PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0028

UKPAR

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LAY SUMMARY

On 3rd August 2010, the MHRA granted APSLA Limited a Marketing Authorisation (licence) for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 33410/0028). This product is available as a prescription-only medicine (POM).

Paclitaxel is used to treat ovarian cancer, breast carcinoma, non-small cell lung cancer and AIDS-related Kaposi’s sarcoma

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Paclitaxel 6mg/ml Concentrate for Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 33410/0028) to APSLA Limited on the 3rd August 2010. This is a prescription-only medicine (POM) used to treat:

- **Ovarian carcinoma**: in the first-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of 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, paclitaxel is indicated 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 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 failed, 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 (KS) who have failed prior liposomal anthracycline therapy.

This is a national application for Paclitaxel 6mg/ml Concentrate for Solution for Infusion submitted under Article 10(1) of Directive 2001/83/EC, as amended. The application claims to be a generic medicinal product of Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026), which was originally granted a marketing authorisation to Bristol-Myers Squibb Pharmaceuticals Ltd on 18th November 1993.

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation 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.
Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for not submitting a risk management plan for this product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
INN: Paclitaxel

Chemical Name: (2aR,4S,4As,6R,9S,11S,12S,12Ar, 12BbS)-1,2a, 3,4,4a,6,9,10,11,12,12a, 12b-Dodecahydro-4,6,9,10,11,12,12a, 12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5H-cyclodeca[3,4]benz[1,2-b]oxet-5-one 6,12b-diacetate, 12-benzoate,9-ester with(2R,3S)-N-benzoyl-3-phenylisoserine

Chemical Structure:

![Chemical Structure Image]

Molecular Formula: C_{47}H_{51}N_{14}
Molecular Weight: 854
Physical form: White to almost white crystalline powder. Practically insoluble in water, freely soluble in methanol and in methylene dichloride.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of pharmaceutical excipients, namely polyoxyl castor oil, anhydrous citric acid and ethanol.

All excipients are controlled to their respective European Pharmacopoeia specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical development**
The objective of the pharmaceutical development programme was to obtain stable products containing paclitaxel that could be considered generic medicinal product of Taxol 6mg/ml Concentrate for Solution for Infusion. Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles for both the innovator and proposed product are provided. These are satisfactory.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of product. The results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The solution is contained in a Type I flint glass vials with fluororesin laminated bromobutyl rubber stopper and aluminium flip-off tear-off seal, containing 30mg, 100mg, and 300mg of Paclitaxel in 5ml, 16.7ml, or 50ml solution respectively.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with guidelines concerning materials in contact with parenteral products.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years for unopened vials has been set, with no special storage conditions.

After opening before dilution:
After first use and following multiple needle entries and product withdrawals, any unused concentrate maintains microbial, chemical and physical stability when stored below 25°C, protected from light for up to 28 days, unless product has been kept in controlled and validated aseptic conditions. Other in-use storage times and conditions are the responsibility of the user.

After dilution:
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2°C to 8°C and at 25°C for 7 days when diluted in 5% dextrose solution, 5% dextrose in Ringer’s solution, 5% dextrose and 0.9% sodium chloride solution and for 14 days when diluted in 0.9% sodium chloride injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions, the product is recommended for single-dose use only. Any unused product should be discarded immediately after initial use.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application Form (MAA)
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There is no objection to the approval of the product from a pharmaceutical point of view.
PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of paclitaxel are well-known. Thus, the applicant has not provided any new pre-clinical data and none are required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There is no objection to the approval of the product from a pre-clinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics
No new data have been submitted and none are required for applications of this type. This application is for a generic medicinal product of Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026), which was first granted in the UK to Bristol-Myers Squibb Pharmaceuticals Ltd on 18th November 1993. The use of the reference product is well-established in the UK, and both products contain the same quantitative and qualitative composition of the active substance, paclitaxel.

According to Committee for Proprietary Medicinal Products Notes for Guidance on the Investigation of Bioavailability and Bioequivalence, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/QWP/1401/98, sub point 5.1.6, Parenteral solution).

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
No new data have been submitted and none are required for applications of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Marketing Authorisation Application (MAA) Forms
The MAA form is medically satisfactory.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Paclitaxel 6mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
This application is for a generic medicinal product of Taxol 6mg/ml Concentrate for Solution for Infusion, which was first granted in the UK to Bristol-Myers Squibb Pharmaceuticals Ltd on 18th November 1993. The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, paclitaxel.

