

**PACLITAXEL 6 MG/ML CONCENTRATE  
FOR SOLUTION FOR INFUSION**

**(PACLITAXEL)**

**PL 18727/0009**

**UKPAR**

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**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dabur Oncology plc a Marketing Authorisation (licence) for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 18727/0009) on 7<sup>th</sup> June 2007. This is a prescription-only medicine (POM) used to treat various types of cancer.

Paclitaxel 6mg/ml Concentrate for Solution for Infusion contains the active ingredient Paclitaxel. Paclitaxel is derived from the bark and needles of the European Yew Tree, *Taxus baccata*. A number of anti-cancer drugs have been isolated from this source and are known as taxanes. Paclitaxel is used either on its own, or in combination with other anti-cancer agents, to treat a variety of cancers, including ovarian cancer, breast cancer, non-small cell lung cancer, and AIDS-related Kaposi's sarcoma.

The proposed product was considered to be a generic version of the reference product Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026, Bristol-Myers Squibb Pharmaceuticals Ltd).

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

**PACLITAXEL 6 MG/ML CONCENTRATE  
FOR SOLUTION FOR INFUSION  
(PACLITAXEL)  
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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted Dabur Oncology plc a Marketing Authorisation for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 18727/0009) on 7<sup>th</sup> June 2007. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged, complex application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026), marketed by Bristol-Myers Squibb Pharmaceuticals Ltd and authorised on 18 November 1993.

Paclitaxel 6mg/ml Concentrate for Solution for Infusion contains the active ingredient paclitaxel and is indicated for the treatment of ovarian carcinoma, breast carcinoma, advanced non-small cell lung carcinoma, and AIDS-related Kaposi's sarcoma, either on its own or in combination with other anti-cancer agents, and as initial or secondary therapy, as described in the SPC.

Paclitaxel is a member of the taxane group of antineoplastic agents. It is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. 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.

## PHARMACEUTICAL ASSESSMENT

### ACTIVE SUBSTANCE

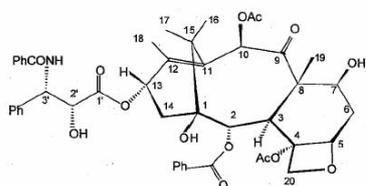
#### Paclitaxel

Nomenclature:

INN: Paclitaxel

Chemical name: [2aR-[2a $\alpha$ ,4 $\beta$ ,4a $\beta$ ,6 $\beta$ ,9 $\alpha$ ( $\alpha$ R\*, $\beta$ S\*)11 $\alpha$ ,12 $\alpha$ ,12a $\alpha$ ,12b $\alpha$ ]]- $\beta$ -(Benzoylamino)- $\alpha$ -hydroxybenzenepropanoic acid 6, 12b-bis(acetyloxy)-12-(benzyloxy)-2a,3,4,4a,5,6,9,10, 11, 12, 12a, 12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cycleodeca[3,4]benz[1,2-b]oxet-9-yl ester

Structure:



Molecular formula: C<sub>47</sub>H<sub>51</sub>NO<sub>14</sub>

Molecular weight: 854

CAS No: 33069-62-4

Physical form: A white or almost white crystalline powder

Solubility: Practically insoluble in water, freely soluble in methanol and in methylene dichloride

The active substance, paclitaxel, is the subject of a European Pharmacopoeia monograph.

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 specifications are in place for all starting materials and reagents, as well as for reference standards used, and these are supported by relevant Certificates of Analysis.

Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided based on the US Pharmacopoeia monograph. Satisfactory details have been provided for the compendial and non-compendial test methods.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The active substance, paclitaxel, is stored in appropriate packaging. It is packed in double LDPE (low density polyethylene) bags which are placed into plastic jars whose lids are wrapped with parafilm; these are then placed in opaque fibreboard drums and sealed. Specifications and Certificates of Analysis for all packaging components used have been provided. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

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

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 24 months, when stored in the proposed packaging.

## **DRUG PRODUCT**

### **Description & Composition**

The drug product is presented as a clear, colourless to yellow, slightly viscous 6mg/ml solution, which has to be diluted before being given to you.

Other ingredients consist of pharmaceutical excipients, namely macrogolglycerol ricinoleate and ethanol. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used.

A 2% overage of ethanol is added to compensate for losses during the manufacturing process. This is acceptable.

### **Impurity profiles**

Satisfactory comparative impurity data were presented for the test and reference products. The impurities were within the specification limits.

### **Pharmaceutical development**

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

### **Finished product specification**

The finished product specification is satisfactory and complies with the requirements of the Ph. Eur. monograph. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 drug product is packed in Type I transparent glass vials of size 5ml, 20ml, and 50ml, containing 30mg, 100mg, and 300mg paclitaxel respectively in a 6mg/ml strength solution. The vials are sealed with chlorobutyl rubber stoppers and

aluminium flip-off caps. The vials are packaged individually, with the product information leaflet, in cardboard outer cartons.

All primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, with storage instructions 'Do not store above 25°C' and 'Store in the original package to protect from light'. This is satisfactory. For storage conditions of the diluted medicinal product, refer to the SPC.

### **Bioequivalence Study**

Bioequivalence studies are not necessary to support this application for a parenteral product.

### **EXPERT REPORT**

The quality overview is written by an appropriately qualified expert and is satisfactory. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

### **PRODUCT INFORMATION:**

#### **Summary of Product Characteristics**

The approved SPC is consistent with that for the reference product and is satisfactory.

#### **Patient Information Leaflet**

The approved PIL is in line with the final SPC and is satisfactory.

#### **Labelling**

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

#### **Conclusion**

The proposed product, Paclitaxel 6mg/ml Concentrate for Solution for Infusion, has been shown to be a generic version of the reference product, Taxol 6mg/ml Concentrate for Solution for Infusion, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

## **PRECLINICAL ASSESSMENT**

The application was submitted as a national, abridged, complex application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

## **CLINICAL ASSESSMENT**

### **INDICATIONS**

Paclitaxel 6mg/ml Concentrate for Solution for Infusion is indicated for the treatment of ovarian carcinoma, breast carcinoma, advanced non-small cell lung carcinoma, and AIDS-related Kaposi's sarcoma, either on its own or in combination with other anti-cancer agents, and as initial or secondary therapy, as described in the SPC.

### **CLINICAL PHARMACOLOGY**

No new data are submitted and none are required for this type of application.

### **EFFICACY**

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical expert report

Paclitaxel 6mg/ml Concentrate for Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product Taxol. Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

### **SAFETY**

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical expert report.

### **EXPERT REPORT**

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

### **CONCLUSION**

The grounds for establishing the proposed product as a generic version of the reference product, Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Paclitaxel 6mg/ml Concentrate for Solution for Infusion has a favourable benefit-to-risk ratio. Therefore, the grant of a Marketing Authorisation is recommended on medical grounds.

## **OVERALL CONCLUSION AND RISK BENEFIT 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 an application of this type.

### **EFFICACY**

The applicant's Paclitaxel 6mg/ml Concentrate for Solution for Infusion (PL 18727/0009) has been demonstrated to be a generic version of the reference product, Taxol 6mg/ml Concentrate for Solution for Infusion (PL 11184/0026, Bristol-Myers Squibb Pharmaceuticals Ltd).

No new or unexpected safety concerns arise from this application.

### **PRODUCT LITERATURE**

The approved SPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with paclitaxel is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

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**STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the marketing authorisation application on 5<sup>th</sup> January 2007
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 6<sup>th</sup> March 2007
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 20<sup>th</sup> March 2007
- 4 The applicant responded to the MHRA's request, providing further information for the quality sections on 2<sup>nd</sup> May 2007
- 5 The application was determined on 7<sup>th</sup> June 2007

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Paclitaxel 6mg/ml Concentrate for Solution for Infusion is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml Concentrate for Solution for Infusion contains 6 mg Paclitaxel.

Each vial of 5 ml contains 30 mg, 16.7 ml contains 100 mg and 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.

Paclitaxel is a clear, colourless to slightly yellow 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 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 H<sub>2</sub> antagonists prior to Paclitaxel, e.g.

Drug	Dose	Administration prior to Paclitaxel
Dexamethasone	20 mg oral* or I.V.	For oral administration: approximately 12 and 6 hours or for I.V. administration: 30 to 60 min
Diphenhydramine**	50 mg I.V.	30 to 60 min
cimetidine or ranitidine	300 mg I.V. 50 mg I.V.	30 to 60 min

\* 8 to 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 Special precautions for disposal and other handling).

**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/m<sup>2</sup> administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m<sup>2</sup> every three weeks or Paclitaxel 135 mg/m<sup>2</sup>, in a 24-hour infusion, followed by cisplatin 75 mg/m<sup>2</sup>, with a 3 week interval between courses (see Section 5.1 Pharmacodynamic Properties).

**Second-line chemotherapy of ovarian 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.

**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 (see 4.5 and 5.1).

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 (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 Herceptin<sup>®</sup>).

**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.

**Treatment of advanced NSCLC:** the recommended dose of Paclitaxel is 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.

**Treatment of AIDS-related KS:** the recommended dose of Paclitaxel is 100 mg/m<sup>2</sup> 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  $\geq 1,500/\text{mm}^3$  ( $\geq 1,000/\text{mm}^3$  for KS patients) and the platelet count is  $\geq 100,000/\text{mm}^3$  ( $\geq 75,000/\text{mm}^3$  for KS patients). Patients who experience severe neutropenia (neutrophil count  $< 500/\text{mm}^3$  for  $\geq 7$  days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (see 4.4).

**Patients with hepatic impairment:** Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see 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 Macrogolglycerol Ricinoleate (Purified, Cremophor ELP – CR) (see 4.4).

