AUSTRALIAN PI – PACLITAXIN (PACLITAXEL) INJECTION

1 NAME OF THE MEDICINE
Paclitaxin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Paclitaxel is a natural product with antitumour activity. It is a white to off white crystalline powder that is highly lipophilic and insoluble in water. It is the first of a class of anticancer agents known as taxanes.

Molecular formula: C_{47}H_{51}NO_{14}
MW: 853.929

Each mL of Paclitaxin contains paclitaxel 6 mg. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM
Solution (sterile, nonpyrogenic, nonaqueous, concentrate for dilution).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
- Primary treatment of ovarian cancer in combination with a platinum agent.
- Treatment of metastatic carcinoma of the ovary and of the breast after failure of standard therapy.
- 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.
- Paclitaxin, in combination with gemcitabine (Gemzar), is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/ neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
- Treatment of non-small cell lung cancer (NSCLC).
4.2 Dose and Method of Administration

Product is for single use in one patient only. Discard any residue.

All patients must be premedicated prior to Paclitaxin administration [to prevent severe hypersensitivity reactions]. Such premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 and 6 hours before Paclitaxin; promethazine 25 mg or 50 mg intravenously 30 to 60 minutes prior to Paclitaxin; and cimetidine 300 mg or ranitidine 50 mg intravenously 30 to 60 minutes before Paclitaxin.

Repeat courses of Paclitaxin should not be administered to patients with solid tumours until the neutrophil count is at least 1.5 x 10⁹ cells/L and the platelet count is at least 100 x 10⁹ cells/L. Patients who experience severe neutropenia (<0.5 x 10⁹ 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.

1. The recommended dose of Paclitaxin for the primary treatment of ovarian cancer is:
   (a) 175 mg/m² administered over three hours, followed by cisplatin 75 mg/m², with a three week interval between courses. OR
   (b) 135 mg/m² administered intravenously over 24 hours, followed by cisplatin 75 mg/m², with a three week interval between courses.

   The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given before cisplatin. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

2. The recommended dose of Paclitaxin for the secondary treatment of ovarian or breast cancer is 175 mg/m² administered intravenously over three hours every three weeks.

3. Primary or secondary treatment of non-small cell lung cancer (NSCLC):
The recommended dose of Paclitaxin is 175 mg/m² administered intravenously over three hours, with a three week interval between courses.

4. Node positive breast cancer:
Paclitaxin 175 mg/m² administered intravenously over three hours every three weeks for four courses following doxorubicin and cyclophosphamide combination therapy.

5. Overexpressed HER-2 breast cancer:
Paclitaxin 175 mg/m² 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.

6. Metastatic breast cancer:
Paclitaxin 175 mg/m² administered intravenously over three hours on day 1 followed by gemcitabine 1,250 mg/m² 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.
Dose Adjustment Considerations

Metastatic breast carcinoma (MBC), ovarian cancer (MOC) and non-small cell lung carcinoma (NSCLC)

Courses of paclitaxel should not be repeated 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.

Gemcitabine

Patients receiving gemcitabine in combination with Paclitaxin for breast cancer should have an absolute granulocyte count of at least $1.5 (x10^9/L)$ and a platelet count of greater than or equal to $100 (x10^9/L)$ prior to initiation cycle. Table 1 presents appropriate gemcitabine dose adjustments within a cycle for haematological toxicities.

Table 1: Gemcitabine Dose Adjustments

<table>
<thead>
<tr>
<th>Absolute granulocyte count $(x\ 10^9/L)$</th>
<th>Platelet count $(x\ 10^9/L)$</th>
<th>% of Day 1 gemcitabine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1.2$</td>
<td>and $&gt; 75$</td>
<td>100</td>
</tr>
<tr>
<td>$1.0 - &lt;1.2$</td>
<td>or $50 - 75$</td>
<td>75</td>
</tr>
<tr>
<td>$0.7 - &lt;1.0$</td>
<td>and $\geq 50$</td>
<td>50</td>
</tr>
<tr>
<td>$&lt;0.7$</td>
<td>or $&lt;50$</td>
<td>Hold*</td>
</tr>
</tbody>
</table>

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

Paclitaxin should be administered through an in-line filter with a microporous membrane not greater than 0.22 micron (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 Paclitaxin 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-2 filters which incorporate short inlet and outlet PVC coated tubing has not resulted in a significant leaching of DEHP.

