

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Name of the medicinal product

Paclitaxel 260 mg per 43.4 mL concentrate for solution for infusion  
P-Tax 260

Paclitaxel 300 mg per 50 mL concentrate for solution for infusion  
P-Tax 300

### 2. Qualitative and quantitative composition

Each mL of solution contains 6 mg of paclitaxel.

#### Excipient with known effect

Each mL of solution **also** contains 527 mg of castor oil polyoxyl hydrogenated and 0.497 mL of dehydrated alcohol (see section 4.4).

For the full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Concentrate for solution for infusion.

A clear colourless to pale yellow solution, free from visible extraneous particulate matter.

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Paclitaxel is indicated in the treatment of

##### **Ovarian Carcinoma**

In the first-line chemotherapy of ovarian cancer for patients with advanced carcinoma of the ovary or with residual disease (>1 cm) after initial laparotomy, in combination with cisplatin.

In the second-line chemotherapy of ovarian cancer for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum-containing therapy.

##### **Breast Carcinoma**

In the adjuvant setting, paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.

Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.

As a single agent, paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have either failed or relapse within 6 months of adjuvant chemotherapy or are not candidates for standard, anthracycline-containing therapy.

### Advanced Non-Small Cell Lung Carcinoma

Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

### AIDS-related Kaposi's sarcoma

Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy.

## 4.2 Posology and method of administration

Note: Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl) phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients must be pre-medicated with corticosteroids, antihistamines and H2 antagonists prior to paclitaxel treatment, as in the examples given below:

Drug	Dose	Administration Prior to Paclitaxel
Dexamethasone	20 mg oral* or intravenous	<i>For oral administration:</i> Approximately 12 and 6 hours, or <i>for intravenous administration:</i> 30–60 minutes
Diphenhydramine**	50 mg intravenous	30–60 minutes
Cimetidine or ranitidine	300 mg intravenous 50 mg intravenous	30–60 minutes

\* 8–20 mg for Kaposi's sarcoma patients

\*\* Or, an equivalent antihistamine, e.g. chlorphenamine

Paclitaxel should be administered through an in-line filter with a microporous membrane  $\leq 0.22$   $\mu\text{m}$ .

### First-line Chemotherapy of Ovarian Carcinoma

For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. In selecting the appropriate regimen, differences in toxicities should be considered.

Paclitaxel administered intravenously over 3 hours at a dose of 175 mg/m<sup>2</sup> followed by cisplatin at a dose of 75 mg/m<sup>2</sup> or paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m<sup>2</sup> followed by cisplatin at a dose of 75 mg/m<sup>2</sup>.

### Second-line Chemotherapy of Ovarian Carcinoma

In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is paclitaxel 135 mg/m<sup>2</sup> or 175 mg/m<sup>2</sup> administered intravenously over 3 hours every 3 weeks.

## **Patients with Carcinoma of the Breast**

The following regimens are recommended:

### **Adjuvant Chemotherapy in Breast Carcinoma**

The recommended dose of paclitaxel is 175 mg/m<sup>2</sup> administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.

### **First-line Chemotherapy of Breast Carcinoma**

When used in combination with doxorubicin (50 mg/m<sup>2</sup>), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m<sup>2</sup> administered intravenously over a period of 3 hours, with a 3-week interval between courses.

When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m<sup>2</sup> administered intravenously over a period of 3 hours, with a 3-week interval between courses. Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

### **Second-line Chemotherapy of Breast Carcinoma**

The recommended dose of paclitaxel is 175 mg/m<sup>2</sup> administered over a period of 3 hours, with a 3-week interval between courses.

### **Patients with Non-Small Cell Lung Carcinoma**

The recommended regimen, given every 3 weeks, is paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m<sup>2</sup> followed by cisplatin 75 mg/m<sup>2</sup>; or paclitaxel 175 mg/m<sup>2</sup> administered over a period of 3 hours, followed by cisplatin 80 mg/m<sup>2</sup>, with a 3-week interval between courses.

### **Patients with AIDS-related Kaposi's sarcoma**

The recommended regimen is paclitaxel administered at a dose of 135 mg/m<sup>2</sup> given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m<sup>2</sup> given intravenously over 3 hours every 2 weeks (dose intensity: 45–50 mg/m<sup>2</sup>/week).

Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients:

- 1) Reduce the dose of dexamethasone as one of the three pre-medication drugs to 10 mg oral (instead of 20 mg oral).
- 2) Initiate or repeat treatment with paclitaxel only if the neutrophil count is at least 1000 cells/mm<sup>3</sup>.
- 3) Reduce the dose of subsequent courses of paclitaxel by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm<sup>3</sup> for a week or longer).
- 4) Initiate concomitant haematopoietic growth factor (G-CSF) as clinically indicated.

Paclitaxel should not be re-administered until the neutrophil count is  $\geq 1,500/\text{mm}^3$  ( $\geq 1,000/\text{mm}^3$  for Kaposi's sarcoma patients) and the platelet count is  $\geq 1,00,000/\text{mm}^3$  ( $\geq 75,000/\text{mm}^3$  for Kaposi's sarcoma patients). Patients who experienced severe neutropenia (neutrophil count <500/mm<sup>3</sup> for  $\geq 7$  days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for Kaposi's sarcoma patients). 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. Recommendations for dosage adjustment for the first course of therapy is shown in the table below for both 3-hour and 24-hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

Table 2: Recommendations for Dosing in Patients with Hepatic Impairment, Based on Clinical Trial Data<sup>a</sup>

Degree of Hepatic Impairment

Transaminase levels	Bilirubin	Recommended Levels <sup>b</sup>	Paclitaxel Dose <sup>c</sup>
<b>24-hour infusion</b>			
<2 × ULN	and	≤1.5 mg/dL	135 mg/m <sup>2</sup>
2 to <10 × ULN	and	≤1.5 mg/dL	100 mg/m <sup>2</sup>
<10 × ULN	and	1.6–7.5 mg/dL	50 mg/m <sup>2</sup>
≥10 × ULN	or	>7.5 mg/dL	Not recommended
<b>3-hour infusion</b>			
<10 × ULN	and	≤1.25 × ULN	175 mg/m <sup>2</sup>
<10 × ULN	and	1.26–2.0 × ULN	135 mg/m <sup>2</sup>
<10 × ULN	and	2.01–5.0 × ULN	90 mg/m <sup>2</sup>
≥10 × ULN	or	>5.0 × ULN	Not recommended

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

b Differences in criteria for bilirubin levels between the 3-hour 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.

## Paediatric Use

Paclitaxel is not recommended for use in children aged below 18 years due to lack of data on safety and efficacy.

## 4.3 Contraindications

Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipient, especially polyoxyethylated castor oil.

Paclitaxel is contraindicated during pregnancy and lactation and should not be used in patients with baseline neutrophils <1,500/mm<sup>3</sup> (<1,000/mm<sup>3</sup> for Kaposi's sarcoma patients).

In Kaposi's sarcoma, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

## 4.4 Special warnings and precautions for use

### General

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnoea and hypotension requiring treatment, angio-oedema, and generalized urticaria have occurred in 2–4% of patients receiving paclitaxel in clinical trials. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup> (<1,000 cells/mm<sup>3</sup> for patients with Kaposi's sarcoma). Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm<sup>3</sup> (>1,000 cells/mm<sup>3</sup> for patients with Kaposi's sarcoma) and platelets recover to a level >1,00,000 cells/mm<sup>3</sup> ( $\geq 75,000/\text{mm}^3$  for Kaposi's sarcoma patients). In the KS clinical study, the majority of patients were receiving granulocyte-colony stimulating factor (G-CSF).

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

A single case of heart failure related to paclitaxel was seen in the AIDS- Kaposi's sarcoma clinical study.

Contact of the undiluted concentrate with PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di- (2ethylhexyl) phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of paclitaxel. In NSCLC patients and in ovarian cancer patients 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 severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by cisplatin.

Special care should be taken to avoid intra-arterial administration of paclitaxel, since in animal studies testing for local tolerance severe tissue reactions were observed following intra-arterial administration.

Pseudomembranous colitis has been reported rarely, including cases in patients who have not been treated concomitantly 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.

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

Sexually active, fertile female and male patients should use effective methods of contraception during treatment and up to 6 months after treatment for men, and 1 month after treatment for women. Hormonal contraception is contraindicated in hormone-receptor-positive tumours.

In Kaposi's sarcoma patients, severe mucositis is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

#### *Excipients*

This medicine contains **castor oil polyoxyl**, which may cause severe allergic reaction.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Paclitaxel clearance is not affected by cimetidine pre-medication.

The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given before cisplatin. When paclitaxel is given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel was given after cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin.