Paclitaxel is contraindicated during pregnancy and lactation (see 4.6), and should not be used in patients with baseline neutrophils  $< 1,500/\text{mm}^3$  ( $< 1,000/\text{mm}^3$  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  $\text{H}_2$  antagonists (see 4.2).

Paclitaxel should be given before cisplatin when used in combination (see 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  $\geq 1,500/\text{mm}^3$  ( $\geq 1,000/\text{mm}^3$  for KS patients) and platelets recover to  $\geq 100,000/\text{mm}^3$  ( $\geq 75,000/\text{mm}^3$  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 ( $\text{mg}/\text{m}^2$ ) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further

therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1 to 2 cycles). For more details see Summary of Product Characteristics of Herceptin® 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 to 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 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see 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 (393.4 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 gynecological 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 5.2).

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 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 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 have influence on the ability to drive and use machines. However, it should be noted that Paclitaxel does contain alcohol (see 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/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  $<50,000$ /mm<sup>3</sup> 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/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.

**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: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

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
Blood and the 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
Metabolism and nutrition disorders:	<i>Very rare*</i> : <i>anorexia</i>
Psychiatric disorders:	<i>Very rare*</i> : <i>confusional stage</i>
Nervous system disorders:	<i>Very common</i> : <i>neurotoxicity (mainly: peripheral neuropathy)</i>  <i>Rare*</i> : <i>motor neuropathy (with resultant minor distal weakness)</i>  <i>Very rare*</i> : <i>autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia</i>
Eye disorders:	<i>Very rare*</i> : <i>optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended</i>
Ear and labyrinth disorders:	<i>Very rare*</i> : <i>ototoxicity, hearing loss, tinnitus, vertigo</i>
Cardiac disorders:	<i>Common</i> : <i>bradycardia</i>  <i>Uncommon</i> : <i>cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction</i>  <i>Very rare*</i> : <i>atrial fibrillation, supraventricular tachycardia</i>

Vascular disorders:	<i>Very common : hypotension</i> <i>Uncommon: hypertension, thrombosis, thrombophlebitis</i> <i>Very rare* : shock</i>
Respiratory, thoracic and mediastinal disorders:	<i>Rare* : dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure</i> <i>Very rare* : cough</i>
Gastrointestinal disorders:	<i>Very common : nausea, vomiting, diarrhoea, mucosal inflammation</i> <i>Rare* : bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis</i> <i>Very rare* : mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis</i>
Hepato-biliary disorders:	<i>Very rare* : hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)</i>
Skin and subcutaneous tissue disorders:	<i>Very common : alopecia</i> <i>Common: transient and mild nail and skin changes</i> <i>Rare* : pruritus, rash, erythema</i> <i>Very rare* : Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)</i>
Musculoskeletal, connective tissue and bone disorders:	<i>Very common: arthralgia, myalgia</i>
General disorders and administration site conditions:	<i>Common : injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)</i> <i>Rare* : asthenia, pyrexia, dehydration, oedema, malaise</i>
Investigations:	<i>Common : severe elevation in AST (SGOT), severe elevation in alkaline phosphatase</i> <i>Uncommon: severe elevation in bilirubin</i> <i>Rare* : increase in blood creatinine</i>

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 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/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% 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** ( $\geq 20\%$  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/mm<sup>3</sup>) 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 to 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 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/mm<sup>3</sup>) in 9%. Only 14% experienced a drop in their platelet count <75,000 cells/mm<sup>3</sup>, 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 Agents – Plant Alkaloids and other natural products; Taxanes.

ATC Code: L01C D01.

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/m<sup>2</sup> / cisplatin 75 mg/m<sup>2</sup>) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II<sub>b-c</sub>, III or IV primary ovarian cancer received a maximum of 9 treatment courses of Paclitaxel (175 mg/m<sup>2</sup> over 3 hr) followed by cisplatin (75 mg/m<sup>2</sup>) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either Paclitaxel (135 mg/m<sup>2</sup> over 24 hrs) followed by cisplatin (75 mg/m<sup>2</sup>) 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 to 0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95%CI: 0.78 to 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 randomised to receive or not four courses of Paclitaxel at a higher dose of 225 mg/m<sup>2</sup> 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 to 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 to 0.92); in the patient subgroup with hormone receptor negative tumour the risk reduction of disease recurrence was 10% (95%CI: 0.7 to 1.11).

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/m<sup>2</sup>) followed after 24 hours by Paclitaxel (220 mg/m<sup>2</sup> by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>), 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<sup>®</sup> 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<sup>®</sup> 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/m<sup>2</sup>) 3-hour infusion, every three weeks was compared to single-agent Paclitaxel (175 mg/m<sup>2</sup>) 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 4.8).