**Preparation and administration precautions**

Paclitaxin is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Paclitaxin. The use of gloves is recommended. Following topical exposure, tingling, burning and redness have been observed. If Paclitaxin solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Paclitaxin 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

Product is for single use in one patient only – discard any residue.

Paclitaxin concentrated injection must be diluted prior to infusion. Paclitaxin should be diluted in glucose 5% or sodium chloride 0.9% injection to a final concentration of 0.3 to 1.2 mg/mL. Although these solutions for infusion are physically and chemically stable for up to 72 hours at ambient temperature (approximately 25 °C), to reduce microbiological contamination it is recommended that the solution for infusion 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. To decrease the likelihood of microbial contamination, diluted solutions should be stored at 2-8 °C.

Compounding centres which are licensed by the Therapeutic Goods Administration (TGA) to reconstitute and/or further dilute cytotoxic products, and have validated aseptic procedure and regular monitoring of aseptic technique, may apply a shelf life of seven days at 2 to 8 °C (refrigerate; do not freeze) or at 25 °C to Paclitaxin solutions which have been reconstituted with glucose 5% for intravenous infusion and stored in glass bottles.

For Paclitaxin solutions which have been reconstituted with sodium chloride 0.9% for intravenous infusion and stored in glass bottles, a shelf life of 14 days at both 2 to 8 °C (refrigerate; do not freeze) and room temperature (25 °C) may be applied. Reconstituted 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.

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 intravenous tubing containing an in-line 0.22 micron filter.

When dilutions of Paclitaxin are prepared in PVC containers, extractable plasticiser DEHP [di-(2-ethylhexyl) phthalate] levels increase with time and Paclitaxin concentration. Consequently, the use of plasticised PVC containers and administration sets is not recommended. Paclitaxin 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 Paclitaxin since they can cause the stopper to collapse, resulting in a loss of sterile integrity of the Paclitaxin solution.

4.3 CONTRAINDICATIONS

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

Paclitaxin should not be administered to patients with solid tumours who have baseline neutrophil counts of <1.5 x 10^9 cells/L.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

General

Paclitaxin should be administered under the supervision of a doctor experienced in the use of cancer chemotherapeutic agents.

Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Paclitaxin should be administered as a diluted infusion. Special care should be taken to avoid intra-arterial application due to the potential for severe tissue reactions.

WARNING:

Patients must be pretreated with corticosteroids, antihistamines and H2-antagonists (e.g. dexamethasone, promethazine and cimetidine or ranitidine) before receiving Paclitaxin (see also Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Paclitaxel is administered by intravenous infusion only; it should not be administered by intracerebral, intrapleural or intraperitoneal infusion.

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

Gastrointestinal (GI) Toxicity

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

Pseudomembranous colitis has been rarely reported including cases in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.

Anaphylaxis and Severe Hypersensitivity Reactions

Severe hypersensitivity (anaphylactoid) reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred rarely in premedicated patients receiving Paclitaxin.

Rare fatal reactions have occurred in patients despite pretreatment.

Patients receiving Paclitaxin 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, Paclitaxin 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, e.g. flushing and skin reactions, do not require interruption of therapy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).
Haematologic Toxicity

Bone marrow suppression (primarily neutropenia) is the dose limiting toxicity. Frequent monitoring of blood counts should be instituted during Paclitaxin treatment. Paclitaxin should not be administered to patients until the baseline 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.

In the case of severe neutropenia ($<0.5 \times 10^9$ cells/L) during a course of Paclitaxin, a 20% reduction in dose for subsequent courses of therapy is recommended (see Section 4.8 ADVERSE EFFECTS UNDESIRABLE EFFECTS).