According to Committee for Proprietary Medicinal Products Notes for Guidance on the Investigation of Bioavailability and Bioequivalence, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/QWP/1401/98, sub point 5.1.6, Parenteral solution).

No new safety data are supplied or required for this generic application. Paclitaxel has well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with paclitaxel is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.
**PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION**  
PL 33410/0028

**STEPS TAKEN FOR ASSESSMENT**

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<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 13\textsuperscript{th} November 2009</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 14\textsuperscript{th} December 2009</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on the quality section on the 21\textsuperscript{st} January 2010 and 26\textsuperscript{th} April 2010 and for the clinical section on the 25\textsuperscript{th} June 2010 and 21\textsuperscript{st} July 2010.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality section on the 17\textsuperscript{th} April 2010 and 22\textsuperscript{nd} June 2010 and on the clinical section on the 12\textsuperscript{th} July 2010 and 22\textsuperscript{nd} July 2010.</td>
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<tr>
<td>5</td>
<td>The application was determined on 3\textsuperscript{rd} August 2010</td>
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PACLITAXEL 6MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
PL 33410/0028

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Paclitaxel 6 mg/ml Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of concentrate for solution for infusion contains 6 mg paclitaxel.
Each vial of 5 ml contains 30 mg of paclitaxel.
Each vial of 16.7 ml contains 100 mg of paclitaxel.
Each vial of 50 ml contains 300 mg of paclitaxel.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
A clear colourless viscous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ovarian carcinoma: in the first-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of 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, paclitaxel is indicated 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 HER-2 at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable (see section 4.4 and 5.1).
As a single agent, paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, 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 (KS) who have failed prior liposomal anthracycline therapy.
Limited efficacy data supports this indication; a summary of the relevant studies is shown in section 5.1.
4.2 **Posology and method of administration**

All patients must be premedicated with corticosteroids, antihistamines, and H2 antagonists prior to paclitaxel, e.g.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration prior to Paclitaxel</th>
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<tbody>
<tr>
<td>dexamethasone</td>
<td>20 mg oral* or IV</td>
<td>For oral administration:</td>
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<tr>
<td></td>
<td></td>
<td>approximately 12 and 6 hours or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for IV administration: 30 to 60 min</td>
</tr>
<tr>
<td>diphenhydramine**</td>
<td>50 mg IV</td>
<td>30 to 60 min</td>
</tr>
<tr>
<td>cimetidine or</td>
<td>300 mg IV 50 mg IV</td>
<td>30 to 60 min</td>
</tr>
<tr>
<td>ranitidine</td>
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* 8-20 mg for KS patients
** or an equivalent antihistamine e.g. chlorpheniramine

Paclitaxel should be administered through an in-line filter with a microporous membrane < 0.22 μm (see section 6.6).

**First-line chemotherapy of ovarian carcinoma:** although other dosage regimens are under investigation, a combination regimen of paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel are recommended: Paclitaxel 175 mg/m² administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m² every three weeks or paclitaxel 135 mg/m², in a 24-hour infusion, followed by cisplatin 75 mg/m², with a 3 week interval between courses (see section 5.1).

**Second-line chemotherapy of ovarian carcinoma:** the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3 week interval between courses.

**Adjuvant chemotherapy in breast carcinoma:** the recommended dose of paclitaxel is 175 mg/m² 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/m²), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see section 4.5 and 5.1).

When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see 5.1). 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 (for detailed trastuzumab posology see the Summary of Product Characteristics of trastuzumab).

**Second-line chemotherapy of breast carcinoma:** the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3-week interval between courses.

**Treatment of advanced non-small cell lung cancer:** the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, followed by cisplatin 80 mg/m², with a 3 week interval between courses.

**Treatment of AIDS-related KS:** the recommended dose of paclitaxel is 100 mg/m² administered as a 3-hour intravenous infusion every two weeks.

Subsequent doses of paclitaxel should be administered according to individual patient tolerance.

Paclitaxel should not be readministered until the neutrophil count is > 1,500/mm³ (> 1,000/mm³ for KS patients) and the platelet count is > 100,000/mm³ (> 75,000/mm³ for KS patients). Patients who experience severe neutropenia (neutrophil count < 500/mm³ for 7 > days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (see section 4.4).