In the treatment of advanced NSCLC, Paclitaxel 175 mg/m<sup>2</sup> followed by cisplatin 80 mg/m<sup>2</sup> 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/m<sup>2</sup>, the other used teniposide 100 mg/m<sup>2</sup> followed by cisplatin 80 mg/m<sup>2</sup> 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 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 l/hr/m<sup>2</sup> 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 l/m<sup>2</sup> 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 KS patients, the mean C<sub>max</sub> was 1,530 ng/ml (range 761 to 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 ng.hr/ml to 9,428 ng.hr/ml). Clearance was 20.6 l/h/m<sup>2</sup> (range 11 to 38) and the volume of distribution was 291 l/m<sup>2</sup> (range 121 to 638). The terminal elimination half-life averaged 23.7 hours (range 12 to 33).

Inpatient 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 to 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 radiolabeled paclitaxel, an average of 26%, 2% and 6% of the radioactivity was excreted in the faeces as 6 $\alpha$ -hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6 $\alpha$ -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/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.

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

Ethanol (see 4.4).

Macroglycerol Ricinoleate (Purified, Cremophor ELP – CR)

### 6.2 INCOMPATIBILITIES

Macroglycerol Ricinoleate (Purified, Cremophor ELP – CR) 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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 SHELF LIFE

#### Vial before opening

2 years

#### After opening before dilution

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. From a microbiological point of view, once opened, the product should be used immediately.

#### 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 20 ± 5 °C for 14 days when diluted in 5% Glucose injection, 0.9% Sodium Chloride injection, 5% Glucose and 0.9% Sodium Chloride injection, and Ringer's solution containing 5% Glucose.

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 °C to 8 °C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25 °C.

Store in original package to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Type 1 glass vials (with rubber stopper) contain 30 mg, 100 mg or 300 mg of paclitaxel in 5 ml, 16.7 ml or 50 ml solution respectively.

The vials are packaged individually in a carton.

## 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.

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% Glucose injection, or 5% Glucose and 0.9% Sodium Chloride injection, or 5% Glucose in Ringer's injection, to a final concentration of 0.3 mg/ml 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 20 ± 5 °C for 14 days when diluted in 5% Glucose injection, 0.9% Sodium Chloride injection, 5% Glucose and 0.9% Sodium Chloride injection, and Ringer's solution containing 5% Glucose. 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 °C to 8 °C, unless reconstitution and dilution have 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 I.V. 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 supersaturation 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<sup>®</sup>) 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 undergo disposal according to local guidelines for the handling of cytotoxic compounds.

Any unused product or waste material should be disposed of in accordance with local requirements.

**7      MARKETING AUTHORISATION HOLDER**

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**8      MARKETING AUTHORISATION NUMBER(S)**

PL 18727/0009

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

7 June 2007

**10     DATE OF REVISION OF THE TEXT**

April 2007

## PRODUCT INFORMATION LEAFLETS

### PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you are given Paclitaxel

- 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, you should tell immediately your doctor or pharmacist.

#### In this leaflet:

1. What Paclitaxel is and what it is used for
2. Before you are given Paclitaxel
3. How Paclitaxel is given
4. Possible side effects
5. How to store Paclitaxel
6. Further information

#### 1. WHAT PACLITAXEL IS AND WHAT IT IS USED FOR

Paclitaxel is a member of a group of compounds referred to as the taxanes, which are anti-cancer agents. 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, and as an additional therapy following treatment with anthracycline and cyclophosphamide (AC). And 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:** as another treatment i.e. when liposomal anthracyclines have not worked.

#### 2. BEFORE YOU ARE GIVEN PACLITAXEL

##### You should not be given Paclitaxel:

- if you are allergic to paclitaxel or any of the other ingredients
- if you have a very low level of white blood cells in your blood
- if you have a serious, uncontrolled infection.
- if you are pregnant, breast-feeding or planning to become pregnant.

Your doctor should have checked that the results of your last blood test allow you to receive your course of treatment.

##### Take special care with Paclitaxel:

- if you have any liver disease
- if you are taking any other medicines.

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

##### Taking other medicines:

- Paclitaxel is often used in combination with another drug, cisplatin. It is important that paclitaxel is administered before cisplatin. Care will be taken if you have gynaecological cancer and are being treated with paclitaxel and cisplatin.
- If you have breast cancer you may be treated with another drug called doxorubicin. It is important that doxorubicin is given 24 hours after your treatment with paclitaxel.

- Care is required if paclitaxel is administered at the same time as certain drugs which affect liver function including some drugs used to treat virus infections (e.g. ritonavir), some drugs used to treat depression (e.g. fluvoxamine) and rosiglitazone (used in diabetes). Erythroycin and rifampicin, used to treat infections; fluoxetine, a drug used to treat depression; gemfibrozil, a drug used to treat heart disease; carbamazepine and phenytoin used for epilepsy, efavirenz and nevirapine, drugs used to treat HIV.
- Care is required if paclitaxel is administered at the same time as protease inhibitors such as nelfinavir and ritonavir.

You should tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription at a pharmacy or elsewhere, e.g. supermarket.