Cardiovascular Toxicity

Hypotension, hypertension and bradycardia have been observed during paclitaxel administration, but generally do not require treatment. In severe cases, Paclitaxin 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 Paclitaxin infusion is recommended (see Section 4.8 ADVERSE EFFECTS UNDESIRABLE EFFECTS).

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 paclitaxel therapy. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be commenced and performed during subsequent therapy with paclitaxel (see Section 4.8 ADVERSE EFFECTS UNDESIRABLE EFFECTS). Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration, but patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian cancer.

When Paclitaxin is used in combination with trastuzumab or doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended. Paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin.

When patients are candidates for treatment with paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m$^2$) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles).
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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In NSCLC patients and in patients with ovarian cancer treated in the first-line setting, the administration of paclitaxel as a 3 hour infusion in combination with cisplatin resulted in a greater incidence of neurotoxicity than usually seen in patients receiving both single agent paclitaxel alone and cyclophosphamide followed by cisplatin.

Paclitaxin contains dehydrated alcohol 396 mg/mL; consideration should be given to possible central nervous system and other effects of alcohol.

Children may be more sensitive than adults to the effects of ethanol.

Respiratory System

Paclitaxel in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of interstitial pneumonitis.

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.

Use in hepatic impairment

Studies in patients with impaired hepatic function have not been performed. No data is available for patients with severe baseline cholestasis. There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering Paclitaxin to patients with moderate hepatic impairment and dose adjustments should be considered. Treatment with paclitaxel is not recommended in patients with severe hepatic dysfunction. When Paclitaxin 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. Patients should be monitored closely for the development of profound myelosuppression.

Use in renal impairment

Studies in patients with impaired renal function have not been performed and there is insufficient data to permit dosage recommendations.

Use in the elderly

Of 2228 patients who received paclitaxel 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 paclitaxel 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 paclitaxel 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.

**Paediatric use**

The safety and effectiveness of paclitaxel in paediatric patients (under 18 years) 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 paclitaxel 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 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 Paclitaxin for use in this population.

**Effects on laboratory tests**

No data available.

**4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

Medications concomitantly administered with paclitaxel (e.g. corticosteroids, antihistamines and H₂-antagonists) did not appear to interact adversely.

**Effect of other drugs on Paclitaxel**

*Cisplatin*: Paclitaxel should be given before cisplatin when used in combination. In a dose finding trial in which paclitaxel was administered as a 24 hour infusion and cisplatin was administered as a 1 mg/minute infusion, myelosuppression was more profound when paclitaxel was given after cisplatin than when paclitaxel was given before cisplatin. Pharmacokinetic data demonstrated a reduction in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

*Ketoconazole*: Preliminary animal/ex vivo data indicate that ketoconazole may inhibit the metabolism (but not the elimination) of paclitaxel; caution should be exercised when treating patients with paclitaxel if they are receiving ketoconazole.

**Effect of Paclitaxel on other drugs**

*Doxorubicin*: The elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time. 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.

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 concomitantly with known substrates or inhibitors of these isoenzymes.

Trastuzumab: In the clinical trial of paclitaxel in combination with trastuzumab (Herceptin), mean serum trough concentrations of trastuzumab were consistently elevated 1.5-fold as compared with serum concentrations of trastuzumab in combination with anthracycline plus cyclophosphamide (AC).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
At a dose of 1 mg/kg (6 mg/m²) paclitaxel produced low fertility and fetal toxicity in rats. Paclitaxel has also been shown to be embryotoxic and fetotoxic in rabbits receiving the drug at an intravenous dose of 3 mg/kg (33 mg/m²) during organogenesis.