The metabolism of paclitaxel is catalysed, in part, by CYP450 isoenzymes CYP2C8 and 3A4. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel into 6 $\alpha$ -hydroxypaclitaxel is the major metabolic pathway in humans. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment. Further data on the potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g., erythromycin, fluoxetine, gemfibrozil) or induce (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Studies in Kaposi's sarcoma patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

### **Haematology**

Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm<sup>3</sup> and platelets recover to a level >1,00,000 cells/mm<sup>3</sup>. In the case of severe neutropenia (<500 cells/mm<sup>3</sup> for 7 days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, paclitaxel, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1,000 cells/mm<sup>3</sup>.

### **Hypersensitivity Reactions**

Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be pre-medicated with corticosteroids (such as dexamethasone), diphenhydramine and H<sub>2</sub> antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnoea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angio-oedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

### **Cardiovascular**

Hypotension, bradycardia and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. When paclitaxel is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

### **Nervous System**

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for Kaposi's sarcoma patients) is recommended for all subsequent courses of paclitaxel. In NSCLC patients and in ovarian cancer patients 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 severe neurotoxicity than both single-agent paclitaxel and cyclophosphamide followed by cisplatin.

Paclitaxel contains dehydrated alcohol, 396 mg/mL; consideration should be given to possible central nervous system (CNS) and other effects of alcohol.

### **Injection Site Reaction**

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 3-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, skin exfoliation, necrosis and fibrosis 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 10 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.

### **Hepatic Impairment**

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III–IV myelosuppression. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate-to-severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression. There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times the ULN. Extreme caution should be exercised when administering paclitaxel to such patients, with dose reduction as recommended in dosage and administration.

No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should not be treated with paclitaxel.

## **4.6 Pregnancy and lactation**

### Pregnancy Category D

Paclitaxel has shown to be teratogenic, embryotoxic and mutagenic in many experimental systems. In particular, it has been shown to be embryotoxic and foetotoxic in rabbits.

There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm and is, therefore, contraindicated during pregnancy.

Women should be advised to avoid becoming pregnant during therapy with paclitaxel or for at least 6 months after treatment and to inform the treating physician immediately should this occur.

### Lactation

It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation. Breastfeeding should be discontinued for the duration of paclitaxel therapy.

## **4.7 Effects on the ability to drive and use machines**

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that this medicinal product contains alcohol.

The ability to drive or to use machines may be decreased due to the alcohol content of this medicinal product.



#### 4.8 Undesirable effects

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent paclitaxel in clinical studies.

The frequency and severity of undesirable effects, unless otherwise mentioned, are generally similar between patients receiving paclitaxel for the treatment of ovarian carcinoma, breast carcinoma or NSCLC. None of the observed toxicities were clearly influenced by age.

A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) of patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

The most frequent significant undesirable effect was bone marrow suppression. Severe neutropenia (<500 cells/mm<sup>3</sup>) occurred in 28% of patients but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for  $\geq 7$  days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir <50 x 10<sup>9</sup>/l at least once while under study. Anaemia was observed in 64% of patients but was severe (Haemoglobin (Hb) <5 mmol/l) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.

Neurotoxicity, mainly peripheral neuropathy, appeared to be more frequent and severe with a 175 mg/m<sup>2</sup>, 3-hour infusion (85% neurotoxicity; 15% severe) than with a 135 mg/m<sup>2</sup>, 24-hour infusion (25% peripheral neuropathy; 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Arthralgia or myalgia affected 60% of patients and was severe in 13% of patients.

Injection site reactions during intravenous administration may lead to localized oedema, pain, erythema and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discolouration may also occur. 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. A specific treatment for extravasation reactions is unknown at this time.

In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

##### *Skin and subcutaneous tissue disorders*

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  $\geq 50$  % is expected for the majority of patients who experience alopecia.

The table below lists undesirable effects regardless of severity associated with the administration of single-agent paclitaxel administered as a 3-hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the post-marketing surveillance\* of paclitaxel.

The evaluation of adverse reactions is based on the following frequencies: Very common ( $\geq 1/10$ ) Common ( $\geq 1/100$  to  $< 1/10$ ) Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) Very rare ( $< 1/10,000$ ) Unknown (frequency cannot be estimated from the available data).