**Patients with hepatic impairment:** Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 4.4 and 5.2). Patients with severe hepatic impairment should not be treated with paclitaxel.
4.3 Contraindications
Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipient, especially polyoxyethylated castor oil (see section 4.4). Paclitaxel is contraindicated during pregnancy and lactation (see section 4.6), and should not be used in patients with baseline neutrophils < 1,500/mm³ (< 1,000/mm³ for KS patients). In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

4.4 Special warnings and precautions for use
Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. Patients must be pretreated with corticosteroids, antihistamines and H2 antagonists (see section 4.2).

Paclitaxel should be given before cisplatin when used in combination (see section 4.5).

Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in < 1% of patients receiving paclitaxel after adequate premedication. 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 the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to >1,500/mm³ (>1,000/mm³ for KS patients) and platelets recover to > 100,000/mm³ (>75,000/mm³ for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; 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 carcinoma. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. 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/m²) 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). For more details see Summary of Product Characteristics of trastuzumab or doxorubicin.

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) for all subsequent courses of paclitaxel is recommended. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of paclitaxel as a three hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by cisplatin.

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. 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 (see section 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 5.2). No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should not be treated with paclitaxel. Since paclitaxel contains ethanol (392.63 mg/ml), consideration should be given to possible CNS and other effects. Special care should be taken to avoid intra-arterial application of paclitaxel, since in animal studies testing for local tolerance severe tissue reactions were observed after intra-arterial application.

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

In KS patients, **severe mucositis** is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

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

Paclitaxel clearance is not affected by cimetidine premedication. 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 (see section 5.2). The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see section 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6α-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 3A4. Studies in KS 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.

4.6 **Pregnancy and lactation**

Paclitaxel has been shown to be embryotoxic and foetotoxic in rabbits, and to decrease fertility in rats. 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, and to inform the treating physician immediately should this occur.

It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation. Breastfeeding should be discontinued for the duration of therapy.
4.7 Effects on ability to drive and use machines
Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that paclitaxel does contain alcohol (see section 4.4 and 6.1).

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. As the KS population is very specific, a special chapter based on a clinical study with 107 patients, is presented at the end of this section.

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. The most frequent significant undesirable effect was bone marrow suppression. Severe neutropenia (< 500 cells/mm³) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir < 50,000/mm³ at least once while on study. Anaemia was observed in 64% of patients, but was severe (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/m² 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m² 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. 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.

Injection site reactions during intravenous administration may lead to localised 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 discoloration 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.

The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the postmarketing surveillance* of paclitaxel.
The frequency of undesirable effects listed below is defined using the following convention:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ System</th>
<th>Very Common ((≥1/10))</th>
<th>Common ((≥1/100 \text{ to } &lt;1/10))</th>
<th>Uncommon ((≥1/1,000 \text{ to } &lt;1/100))</th>
<th>Rare ((≥1/10,000 \text{ to } &lt;1/1000))</th>
<th>Very rare ((&lt;1/10,000), \text{ not known (cannot be estimated from the available data)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome.</td>
<td>septic shock</td>
<td></td>
<td></td>
<td>Pneumonia, peritonitis, sepsis</td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders:</td>
<td>Myelo suppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding.</td>
<td></td>
<td>febrile neutropenia</td>
<td></td>
<td>acute myeloid leukaemia, myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>minor hypersensitivity reactions (mainly flushing and rash)</td>
<td>significant hypersensitivity reactions requiring therapy (e.g., hypotension, angiooedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension)</td>
<td></td>
<td>Anaphylactic reactions</td>
<td>anaphylactic shock</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>anorexia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>confusional stage</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>neurotoxicity (mainly: peripheral neuropathy)</td>
<td></td>
<td></td>
<td></td>
<td>motor neuropathy (with resultant minor distal weakness)</td>
<td>autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td>ototoxicity, hearing loss, tinnitus, vertigo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Brady cardia</td>
<td>Cardiomyopathy, symptomatic entricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction</td>
<td>atrial fibrillation, supraventricular tachycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>Hypertension, thrombosis, thrombo phlebitis</td>
<td>shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure</td>
<td>cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting, diarrhoea, mucosal inflammation</td>
<td>bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis</td>
<td>mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, transient and mild nail and skin changes.</td>
<td>pruritus, rash, erythema</td>
<td>Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>--------------------------------------</td>
<td>-------------------------------------------------</td>
<td>--------------------------</td>
<td>-----------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>arthralgia, myalgia.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>injection site reactions (including localised oedema, pain, erythema, induration, on occasion extra vacation can result in cellulitis, skin fibrosis and skin necrosis).</td>
<td>asthenia, pyrexia, dehydration, oedema, malaise</td>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>severe elevation in AST (SGOT), severe elevation in alkaline phosphatase</td>
<td>severe elevation in bilirubin</td>
<td>increase in blood creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients), another one investigating the combination with trastuzumab (planned subgroup analysis paclitaxel + trastuzumab: 188 patients) and two phase
III trials for the treatment of advanced NSCLC (paclitaxel + cisplatin: over 360 patients) (see section 5.1).