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Use in pregnancy – Pregnancy Category D
Drugs which have caused, are expected to have caused or may be expected to cause, an increased risk of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Paclitaxin may cause foetal harm when administered to a pregnant woman. Paclitaxel has also been shown to be embryotoxic and foetotoxic in rabbits receiving the drug at an IV dose of 3 mg/kg (33 mg/m²) during organogenesis. At a dose of 1 mg/kg (6 mg/m²) paclitaxel 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 Paclitaxin due to the potential for foetal harm. If Paclitaxin is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard and inform the treating physician immediately. Female and male patients of fertile age and/or their partners should use contraceptions for at least 6 months after treatment with paclitaxin.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Paclitaxel has not been demonstrated to interfere with the ability to drive and use machines. However, it should be noted that the product does contain alcohol (see Section 4.4 “SPECIAL WARNINGS AND PRECAUTIONS FOR USE”).
4.8 ADVERSE EFFECTS (UNDESIRABLE 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 paclitaxel for the treatment of ovarian, breast or lung cancer. None of the observed effects were clearly influenced by age. Unless stated otherwise the 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 non-small cell lung cancer (NSCLC) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 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 paclitaxel followed by cisplatin, than patients treated with cyclophosphamide followed by cisplatin.

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;
Very rare: <1/10,000.

Infections and Infestations
Very common: infection.
Uncommon: septic shock.

Cardiac Disorders
Very common: hypotension.
Common: bradycardia, ECG abnormalities (nonspecific repolarisation and sinus tachycardia).
Uncommon: ECG abnormalities (premature beats), AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy.
Rare: myocardial infarction, cardiac failure, 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).

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 eleven days after paclitaxel 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 urinary tract infection and upper respiratory tract infection).

Rare: five septic episodes, which were associated with severe neutropenia attributable to paclitaxel 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 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, Connective tissue and Bone Disorders**

*Very common:* arthralgia, myalgia (the symptoms were usually transient occurring two to three days after paclitaxel 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. 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.

**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, skin fibrosis and skin necrosis).

**Investigations**

Common: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase

Uncommon: severe elevation in bilirubin.

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discolouration or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the three hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. 'recall', has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration and skin exfoliation have been received as part of the continuing surveillance of paclitaxel 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. In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported.

Alopecia was observed in >80% of the patients treated with paclitaxel. The majority of alopecia events occurred less than one month after initiation of paclitaxel. Pronounced hair loss ≥50% is expected for the majority of patients who experience alopecia.

Radiation pneumonitis has been reported in patients receiving concurrent radio therapy.

**Combination treatment with trastuzumab:**

When paclitaxel 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 paclitaxel or trastuzumab) were reported more frequently than with single agent paclitaxel: 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 paclitaxel/trastuzumab combination vs single agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single agent paclitaxel.

Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with paclitaxel 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 paclitaxel. Because the 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, peritonitis, sepsis

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

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

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

Metabolism and Nutrition Disorders: Anorexia, tumour lysis syndrome

Psychiatric Disorders: Confusional state

Vascular Disorders: Shock, phlebitis

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, neutropenic colitis

Neurological Disorders: Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia, paresthesia, hyperesthesia, motor neuropathy (with resultant minor distal weakness)

Eye Disorders: Photopsia, visual floaters, macular oedema, optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended
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, cutaneous lupus erythematosus
Musculoskeletal, Connective Tissue and Bone Disorders: Systemic lupus erythematosus
Investigations: Increase in blood creatine
General Disorders and Administration Site Conditions: Asthenia, malaise, pyrexia, dehydration, oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known antidote for Paclitaxin overdosage. In the case of overdose, patients should be closely monitored.

Treatment should be directed towards the primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Treatment should be supportive. Overdoses in paediatric patients may be associated with acute ethanol toxicity.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 paclitaxel 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 paclitaxel (135 mg/m² over 24 hours)/ cisplatin (75 mg/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 paclitaxel/ 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 paclitaxel/ cisplatin group than in the cyclophosphamide/ cisplatin group (median 16.6 versus 13 months). Survival was also significantly longer (P = 0.0002) in the paclitaxel/ cisplatin group (median 35.5 versus 24.2 months).

The second was a multicentre randomised, controlled trial in which 342 patients received paclitaxel (175 mg/m² over three hours) in combination with cisplatin (75 mg/m²) every three weeks and 338 received cyclophosphamide plus cisplatin. The trial demonstrated significantly increased time to progression (15.3 versus 11.5 months) and significantly increased overall survival (35.6 versus 25.9 months) in favour of the paclitaxel/ 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 175 mg/m²/3 hour regimen may be associated with greater neurotoxicity compared to the 135 mg/m²/24 hour regimen, this is offset by reduced haematological toxicity.