**Taking Paclitaxel with food and drink:**

There is no known interaction between Paclitaxel and food or alcohol. However, you should check with your doctor whether drinking is advisable for you.

**Pregnancy and Breast-Feeding:**

Ask your doctor and pharmacist for advice before taking any medicine. If you are pregnant, make sure you tell your doctor immediately, as you should not receive Paclitaxel during pregnancy. Paclitaxel may cause serious birth defects. Female patients should also avoid getting pregnant while being treated with paclitaxel and for at least six months afterwards. Male patients receiving paclitaxel should take adequate precautions to ensure that their partner does not become pregnant for the same period. If you are considering becoming parents after the treatment, you should discuss this with your doctor. Men who wish to father children in the future should seek advice about freezing sperm before the paclitaxel treatment is started. You should not breast-feed while you are being treated with Paclitaxel, as Paclitaxel might pass into breast milk. Do not restart breast-feeding until your doctor tells you it is safe to do so.

**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 immediately after a course of treatment. As in all cases, you should not drive if you feel dizzy or lightheaded. If this happens, you should avoid driving or operating machinery until these have worn off.

**Important information about some of the ingredients of Paclitaxel:**

This medicinal product contains the ingredient Macrogolglycerol Ricinolate (Purified, Cremophor ELP - CR) which may cause severe allergic reaction. If you know that you are allergic to this ingredient you should let your doctor know.

### **3. HOW PACLITAXEL IS GIVEN**

This product is a concentrate and it must be diluted before use. .

**Dosage:**

Paclitaxel is given into a vein from an intravenous drip. 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 175 mg/m<sup>2</sup>, body surface area, given over 3 hours.

**When receiving paclitaxel for first-line treatment of ovarian cancer**

The usual dosage of paclitaxel is 175 mg per square metre of body surface area given over three hours, or 135 mg per square metre of body surface area given over a 24-hour period, followed by treatment with 75 mg of cisplatin per square metre of body surface area. There is a three-week interval between each course of treatment.

**When receiving paclitaxel for second-line treatment of ovarian cancer**

The usual dosage of paclitaxel is 175 mg per square metre of body surface area given over three hours, every three weeks for four courses of treatment.

**When receiving paclitaxel for adjuvant treatment of breast cancer**

The usual dosage of paclitaxel is 175 mg per square metre of body surface area given over three hours. It is usually given in combination with another drug, trastuzumab. There is a three-week interval between treatment courses.

**When receiving paclitaxel for first-line treatment of breast cancer**

The usual dosage of paclitaxel is 175 mg per square metre of body surface area given over three hours. It is usually given in combination with another drug, trastuzumab. There is a three-week interval between treatment courses.

Paclitaxel can also be used in combination with doxorubicin. The usual dosage is 220 mg per square metre given over three hours with a three-week interval between treatment courses.

**When receiving paclitaxel for second-line treatment of breast cancer**

The usual dosage of paclitaxel is 175 mg per square metre of body surface area given over three hours. There is a three-week interval between treatment courses.

**When receiving paclitaxel for treatment of advanced non-small cell lung cancer**

The usual dosage of paclitaxel is 175 mg per square metre of body surface area given over three hours followed by treatment with 80 mg of cisplatin per square metre of body surface area. There is a three-week interval between each course of treatment. Further treatments will depend on how well you react to the treatment.

**When receiving paclitaxel for treatment of AIDS related Kaposi's Sarcoma.**

The usual dosage is 100 mg per square metre given over three hours every two weeks. Your general condition and your response to the treatment will be closely observed before, during and after the paclitaxel treatment. Before your treatment starts you will be treated with a steroid (such as dexamethasone), an antihistamine (such as diphenhydramine) and an H2-blocker (such as cimetidine). For certain types of treatment you may need to have your heart monitored before, during and after treatment with paclitaxel. Your doctor will also check your blood before, during and after every treatment. If the results of any of these tests are abnormal treatment will only be resumed when all readings are back to normal. Paclitaxel is usually given every 3 weeks. This may vary, depending on the results of regular blood tests.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

#### **4. POSSIBLE SIDE EFFECTS**

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

**Common side-effects with Paclitaxel are:**

Hair loss, nausea, vomiting and diarrhoea, allergic reactions such as flushing, skin rash, itching and other general infections. Changes in heart beat rate or rhythm, high or low blood pressure and bleeding. Blood disorders (hence the reason for regular blood tests), which might make you slightly anaemic or increase your risk of infection, or make you bruise more readily. Patients with Kaposi's sarcoma may experience severe liver disorders.

Numbness and/or tingling in hands and/or feet, muscle and joint pain, soreness of the mouth and tongue and temporary changes to the nails and skin. Sometimes there is pain, swelling and possibly skin peeling at the site of the injection. Other skin disorders.

Inflammation of a vein occurs less commonly.

Chest pain and/or shortness of breath may occur if you are also receiving other chemotherapy agents and/or radiotherapy. Bowel disorders, abdominal pain, increased sweating and pain in the limbs have also been reported.