When administered as a three 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 three 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/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m²) / doxorubicin (50 mg/m²) 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% vs 1%), infection (46% vs 27%), chills (42% vs 4%), fever (47% vs 23%), cough (42% vs 22%), rash (39% vs 18%), arthralgia (37% vs 21%), tachycardia (12% vs 4%), diarrhoea (45% vs 30%), hypertonia (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 3%), herpes simplex (12% vs 3%), accidental injury (13% vs 3%), insomnia (25% vs 13%), rhinitis (22% vs 5%), sinusitis (21% vs 7%), and injection site reaction (7% vs 1%). 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.

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, cardiac contraction abnormalities (20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with 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 (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). 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 KS 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 (< 500 cells/mm³) 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 > 7 days was 22%.

Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 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 (< 50,000 cells/mm³) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm³, at least once while on treatment. Bleeding episodes related to paclitaxel were reported in < 3% of patients, but the haemorrhagic episodes were localised.
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.

**Hepato-biliary 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.

### 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.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group**: Antineoplastic agent  
**ATC code**: L01CD01

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation 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.

In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750 mg/m² / cisplatin 75 mg/m²) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage IIb-c, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m² over 3 hr) followed by cisplatin (75 mg/m²) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either paclitaxel (135 mg/m² over 24 hrs) followed by cisplatin (75 mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residual disease after staging laparotomy, or with distant metastases. While the two different paclitaxel posologies were not compared with each other directly, in both trials patients treated with paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant paclitaxel therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p = 0.0014), and a significant reduction of 19% in the risk of death (p = 0.0044) relative to patients receiving AC alone. Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/ unknown tumours, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95%CI: 0.78-1.07). However, the design of the study did not investigate the effect of extended AC therapy beyond 4 cycles. It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel 8 cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225 mg/m² following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006) ; paclitaxel treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumour had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92); in the
In the first-line treatment of metastatic breast cancer, the efficacy and safety of paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials.

In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m²) followed after 24 hours by paclitaxel (220 mg/m² by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), both administered every three weeks for eight courses. In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of paclitaxel/doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the paclitaxel/doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second pivotal study, the efficacy and safety of the paclitaxel and Herceptin® combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of Herceptin® in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and paclitaxel (175 mg/m²) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175 mg/m²) 3-hour infusion, every three weeks in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. Paclitaxel was administered every three weeks for at least six courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for the paclitaxel/trastuzumab combination in terms of time to progression (6.9 vs. 3.0 months), response rate (41% vs. 17%), and duration of response (10.5 vs. 4.5 months) when compared to paclitaxel alone. The most significant toxicity observed with the paclitaxel/trastuzumab combination was cardiac dysfunction (see section 4.8).

In the treatment of advanced NSCLC, paclitaxel 175 mg/m² followed by cisplatin 80 mg/m² has been evaluated in two phase III trials (367 patients on paclitaxel containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100 mg/m², the other used teniposide 100 mg/m² followed by cisplatin 80 mg/m² as comparator (367 patients on comparator). Results in each trial were similar. For the primary outcome of mortality, there was no significant difference between the paclitaxel containing regimen and the comparator (median survival times 8.1 and 9.5 months on paclitaxel containing regimens, 8.6 and 9.9 months on comparators). Similarly, for progression-free survival there was no significant difference between treatments. There was a significant benefit in terms of clinical response rate. Quality of life results are suggestive of a benefit on paclitaxel containing regimens in terms of appetite loss and provide clear evidence of the inferiority of paclitaxel containing regimens in terms of peripheral neuropathy (p < 0.008).

In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in a non-comparative study in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was best tumour response. Of the 107 patients, 63 were considered resistant to liposomal anthracyclines. This subgroup is considered to constitute the core efficacy population. The overall success rate (complete/partial response) after 15 cycles of treatment was 57% (CI 44 - 70%) in liposomal anthracycline-resistant patients. Over 50% of the responses were apparent after the first 3 cycles. In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one at least 2 months prior to treatment with paclitaxel (60.9%). The median time to progression in the core population was 468 days (95% CI 257-NE). Median survival could not be computed, but the lower 95% bound was 617 days in core patients.
5.2 Pharmacokinetic properties

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations.