**Non-small cell lung carcinoma:**

Four open label phase II studies were conducted in 224 patients with advanced non-small cell lung cancer (NSCLC) and no prior chemotherapy; 131 received paclitaxel and 93 received investigational agents in a randomised phase II trial.

In the earliest two trials (CA139-027 and CA139-029), paclitaxel was administered as a 24 hour infusion at initial doses of 200 mg/m² and 250 mg/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 to 13.0 months) and 4.4 months (95% CI 3.0 to 16.2 months). In the later two trials (CA139-127 and CA139-201), paclitaxel was administered as a three hour infusion at initial doses of 200 mg/m² and 225 mg/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 to 16.8 months) and 9.0 months (95% CI 5.9 to 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. 565 patients were randomised to receive paclitaxel 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 paclitaxel 175
mg/m² as a three hour infusion followed by cisplatin 80 mg/m² or cisplatin 80 mg/m² on day 1 followed by teniposide 100 mg/m² on days 1, 3 and 5 (control). In a study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomised to either paclitaxel 135 mg/m² as a 24 hour infusion followed by cisplatin 75 mg/m², paclitaxel 250 mg/m² as a 24 hour infusion followed by cisplatin 75 mg/m² with G-CSF support, or cisplatin 75 mg/m² on day 1, followed by etoposide 100 mg/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 Table 2. The paclitaxel combinations showed improvement in response rates (>20%) and median time to progression (> four months), but no significant increase in survival.

Table 2

Key efficacy parameters in phase III studies of non-small cell lung cancer (NSCLC)

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>European Organization for Research and Treatment of Cancer (EORTC) study</th>
<th>Eastern Cooperative Oncology Group (ECOG) study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAX 175 mg/m² + CIS 80 mg/m² (n = 166)</td>
<td>TAX 135 mg/m² + CIS 80 mg/m² (n = 198)</td>
</tr>
<tr>
<td></td>
<td>VM 100 mg/m² + CIS 80 mg/m² (n = 166)</td>
<td>TAX 250 mg/m² + CIS 75 mg/m² (n = 201)</td>
</tr>
<tr>
<td>Response rate (evaluable patients)</td>
<td>Rate (%)</td>
<td>36</td>
</tr>
<tr>
<td>95% CI</td>
<td>29-44</td>
<td>20-34</td>
</tr>
<tr>
<td>Time to progression</td>
<td>Median (months)</td>
<td>5.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.3-5.9</td>
<td>3.3-6.1</td>
</tr>
<tr>
<td>Survival</td>
<td>Median (months)</td>
<td>9.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.2-11.7</td>
<td>8.0-10.4</td>
</tr>
<tr>
<td>One year survival</td>
<td>Patients (%)</td>
<td>41</td>
</tr>
<tr>
<td>95% CI</td>
<td>33-49</td>
<td>30-43</td>
</tr>
</tbody>
</table>

TAX = taxotere; CIS = cisplatin; VM = teniposide; VP = etoposide
* Administered intravenously on days 1, 3 and 5
** Administered intravenously on days 1, 2 and 3

Breast carcinoma:

A randomised phase III intergroup multicentre, 3 x 2 factorial study of the adjuvant use of paclitaxel was conducted in 3,170 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 paclitaxel 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/m² and doxorubicin at doses of either 60 mg/m² (on day 1), 75 mg/m² (in two divided doses on days 1 and 2) or 90 mg/m² (in two
divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every three weeks for four courses and either paclitaxel 175 mg/m² as a three hour infusion every three 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 five 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 paclitaxel 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 paclitaxel 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 to 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 to 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 3).
Table 3

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>No. of positive nodes</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>Tumour size (cm)</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>Menopausal status</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>Receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive⁠a</td>
<td>2066</td>
<td>293</td>
</tr>
<tr>
<td>Negative/Unknown⁠b</td>
<td>1055</td>
<td>331</td>
</tr>
</tbody>
</table>

a Positive for either oestrogen or progesterone receptors
b Negative or missing for both oestrogen and progesterone receptors
(both missing: n = 15)