**Rare side-effects with Paclitaxel are:**

Raised temperature, dehydration and anaphylaxis - swelling of the face/throat, wheezing, feeling faint and shortness of breath. Chills and back pain associated with allergic reaction. Pneumonia and other lung disorders. Swelling and/or weakness in the hands and/or feet have also been reported. Peritonitis (serious abdominal pain).

Heart failure is rare and usually occurs in patients who have received other chemotherapy especially an anthracycline or trastuzumab. Other heart disorders have also been reported.

**Very Rare side-effects with Paclitaxel are:**

Severe infections, disturbances to your sight and hearing, vertigo, dizziness, cough, severe allergic reactions such as Stevens-Johnson Syndrome (a rash that may affect limbs, hands, feet and mouth), epileptic type fits, confusion and other effects on the brain. Liver disorders, loss of appetite, constipation, headache, difficulty coordinating movement, hearing and/or balance effects, fast heart beat, weight loss (anorexia) have also been reported.

Most of these side-effects will occur during treatment. If you notice any of these, or any other effects, between courses of treatment or after your treatment has finished, tell your doctor.

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

#### **5. HOW TO STORE PACLITAXEL**

Keep out of the reach and sight of children.

This medicine will be stored in the pharmacy and made up in a special area before the doctor or nurse gives it to you. Do not store above 25 °C. Store in the original container. An expiry date is given on the outer carton and vial label of the product. It should not be used after this date.

This medicine should not be disposed of via waste water or household waste. These measures will help to protect the environment.

#### **6. FURTHER INFORMATION**

##### **What Paclitaxel contains**

The active substance is Paclitaxel. The other ingredients are Ethanol and Macrogolglycerol Ricinoleate (Purified, Cremophor ELP - CR).

##### **What Paclitaxel looks like and contents of the pack**

Paclitaxel is available as vials containing 30 mg, 100 mg or 300 mg paclitaxel in a 6 mg/ml solution which has to be diluted before being given to you.

##### **Marketing Authorisation Holder and Manufacturer**

Dabur Oncology Plc., Lion Court, Farnham Road

Bordon, Hampshire, GU35 0NF, United Kingdom.

Tel: +44 (0) 1420 477 115, Fax: +44 (0) 1420 477 047

email: [info@daburoncology.com](mailto:info@daburoncology.com)

Revised: April 2007

**INFORMATION FOR HEALTH PROFESSIONALS**

Below is a summary of information to assist in the administration of Paclitaxel. You should be experienced in the handling and use of cytotoxic agents and be familiar with the SPC for Paclitaxel. Reference should be made to guidelines on the safe handling of antineoplastic agents.

**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.

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, storage and administration should be carried out in non-PVC containing equipment.

**Preparation for I.V. administration:** Prior to infusion, Paclitaxel must be diluted using aseptic techniques in 0.9% Sodium Chloride injection, or 5% Glucose injection, or 5% Glucose and 0.9% Sodium Chloride injection, or 5% Glucose in Ringer's injection, to a final concentration of 0.3 mg/ml 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 20 ± 5 °C for 14 days when diluted in 5% Glucose injection, 0.9% Sodium Chloride injection, 5% Glucose and 0.9% Sodium Chloride injection, and Ringer's solution containing 5% Glucose. 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 °C to 8 °C, unless reconstitution and dilution have 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 I.V. tubing containing an in line filter.

There have been rare reports of precipitation during Paclitaxel infusions, usually towards the end of a 24-hr infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation 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.

**Administration and dosage:** All patients should be premedicated with corticosteroids, antihistamines and H<sub>2</sub> antagonists prior to administration. The diluted Paclitaxel infusion should be administered using non-PVC containing equipment through an in-line filter with a microporous membrane <0.22 µm.

The recommended doses for the intravenous infusion of Paclitaxel are as follows:

First-line ovarian cancer:	135 mg/m <sup>2</sup> over 24 hours, followed by cisplatin 75 mg/m <sup>2</sup> ; <u>or</u> 175 mg/m <sup>2</sup> over 3 hours, followed by cisplatin 75 mg/m <sup>2</sup> ;
Second-line ovarian or breast cancer:	175 mg/m <sup>2</sup> over 3 hours;
Adjuvant breast cancer:	175 mg/m <sup>2</sup> over 3 hours; following anthracycline and cyclophosphamide (AC) therapy;
First-line breast cancer:	220 mg/m <sup>2</sup> over 3 hours, 24 hours after doxorubicin (50 mg/m <sup>2</sup> ), 175 mg/m <sup>2</sup> over 3 hours, after trastuzumab (see trastuzumab SPC);
Non-small cell lung cancer:	175 mg/m <sup>2</sup> over 3 hours, followed by cisplatin 80 mg/m <sup>2</sup> ;
AIDs related Kaposi's sarcoma:	100 mg/m <sup>2</sup> over 3 hours.