The pharmacokinetics of paclitaxel were determined following 3 and 24 hour infusions at doses of 135 and 175 mg/m². 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/m²; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m², 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/m² to 175 mg/m², the C_max and AUC→∞ values increased 75% and 81%, respectively.

Following an intravenous dose of 100 mg/m² given as a 3-hour infusion to 19 KS patients, the mean C_max 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/hr/m² (range 11-38) and the volume of distribution was 291 l/m² (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

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

In vitro studies of binding to human serum proteins indicate that 89-98% of drug is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.

The disposition of paclitaxel has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome P450 enzymes. Following administration of a radiolabelled paclitaxel, an average of 26, 2 and 6% of the radioactivity was excreted in the faeces as 6α-hydroxy paclitaxel, 3'-p-hydroxy paclitaxel, and 6α-3'-p-dihydroxy paclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, -3A4, and both -2C8 and -3A4 respectively. The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a 3-hour infusion of paclitaxel 135 mg/m² 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.

For use of paclitaxel in combination with other therapies, please consult the Summary of Product Characteristics of cisplatin, doxorubicin or trastuzumab for information on the use of these medicinal products.

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel is a potential carcinogenic and genotoxic agent, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be mutagenic in both in vitro and in vivo mammalian test systems.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Ethanol
Polyoxyl castor oil (Cremophor)
6.2 Incompatibilities
Polyoxyethylated castor oil can result in DEHP (di-(2-ethylhexyl) phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted paclitaxel should be carried out using non-PVC-containing equipment.

6.3 Shelf life
Vial before opening:
2 years

After opening before dilution:
After first use and following multiple needle entries and product withdrawals, any unused concentrate maintains microbial, chemical and physical stability when stored below 25°C, protected from light for up to 28 days, unless product has been kept in controlled and validated aseptic conditions. Other in-use storage times and conditions are the responsibility of the user.

After dilution:
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2°C to 8°C and at 25°C for 7 days when diluted in 5% dextrose solution, 5% dextrose in Ringer’s solution, 5% dextrose and 0.9% sodium chloride solution and for 14 days when diluted in 0.9% sodium chloride injection.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Vial before opening:
This medicinal product does not require any special temperature storage conditions.

After opening before dilution:
Do not store above 25°C. Store in the original package in order to protect from light.

Diluted solutions: See section 6.3.
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.

6.5 Nature and contents of container
Type 1flint glass vials (with 13 mm & 20 mm fluororesin laminated bromobutyl rubber stopper and aluminium flip-off tear-off seal) contain 30 mg, 100 mg, and 300 mg of Paclitaxel in 5 ml, 16.7 ml, or 50 ml solution respectively.

The vials are packaged individually in a carton. Boxes containing 10 cartons are also available. Not all presentations may be marketed.
6.6 Special precautions for disposal

Handling: as with all antineoplastic agents, caution should be exercised when handling paclitaxel. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Adequate protective gloves should be worn. Precautions should be taken to avoid contact with the skin and mucous membranes. In the event of contact with the skin, the area should be washed with soap and water. Following topical exposure, tingling, burning and redness have been observed. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

If unopened vials are refrigerated, a precipitate may form that redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

Following multiple needle entries and product withdrawals, the vials maintain microbial, chemical and physical stability for up to 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

The Chemo-Dispensing Pin device or similar devices with spikes should not be used since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.

Preparation for IV administration: prior to infusion, paclitaxel must be diluted using aseptic techniques in 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or 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.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2°C to 8°C and at 25°C for 7 days when diluted in 5% dextrose solution, 5% dextrose in Ringer’s solution, 5% dextrose and 0.9% sodium chloride solution and for 14 days when diluted in 0.9% sodium chloride injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

After dilution the solution is for single use only.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Paclitaxel should be administered through an in-line filter with a microporous membrane 0.22 μm. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.

There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24 hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the super saturation of the diluted solution. To reduce the precipitation risk, paclitaxel should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

To minimise patient exposure to DEHP which may be leached from plasticised PVC infusion bags, sets, or other medical instruments, diluted paclitaxel solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Use of filter devices (e.g. IVEX-2®) which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Disposal: All items used for preparation, administration 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 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland.

