**Eye Disorders:**
- Photopsia, visual floaters.

**Ear and Labyrinth Disorders:**
- Hearing loss, tinnitus, vertigo, ototoxicity.

**Skin and Subcutaneous Tissue Disorders:**
- Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet), scleroderma, pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis.

**Investigations:**
- Increase in blood creatine.

**General Disorders and Administration Site Conditions:**
- Asthenia, malaise, pyrexia, dehydration, oedema.

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**DOSAGE AND ADMINISTRATION**

All patients must be premedicated prior to TAXOL administration [to prevent severe hypersensitivity reactions.] Such premedication may consist of dexamethasone 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.

Repeat courses of TAXOL should not be administered to patients with solid tumours until the neutrophil count is at least $1.5 \times 10^9$ cells/L and the platelet count is at least $100 \times 10^9$ cells/L. Patients who experience severe neutropenia ($< 0.5 \times 10^9$ cells/L) or severe peripheral neuropathy should receive a dosage reduced by 20% for subsequent courses. The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

For patients with ovarian cancer, the recommend doses are following (see CLINICAL TRIALS-Ovarian Carcinoma):

1. The recommended dose of TAXOL for the primary treatment of ovarian cancer is:
   (a) $175\text{mg/m}^2$ administered over 3 hours, followed by cisplatin $75\text{mg/ m}^2$, with a 3 week interval between courses.
   (b) $135\text{mg/m}^2$ administered intravenously over 24 hours, followed by cisplatin $75\text{mg/m}^2$, with a 3 week interval between courses.

2. The recommended dose of TAXOL for the secondary treatment of ovarian or breast cancer is $175\text{mg/m}^2$ administered intravenously over 3 hours every three weeks.

For patients with Breast Cancer, the recommend doses are following (See CLINICAL TRIALS-Breast Carcinoma):

1. Node-Positive Breast Cancer:
   TAXOL $175 \text{mg/m}^2$ administered intravenously over 3 hours every 3 weeks for 4 courses following doxorubicin and cyclophosphamide combination therapy (See CLINICAL TRIALS-Breast Carcinoma).

2. Adjuvant therapy: TRADEMARK $175 \text{mg/m}^2$ administered intravenously over 3 hours every 3 weeks for 4 courses sequentially to standard combination therapy.

3. Combined with Gemcitabine:
   TAXOL $175\text{mg/m}^2$ administered intravenously over 3 hours on Day 1 followed by gemcitabine $1250\text{mg/ m}^2$ as a 30-minute intravenous infusion on Days 1 and 8 of each 21 day cycle. Dose reduction each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

   Patients receiving gemcitabine in combination with paclitaxel for breast cancer should have an absolute granulocyte count of at least $1.5(\times 10^9/L)$ and a platelet count of $\geq 100(\times 10^9/L)$ prior to initiation cycle.

The following table (Table 4) presents appropriate gemcitabine dose adjustments within a cycle for haematologic toxicities.
Table 4: Gemcitabine Dose Adjustments

<table>
<thead>
<tr>
<th>Absolute Granulocyte Count (x10^9/L)</th>
<th>Platelet Count (x10^9/L)</th>
<th>% of Day 1 Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.2</td>
<td>and</td>
<td>100</td>
</tr>
<tr>
<td>1.0 -&lt;1.2</td>
<td>or</td>
<td>75</td>
</tr>
<tr>
<td>0.7-&lt;1.0</td>
<td>and</td>
<td>50</td>
</tr>
<tr>
<td>&lt;0.7</td>
<td>or</td>
<td>Hold*</td>
</tr>
</tbody>
</table>

*Treatment may be reinstated on Day 1 of the next cycle

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemzar should be held or decreased by 50% depending on the judgment of the treating physician.

4. Combined with Herceptin: The following recommendations of loading dose and maintenance dose refer to combination with Taxol.

Loading Dose: The recommended initial loading dose of Herceptin is 4 mg/kg body weight. IV infusion for 90 minutes.

Maintenance dose: The recommended initial loading dose of Herceptin is 2 mg/kg body weight. IV infusion for 30 minutes.

Primary or Secondary Treatment of NSCLC:

The recommended dose of TAXOL is administered intravenously 135 mg/m^2 over 24 hours followed by a cisplatin, with a 3-week interval between courses.

AIDS-related Kaposi’s sarcoma:
The recommended dose of TAXOL is 135 mg/m^2 administered intravenously over 3 hours with a 3-week interval between courses or 100 mg/m^2 administered intravenously over 3 hours with a 2-week interval between courses (dose intensity 45-50 mg/m^2/week)

Based upon the immunosuppression observed in patients with advanced HIV disease, the following modifications are recommended in these patients:
1) The dose of dexamethasone as one of the three premedication drugs should be reduced to 10 mg orally.
2) Treatment with TRADEMARK should be initiated or repeated only if the neutrophil count is at least 1000 cells/mm^3.
3) The dose of subsequent courses of TRADEMARK should be reduced by 20% for those patients who experience severe neutropenia (<500 cell/mm^3 for a week or longer).
4) Concomitant hematopoietic growth factor (G-CSF) should be initiated as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of TAXOL should not be repeated until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. TAXOL should not be given to patients with AIDS-related Kaposi’s sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during TAXOL therapy should have dosage reduced by 20% for subsequent courses of TAXOL. The incidence of neurotoxicity and the
severity of neutropenia increase with dose.

**Hepatic impairment**

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Dose adjustment is recommended, as shown in the following Table for both 3- and 24-hour infusions. Patients should be monitored closely for the development of profound myelosuppression.

Recommendations for Dosing in Patients with Hepatic Impairment Based on Clinical Trial Data

<table>
<thead>
<tr>
<th>Degree of Hepatic Impairment</th>
<th>Transaminase Levels</th>
<th>Bilirubin Levels</th>
<th>Recommended TAXOL Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 x ULN and ≤ 1.5 mg/dL</td>
<td>135 mg/m^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-&lt;10 x ULN and ≤ 1.5 mg/dL</td>
<td>100 mg/m^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 x ULN and 1.6-7.5 mg/dL</td>
<td>50 mg/m^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 x ULN or &gt;7.5 mg/dL</td>
<td>Not suggest</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 3-hour infusion              |                     |                  |                        |
| <10 x ULN and ≤ 1.25 x ULN  | 175 mg/m^2          |
| <10 x ULN and 1.26-2.0 x ULN| 135 mg/m^2          |
| <10 x ULN and 2.01-5.0 x ULN| 90 mg/m^2           |
| ≥ 10 x ULN or >5.0 x ULN    | Not suggest         |

a These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (eg, for AIDS-related Kaposi’s sarcoma).

b Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

c Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

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).

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 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, dyspnoea, 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 must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer’s Injection to a final concentration of 0.3 to 1.2mg/mL. Although these solutions for infusion are physically and chemically stable for up to 72 hours at ambient temperature (approximately 25°C) it is recommended that the solution for infusion should be administered as soon as practicable after preparation as it does not contain an antimicrobial agent. The infusion should be completed within 24 hours of preparation of the solution and any residue discarded. Diluted solutions should be refrigerated if not used immediately so as to decrease the likelihood of microbial contamination.

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 plasticized 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 a loss of sterile integrity of the TAXOL solution.

Stability

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

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.

PRESENTATION

TAXOL is available in 5mL, 16.7mL and 50mL single-dose vials.

STORAGE

Store the vials in original cartons below 15-30°C. Protect from light.
HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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.

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