The safety and efficacy of paclitaxel 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 60 mg/m² or epirubicin 75 mg/m²) plus cyclophosphamide (600 mg/m²) with Herceptin (H+AC) or without Herceptin (AC alone), or paclitaxel (175 mg/m² infused over three hours every three weeks) with Herceptin (H+P) or without Herceptin (P alone). 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 4 mg/kg intravenous loading dose of Herceptin on day 0. From day 7, patients received weekly infusions of Herceptin 2 mg/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 overexpressed HER-2. The addition of Herceptin to chemotherapy extended the median time to disease progression by 2.8 months, 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. (See Table 4)

### Table 4

<table>
<thead>
<tr>
<th>Efficacy outcomes in combined therapy trial H0648g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Herceptin + chemo n = 235</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Median time to disease progression (months, 95% CI)</td>
</tr>
<tr>
<td>7.4 (7.0, 9.0)</td>
</tr>
<tr>
<td>Response rate n (%)</td>
</tr>
<tr>
<td>118 (50%)</td>
</tr>
<tr>
<td>Median duration of response (months, 95% CI)</td>
</tr>
<tr>
<td>9.1 (7.7, 11.0)</td>
</tr>
<tr>
<td>One year survival</td>
</tr>
<tr>
<td>79%</td>
</tr>
</tbody>
</table>

\( \text{AC = anthracycline + cyclophosphamide; Chemo = chemotherapy} \)

One year survival rates (the prospectively defined survival endpoint) were significantly better for chemotherapy + Herceptin versus the 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 + Herceptin, while it remained low in the chemotherapy only arm.

The safety and efficacy of paclitaxel 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 (1,250 mg/m²) was administered intravenously over 30 to 60 minutes on days 1 and 8 of a 21 day cycle and paclitaxel (175 mg/m²) was administered intravenously over three hours before gemcitabine on day 1 of a 21 day cycle. In the T arm paclitaxel (175 mg/m²) was administered intravenously over three 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 nonanthracycline 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.

5.2 Pharmacokinetic Properties

Absorption
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/hour/m².

Variability in systemic paclitaxel exposure, as measured by area under the curve (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 nonlinear. 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.

**Distribution**

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 three 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/hour/m².

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/hour/m² to 8.6 L/hour/m².

**Metabolism**

Hepatic metabolism has been demonstrated in animals. Hydroxylated metabolites isolated in bile have been demonstrated to be the principal metabolites.

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 Section 4.4 “SPECIAL WARNINGS AND PRECAUTIONS FOR USE” and Section 4.5 “INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS”).

**Excretion**

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. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6α hydroxypaclitaxel, is the major metabolic pathway in humans. 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.

### 5.3 Preclinical safety data

**Genotoxicity**

Paclitaxel 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.

**Carcinogenicity**

The carcinogenic potential of paclitaxel has not been studied.
6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each mL of Paclitaxin contains paclitaxel 6 mg, PEG-35 castor oil 527 mg, ethanol 396 mg and anhydrous citric acid 2 mg.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

2 Years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store the vials in original cartons below 25°C. Protect from light.

Unopened single dose vials of Paclitaxin (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.)

6.5 NATURE AND CONTENTS OF CONTAINER

Paclitaxel is available in the following single dose vials in packs of 1:
30 mg/5 mL; 100 mg/16.7 mL; 150 mg/25 mL; 300 mg/50 mL

6.6 SPECIAL PRECAUTIONS FOR 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.
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

![Chemical structure of Paclitaxel](image)

CAS number

33069-62-4 (USAN).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Teva Pharma Australia Pty Ltd
37 Epping Rd
Macquarie Park
NSW 2113
Telephone: 1800 288 382

9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 10 November 2009

10 DATE OF REVISION

22 May 2018

SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>Correction of typo for platelet counts – missing base power 10 in calculation</td>
</tr>
<tr>
<td>4.8</td>
<td>Addition of more detailed text on injection site reactions and reports of disseminated intravascular coagulation (DIC)</td>
</tr>
</tbody>
</table>