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0028
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  
03/08/2010

10 DATE OF REVISION OF THE TEXT  
03/08/2010
PATIENT INFORMATION LEAFLET (PIL)

PACKAGE LEAFLET: INFORMATION FOR THE USER

PACLITAXEL 6 mg/ ml
CONCENTRATE FOR SOLUTION FOR INFUSION
(Paclitaxel)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Paclitaxel is and what it is used for
2. Before you use Paclitaxel
3. How to use Paclitaxel
4. Possible side effects
5. How to store Paclitaxel
6. Further information

1. WHAT PACLITAXEL IS AND WHAT IT IS USED FOR

The name of your medicine is Paclitaxel 6 mg/ ml concentrate for solution for infusion. Paclitaxel is available as vials containing 30 mg, 100 mg, or 200 mg paclitaxel in a 6 mg/ml solution which has to be diluted before being given to you.

Paclitaxel is used to treat:
Ovarian cancer: either as initial therapy in combination with the platinum-containing medicine, cisplatin, or as a second-line treatment when other platinum-containing treatments have not worked. Breast cancer: As initial therapy either in combination with a medicine belonging to the group known as anthracyclines (i.e. doxorubicin, epirubicin, daunorubicin) for patients that are suitable, or with a medicine called trastuzumab. As adjuvant therapy following treatment with anthracycline and cyclophosphamide (AC). On its own in patients who have not responded to standard treatments using anthracyclines, or for whom such treatment should not be used. Non-small cell lung cancer: in combination with cisplatin, in patients who are not candidates for potentially curative surgery and/or radiotherapy. AIDS-related Kaposi's sarcoma: where other treatments i.e. liposomal anthracyclines have not worked.

2. BEFORE YOU USE PACLITAXEL

Do not use PACLITAXEL
- if you have shown signs of hypersensitivity (severe) allergy to paclitaxel or any other ingredients on previous occasions
- if you are pregnant or breastfeeding
- if the number of white blood cells (neutrophils) is too low. This is measured by a doctor or nurse.
- in patients with Kaposi's sarcoma, this product should not be used if you have a serious uncontrolled infection.
- if you are unsure about anything, ask your doctor or pharmacist.

Take special care with PACLITAXEL
- if you have heart disease or liver problems
- when diarrhoea occurs during or shortly after the treatment with paclitaxel (pseudomembranous colitis)
- if you have Kaposi's sarcoma and severe inflammation of the mucus membrane (membranes lining the passages of the body that open to the outside) occurs
- if you have had nerve problems in your hands or in feet, such as numbness, tingling or burning (peripheral neuropathy)
- if you have blood problems, such as changes in the number of some cells
- if paclitaxel is given to you in combination with radiotherapy of the lung.

It is important to tell the doctor about any of your medical conditions, whether they are included in the above lists or not. Please tell your doctor if you are taking, or have recently taken, any other medicines, including ones that are not prescribed for you.

**Using other medicines**
- please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription
- when used in combination, paclitaxel should be given before cisplatin
- paclitaxel should be given 24 hours after dexamethasone
- special care should be observed if you are taking medicines which influence the metabolism of paclitaxel such as: erythromycin, fluoxetine, gemfibrozil, rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, and nevirapine and for HIV patients receiving protease inhibitors (ritonavir, nelfinavir) as concomitant therapy
- if you go into hospital, let the medical staff know you are taking paclitaxel.

**Pregnancy and breast-feeding**

**Pregnancy**
Do not use paclitaxel if you think you are pregnant or you are trying to become pregnant. Paclitaxel can damage the unborn baby.

Pregnancy must be avoided and both partners should use reliable contraception during treatment with paclitaxel and for at least 6 months after treatment. Tell your doctor immediately if you do become pregnant.

**Breast-feeding**
Paclitaxel should not be used when you are breast-feeding. You should stop breast feeding while you are being treated with paclitaxel. Do not restart breast feeding until your doctor tells you it is safe to do so.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
There is no reason why you cannot continue driving between courses of paclitaxel but you should remember that this medicine contains some alcohol and it may be unwise to drive or use machines immediately after a course of treatment. As in all cases, you should not drive or use machines if you feel dizzy or light-headed.

**Important Information about PACLITAXEL**

This medicinal product contains polyoxyl castor oil which may cause severe allergic reactions.

It also contains 49.7% vol ethanol (alcohol), i.e. up to 21 g (19.5 g) per average dose, equivalent to 740 ml (687 ml) of a 3.5% vol beer, 190 ml (176.4) of a 14% vol wine per dose. This may be harmful to patients suffering from alcoholism.