Infections and infestations:	<i>Very common:</i> infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome <i>Uncommon:</i> septic shock <i>Rare:</i> pneumonia*, peritonitis*, sepsis* <i>Very rare*:</i> Pseudomembranous colitis
Blood and lymphatic system disorders:	<i>Very common:</i> myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding <i>Rare :</i> febrile neutropenia* <i>Very rare:</i> acute myeloid leukaemia*, myelodysplastic syndrome*
Immune system disorders:	<i>Very common:</i> minor hypersensitivity reactions (mainly flushing and rash) <i>Uncommon:</i> significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension) <i>Rare:</i> anaphylactic reactions* <i>Very rare:</i> anaphylactic shock* <i>Not known*:</i> Bronchospasm
Metabolism and nutrition disorders:	<i>Rare*:</i> Dehydration <i>Very rare :</i> anorexia* <i>Not known:</i> tumour lysis syndrome*
Psychiatric disorders:	<i>Very rare:</i> confusional stage*

Breast cancer patients who received paclitaxel in the adjuvant setting following AC experienced more neurosensory toxicity, hypersensitivity reactions, arthralgia/myalgia, anaemia, infection, fever, nausea/vomiting and diarrhoea than patients who received AC alone. However, the frequency of these events was consistent with the use of single-agent paclitaxel, as reported above.

### Combination Treatment

The following discussion refers to two major trials for the first-line chemotherapy of ovarian carcinoma (paclitaxel plus cisplatin: over 1,050 patients); two Phase III trials in the first-line treatment of metastatic breast cancer: one investigating the combination with doxorubicin

(paclitaxel plus doxorubicin: 267 patients), another one investigating the combination with trastuzumab (planned subgroup analysis paclitaxel plus trastuzumab: 188 patients) and two Phase III trials for the treatment of advanced NSCLC (paclitaxel plus cisplatin; over 360 patients).

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. Myelosuppression appeared to be less frequent and severe with paclitaxel as a 3-hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

For the first-line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever and diarrhoea were reported more frequently and with greater severity when paclitaxel (220 mg/m<sup>2</sup>) was administered as a 3-hour infusion, 24 hours following doxorubicin (50 mg/m<sup>2</sup>) when compared to standard FAC therapy (5-FU 500 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m<sup>2</sup>)/doxorubicin (50 mg/m<sup>2</sup>) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel/doxorubicin arm.

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 (8% versus 1%), infection (46% versus 27%), chills (42% versus 4%), fever (47% versus 23%), cough (42% versus 22%), rash (39% versus 18%), arthralgia (37% versus 21%), tachycardia (12% versus 4%), diarrhoea (45% versus 30%), hypertonia (11% versus 3%), epistaxis (18% versus 4%), acne (11% versus 3%), herpes simplex (12% versus 3%), accidental injury (13% versus 3%), insomnia (25% versus 13%), rhinitis (22% versus 5%), sinusitis (21% versus 7%), and injection site reaction (7% versus 1%). Some of these frequency differences may be due to the increased number and duration of treatments with the paclitaxel/trastuzumab combination versus single-agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single-agent paclitaxel.

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, cardiac contraction abnormalities ( $\geq 20\%$  reduction of left ventricular ejection fraction) were observed in 15% of patients versus 10% with the standard FAC regimen. Congestive heart failure was observed in  $<1\%$  in both paclitaxel/doxorubicin and standard FAC arms. 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 (New York Heart Association (NYHA) Class I/II 10% versus 0%; NYHA Class III/IV 2% versus 1%) and rarely has been associated with death. In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

### **AIDS-related Kaposi's sarcoma**

Except for haematologic and hepatic undesirable effects (see below), the frequency and severity of undesirable effects are generally similar between Kaposi's sarcoma patients and patients treated with paclitaxel monotherapy for other solid tumours, based on a clinical study including 107 patients.

### ***Blood and the Lymphatic System Disorders***

Bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia ( $<0.5 \times 10^9/l$ ) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for  $>7$  days in 41% and for 30–35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting  $\geq 7$  days was 22%.

Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were three septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal.

Thrombocytopenia was observed in 50% of patients and was severe ( $<50 \times 10^9/l$ ) in 9%. Only 14% experienced a drop in their platelet count by  $<75 \times 10^9/l$  at least once while on treatment. Bleeding episodes related to paclitaxel were reported in  $<3\%$  of patients, but the haemorrhagic episodes were localized.