There should be a 3-week interval between courses, dependent upon patient tolerance. Paclitaxel should not be readministered until the neutrophil count is  $\geq 1.5 \times 10^9/L$  and the platelet count is  $\geq 100 \times 10^9/L$ . Patients experiencing severe neutropenia or severe peripheral neuropathy should be subject to a dose reduction of 20% for subsequent courses.

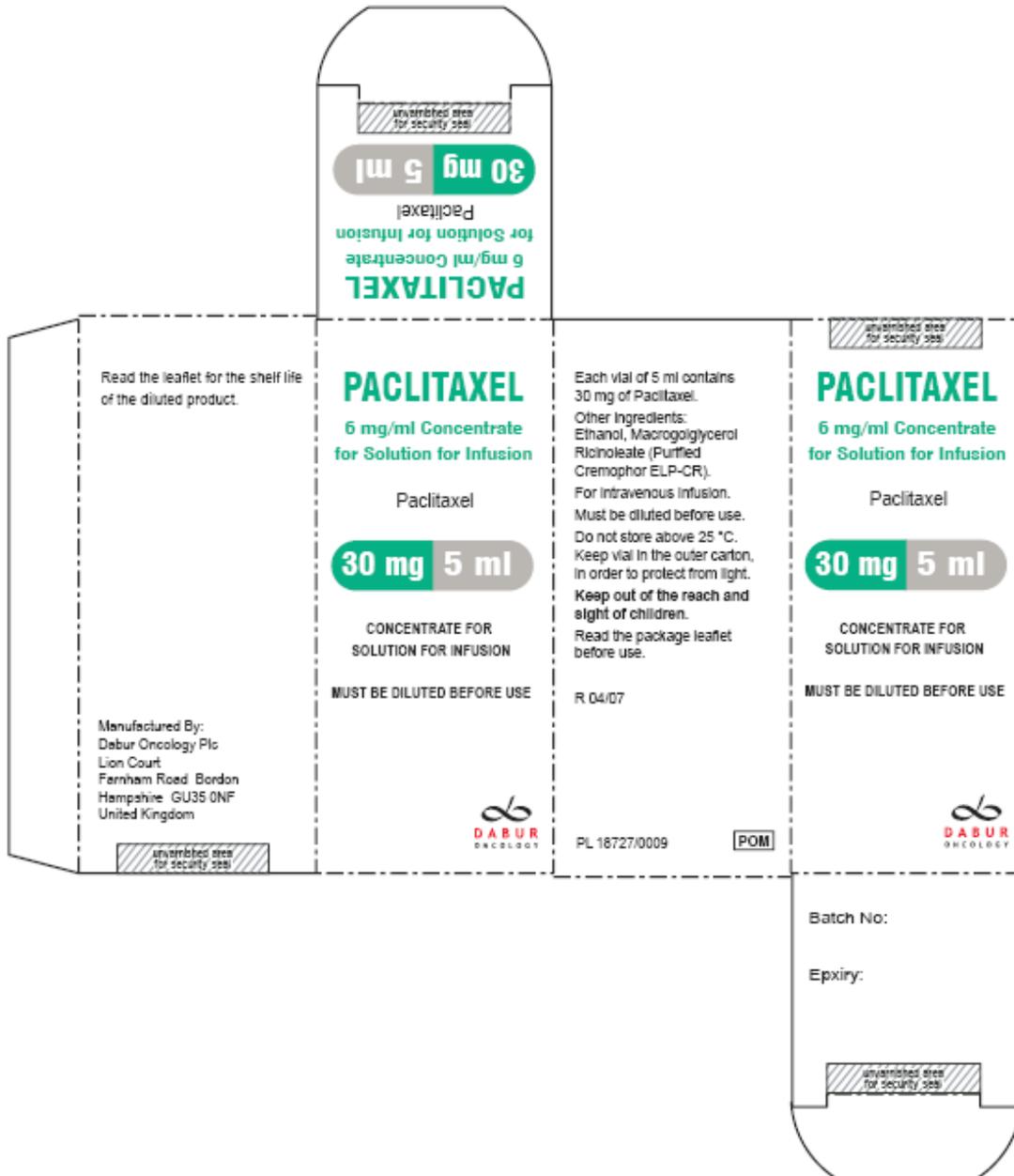
**Storage:** The unopened vials should not be stored above 25 °C and should be stored in the original package to protect from light. If refrigerated, a precipitate may form which redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy, or an insoluble precipitate is noted, the vial should be discarded. Freezing does not adversely affect the product.

An expiry date is given on the outer carton and vial label of the product. It should not be used after this date.