It should also be taken into account when considering using this medicine in children and high risk groups such as those with liver disease or epilepsy. The alcohol in this medicine may also affect the way other medicines work.

3. **HOW TO USE PACLITAXEL**

If you are prescribed Paclitaxel, it will be given to you by doctors or nurses experienced in giving chemotherapy. Paclitaxel will normally be given to you by a doctor or a nurse through a drip (infusion) into a vein. Your doctor will decide what dose to give and the number of days treatment you will receive depending upon your condition. The dose you receive will be based on your body surface area and the result of blood tests carried out before treatment. The usual dose is 175mg/m², body surface area, given over 3 hours followed by the cisplatin for ovarian and lung cancer. You will also receive cisplatin after paclitaxel if you are being treated for lung cancer. For breast cancer recommended dose is 175mg/m² administered over 3 hours following therapy with anthracycline and cyclophosphamide. When used in combination with dexamethasone paclitaxel will be administered 24 hours after dexamethasone at a dose of 220 mg/m². The timing of paclitaxel administration after trastuzumab will depend on how you react to this medicine.
If you are given too much PACLATAXEL
Your dose will be carefully calculated by the doctors, so overdose is unlikely. However, if too much is given this is likely to make the usual side effects worse, particularly blood disorders, numbness/tingling especially of the arms, hands, legs or feet and stomach upsets including vomiting and diarrhoea.

4. POSSIBLE SIDE EFFECTS

Like all medicines, paclitaxel can cause side effects, although not everybody gets them.

The following side effects may occur after treatment with Paclitaxel concentrate for solution for infusion.

The most frequent side effects are hair loss and decreased blood cell count. Your hair grows back and your blood cell count returns to normal after you have finished your paclitaxel treatment.

If any of the following happen, tell the doctor immediately

- any abnormal bruising, bleeding, or signs of infections such as a sore throat and high temperature
- severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
- breathlessness and dry cough due to damage to the lung
- reaction at the injection site, e.g. local swelling, pain, redness.

Other known side effects are

Very common (affects more than 1 out of 10 people):

- an effect on the bone marrow, which can cause decreased numbers of some blood cells. This may cause anaemia. It can also lead to infections, mainly urinary tract and upper respiratory tract infections with reported cases of fatal outcome pain, redness or swelling at the injection site
- decreased number of blood platelets and bleeding
- milder allergic (hypersensitivity) reactions, such as flushing and rash
- nerve problems affecting the hands and or feet (peripheral neuropathy), which can cause tingling feelings in the skin, numbness and/or pain
- low blood pressure
- feeling sick (nausea), being sick (vomiting) and diarrhoea
- hair loss
- muscle or joint pain
- inflammation of areas such as the lining of the mouth.

Common (affects more than 1 out of 100 people):

- slow heart beat (pulse)
- mild changes in nail and skin which soon disappear
- painful swelling and inflammation where the injection is given which may cause tissue hardening (occasionally cellulitis, thickening and scarring of the skin (skin fibrosis), death of skin cells(skin necrosis))
- changes in blood tests that check how the liver is working.

Uncommon (affects less than 1 out of 100 people):

- a state of shock resulting from blood poisoning
- serious allergic (hypersensitivity) reactions with e.g. decreased or increased blood pressure, swelling of the face, difficulty in breathing, skin rash, chills back pain, chest pain, fast heart beat, abdominal pain, pain in arms and legs, sweating
- serious heart problems like heart muscle degeneration (cardiomyopathy), serious changes in your heart's rhythm even with fainting heart attack
- increased blood pressure
- blood clot (thrombosis), inflammation of a vein in connection with blood clots.
- yellowing of the skin (jaundice).
Rare (affects less than 1 out of 1,000 people):
- pneumonia
- reduced number of a type of white blood cell with fever (febrile neutropenia)
- serious allergic (anaphylactic) reaction. Effects on the nerves, which can cause muscle weakness in the arms and legs
- difficulty in breathing, fluid in the lungs, inflammation of the lungs and other lung problems (lung fibrosis, pulmonary embolism), markedly impaired pulmonary function (respiratory failure)
- itching, rash and reddened skin
- weakness, high temperature (fever), dehydration, oedema, feeling ill
- blood poisoning
- blockage of the intestines, penetration of the wall of the small intestine or large bowel, inflammation of the lining of the belly (peritonitis), inflammation of the intestine caused by inadequate blood supply, inflammation of the peritoneum
- increased level of the substance creatinine in the blood.