Anaemia (Hb  $<11$  g/dL) was observed in 61% of patients and was severe (Hb  $<8$  g/dL) in 10%. Red cell transfusions were required in 21% of patients.

### ***Hepatobiliary Disorders***

Among patients ( $>50\%$  on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

### ***Opportunistic Infections***

In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. The most common causative agents were *Cytomegalovirus*, *Herpes Simplex*, *Pneumocystis carinii*, *Mycobacterium avium intracellulare*, *Cryptosporidiosis*, and *Cryptococcal meningitis*.

### ***Renal***

Among the patients treated for Kaposi's sarcoma with paclitaxel, 5 patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other 4 patients had renal impairment with reversible elevations of serum creatinine.

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

## **Accidental Exposure**

Upon inhalation, dyspnoea, chest pain, burning eyes, sore throat and nausea have been reported. Following topical exposure, events have included tingling, burning and redness.

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation 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 via the e-PV desktop applications

([https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD\\_KSExZP/view](https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view)) or search for e-PV Mobile applications on the Google Play or Apple App Store.

## **4.9 Overdose**

There is no known antidote for paclitaxel 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.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacological classification: 9.4 Miscellaneous cytotoxic agents.

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or 'bundles' of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

### **5.2 Pharmacokinetic properties**

The pharmacokinetics of paclitaxel was determined following 3-hour and 24-hour infusions at doses of 135 mg/m<sup>2</sup> and 175 mg/m<sup>2</sup>. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hr/m<sup>2</sup>; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m<sup>2</sup>, indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m<sup>2</sup> to 175 mg/m<sup>2</sup>, the C<sub>max</sub> and AUC<sub>0</sub> values increased 75% and 81%, respectively.

Following an intravenous dose of 100 mg/m<sup>2</sup> given as a 3-hour infusion to 19 Kaposi's sarcoma patients, the mean C<sub>max</sub> was 1,530 ng/ml (range: 761–2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range: 2,609–9,428 ng.hr/ml). Clearance was 20.6 l/h/ m<sup>2</sup> (range: 11–38) and the volume of distribution was 291 l/ m<sup>2</sup> (range: 121–638). The terminal elimination half-life averaged 23.7 hours (range: 12–33).

Inpatient variability in systemic paclitaxel exposure was minimal. There was no evidence of accumulation of paclitaxel with multiple treatment courses.

Following intravenous administration of paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of paclitaxel at dose levels of 135 mg/m<sup>2</sup> and 175 mg/m<sup>2</sup> were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table.

**Table 1: Summary of pharmacokinetic parameters — Mean values**

Dose (mg/m <sup>2</sup> )	Infusion Duration (h)	N (Patients)	C <sub>max</sub> (ng/mL)	AUC(0-∞) (ng·h/mL)	T-half (h)	CLT (L/h/m <sup>2</sup> )
135	24	2	195	6,300	52.7	21.7
175	24	4	365	7,993	15.7	23.8
135	3	7	2170	7,952	13.1	17.7
175	3	5	3650	15,007	20.2	12.2

C<sub>max</sub> = Maximum plasma concentration

AUC(0-∞) = Area under the plasma concentration-time curve from time 0 to infinity CLT = Total body clearance

It appeared that with the 24-hour infusion of paclitaxel, a 30% increase in dose (135 mg/m<sup>2</sup> versus 175 mg/m<sup>2</sup>) increased the C<sub>max</sub> by 87%, whereas the AUC (0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C<sub>max</sub> and AUC (0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at the steady state, with the 24- hour infusion of paclitaxel, ranged from 227 to 688 L/m<sup>2</sup>, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15–135 mg/m<sup>2</sup> given by 1-hour infusions (n=15), 30–275 mg/m<sup>2</sup> given by 6-hour infusions (n=36), and 200–275 mg/m<sup>2</sup> given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CLT and volume of distribution were consistent with the findings in the Phase 3 study.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15–275 mg/m<sup>2</sup> doses of paclitaxel as 1-hour, 6-hour, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m<sup>2</sup> dose of radiolabelled paclitaxel as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the faeces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the faeces, while metabolites, primarily 6α- hydroxypaclitaxel, accounted for the balance. In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α- hydroxypaclitaxel by the cytochrome (CY) P450 isozyme CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel, by CYP3A4. In vitro, the

metabolism of paclitaxel to 6 $\alpha$ hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17 $\alpha$ -ethinyl oestradiol, retinoic acid and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 $\alpha$ hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin  $\leq 2$  times the upper limit of normal (ULN) administered 175 mg/m<sup>2</sup> was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin  $> 2$  times the ULN, there was a statistically non-significant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m<sup>2</sup>), but no observed increase in plasma exposure. The effect of renal dysfunction on the disposition of paclitaxel has not been investigated. Pharmacokinetic parameters obtained from 1 patient undergoing haemodialysis who received a 3-hour infusion of paclitaxel 135 mg/m<sup>2</sup> were within the range of those defined in non-dialysis patients.