Very rare (occurs with less than 1 out of 10,000 of the users):
- acute leukaemia (a type of blood cancer), myelodysplastic syndrome (a diverse collection of blood cell disorders)
- life threatening allergic reaction (anaphylactic shock)
- loss of appetite, shock due to decreased blood pressure, cough
- effects on the nervous system which can cause paralysis of the intestines (gut) and a decrease in blood pressure when standing up or sitting up from a lying down position
- fits (epileptic seizures), cramps, confusion, dizziness, alteration in brain function or structure, headaches, loss of the ability to coordinate muscular movement
- problems with eyesight and visual disturbances, usually in patients given larger doses
- reduction or loss of hearing, ringing in the ears (tinnitus), vertigo
- abnormal heart rhythm (atrial fibrillation, supraventricular tachycardia).
- a blood clot in the mesenteric artery, pseudomembranous colitis (an infection of the colon caused by specific bacteria), inflammation of the oesophagus, constipation, collection of fluid in the abdomen (belly).
- severe inflammation of the large bowel presenting with fever, watery or bloody diarrhoea, and crampy abdominal pain (necrotizing colitis).
- death of liver cells (necrosis of the liver), confusion and other effects (hepatic encephalopathy) caused by changes in the way the liver works (both with reported causes of fatal outcome)
- hives (urticaria) scaling and shedding of the skin usually accompanied by redness
- severe inflammatory eruption of the skin and mucous membranes (severity ranging from erythema multiforme to Stevens-Johnson syndrome to the most serious toxic epidermal necrolysis (TEN)).
- disintegration of nails. Hands and feet should be protected against sunshine during the treatment time.

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PACLITAXEL

Keep out of the reach and sight of children.

This medicine should not be used after the expiry date which is stated on the vial label and carton after “EXP”. The expiry date refers to the last day of that month.

Your medication should not be stored above 25°C. The vials should be kept in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. FURTHER INFORMATION

What PACLITAXEL Concentrate for solution for infusion contains
The active substance is paclitaxel.
The other ingredients are citric acid anhydrous, ethanol and polyoxyl castor oil.
Each ml contains 6 mg of the active ingredient paclitaxel.

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

What PACLITAXEL Concentrate for solution for infusion looks like and contents of the pack
Paclitaxel 6 mg/ml concentrate for solution for infusion is a clear colourless viscous solution and is packed into type 1 flint glass vials.

Pack Sizes:
1 x 5 ml vial (30mg/5ml)
1 x 20 ml vial (100mg/16.7ml)
1 x 50 ml vial (300mg/50ml)
The vials are packaged individually in a carton. Boxes containing 10 cartons are also available.
Not all presentations may be marketed.

Marketing Authorisation Holder:
APSLA Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturer:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97-107 Uxbridge Road, Ealing, London W5 5TL

Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97-107 Uxbridge Road, Ealing, London W5 5TL

This leaflet was last revised in April 2010
UKPAR Paclitaxel 6mg/ml Concentrate for Solution for Infusion

LABELLING

Paclitaxel 6 mg/ml Concentrate for solution for infusion
Cytotoxic
For single use only.
Discard any unused solution immediately after use.
Do not use if you notice any particulate matter or discolouration.
Read the package leaflet before use.

Paclitaxel 6 mg/ml Concentrate for solution for infusion
For intravenous use only.
Must be diluted before use.

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Chemicals (Europo) Ltd., 9th Floor, C.P. House, 9-107 Uxbridge Road, Ealing,
London W5 5TH

Paclitaxel 6 mg/ml Concentrate for solution for infusion
Cytotoxic For intravenous use only.
Read the package leaflet before use.
Must be diluted before use.
Keep the vial in the outer carton in order to protect from light.
Do not store above 25°C.

30 mg in 5 ml

Over Printing Area
Paclitaxel 6 mg/ml Concentrate for solution for infusion

100 mg in 16.7 ml

For intravenous use only.
Must be diluted before use.

Cytotoxic For intravenous use only.
Read the package leaflet before use.
Must be diluted before use.
Keep the vial in the outer carton in order to protect from light.
Do not store above 25°C.
Paclitaxel 6 mg/ml Concentrate for solution for infusion

Cytotoxic

Read the package leaflet before use.
Must be diluted before use.
Keep the vial in the outer carton in order to protect from light.
Do not store above 25°C.