In clinical trials where paclitaxel and doxorubicin were administered concomitantly, the distribution and elimination of doxorubicin and its metabolites were prolonged. Total plasma exposure to doxorubicin was 30% higher when paclitaxel immediately followed doxorubicin than when there was a 24-hour interval between drugs.

### **5.3 Preclinical safety data**

#### Carcinogenesis, mutagenesis and impairment of fertility

The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice).

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m<sup>2</sup> basis). At this dose, to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human on a mg/m<sup>2</sup> basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Polyoxyethylated castor oil

Dehydrated alcohol

### **6.2 Incompatibilities**

Castor oil polyoxyl can result in di-(2-ethylhexyl) phthalate [DEHP] leaching from plasticized polyvinyl chloride (PVC) containers, at levels which increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel 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.

### **6.3 Shelf life**

24 months.

### **6.4 Special precautions for storage**

Store below 30°C.

Freezing does not have an adverse effect on the preparation. Refrigerated product may precipitate but will re-dissolve on reaching room temperature with little or no agitation. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. After first use or after dilution, see section 6.3.

### **6.5 Nature and contents of the container**

A tubular USP type I glass vial closed with a 20mm fluoro-coated rubber stopper and a 20mm aluminium flip-off seal.

#### P-Tax 260

Fill volume: 43.4 mL.

Pack size: 1 vial per carton.

#### P-Tax 300

Fill volume: 50 mL.

Pack size: 1 vial per carton.

### **6.6 Special precautions for disposal and other handling**

*Handling:* Paclitaxel is a cytotoxic anticancer medicinal product and caution should be exercised in handling paclitaxel. Dilution should be carried out under aseptic conditions, by trained personnel in a designated area. Appropriate gloves should be used. Contact of paclitaxel with skin and mucous membranes should be avoided.

If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat, and nausea have been reported.

### **Preparation for Intravenous Administration**

Paclitaxel injection must be diluted prior to infusion. Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 25°C for 27 hours when diluted in 0.9% sodium chloride Injection; 5% dextrose injection; 5% dextrose and 0.9% sodium chloride injection or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 mg/mL. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

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.



### *Protection instructions for preparation of Paclitaxel solution for infusion*

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available, mouth cover and goggles should be used.
2. Pregnant women or women who may become pregnant, should not handle this product.
3. Opened containers, like injection vials and infusion bottles and used canules, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of hazardous waste.
4. Follow the instructions below in case of spillage:
  - protective clothing should be worn
  - broken glass should be collected and placed in the container for hazardous waste
  - contaminated surfaces should be flushed properly with copious amounts of cold water
  - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as hazardous waste.
5. In the event of paclitaxel contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
6. In case of contact of paclitaxel with eyes, wash them thoroughly with plenty of cold water. Contact an ophthalmologist immediately.

*Disposal:* All items used for preparation, administration, infusion, or otherwise coming into contact with paclitaxel should be placed in an appropriate safety container and disposed according to local guidelines for the handling of cytotoxic compounds.

## **7. APPLICANT**

Venus Remedies Limited  
51-52, Industrial Area Phase-I  
Panchkula, Haryana - 134113  
India

## **8. MANUFACTURERS**

Venus Remedies Limited  
Manufacturing Unit II, Hill Top Industrial Estate  
Jharmajri EPIP, Phase-I (Extn.), Bhatoli Kalan, Baddi  
Distt. Solan (Himachal Pradesh) - 173205  
India

## **9. REGISTRATION DETAILS**

### P-Tax 260

Zimbabwe registration number: 2023/9.4/6534

Zimbabwe category for distribution: Prescription Preparations (P.P.)

### P-Tax 300

Zimbabwe registration number: 2023/9.4/6535

Zimbabwe category for distribution: Prescription Preparations (P.P.)

## **10. DATE OF REVISION OF THE TEXT**

February 2024