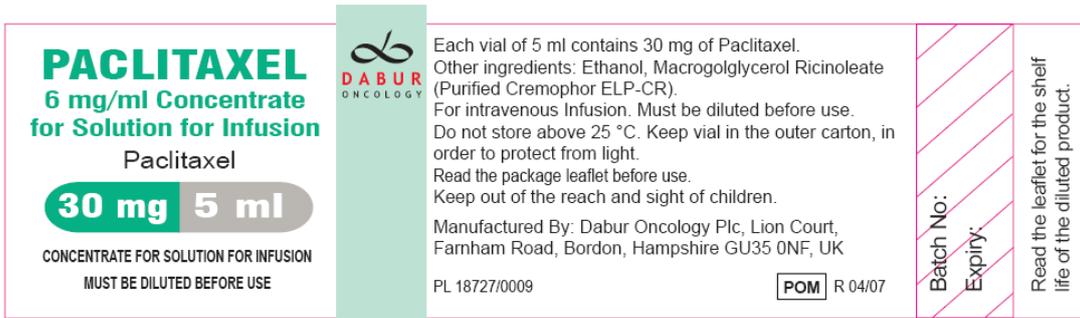
**Disposal:** All items used for preparation, administration or otherwise coming into contact with Paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds. Any unused product or waste material should be disposed of in accordance with local requirements.

Revised: April 2007

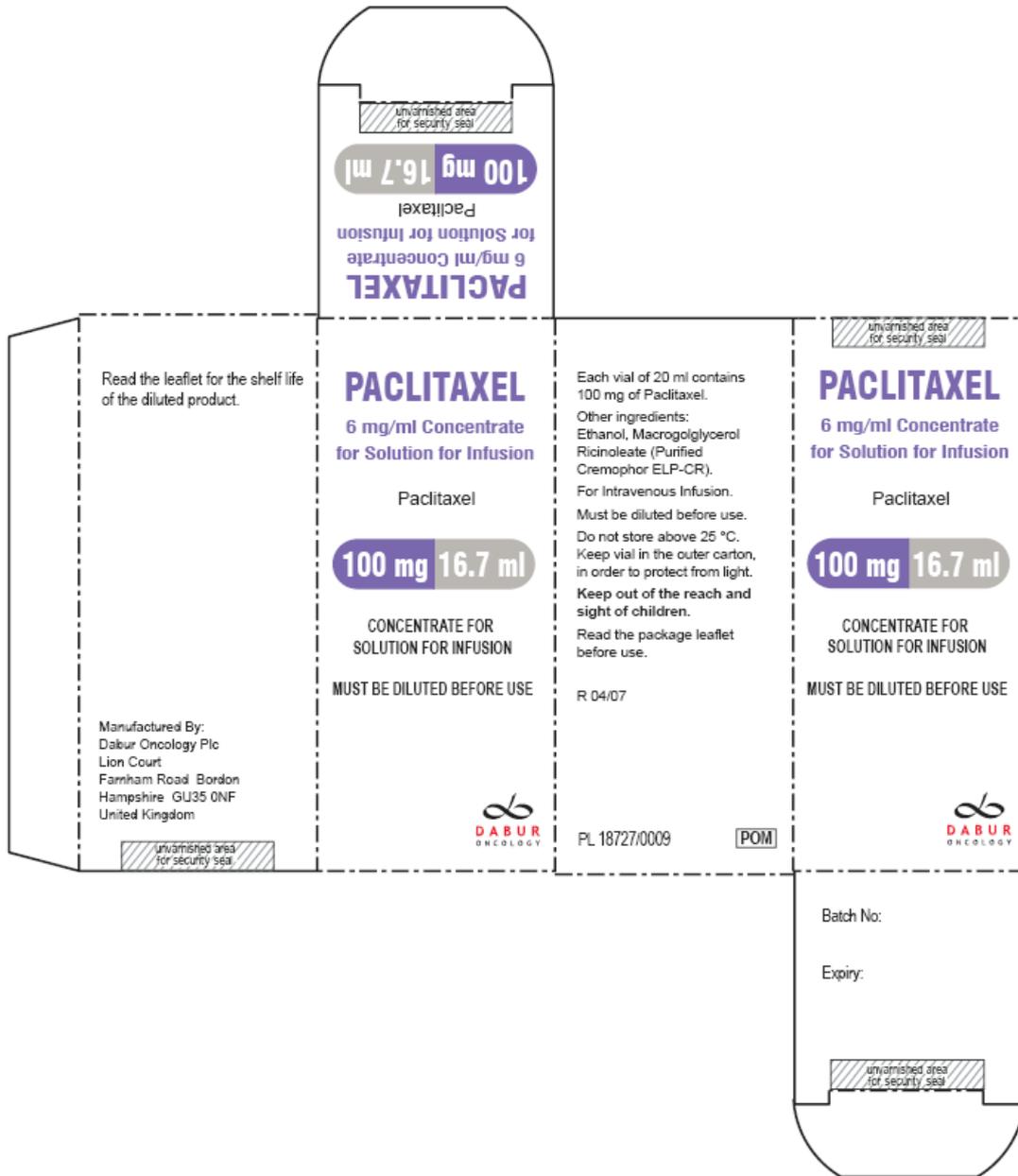
**LABELLING**  
Carton for 30mg / 5ml pack



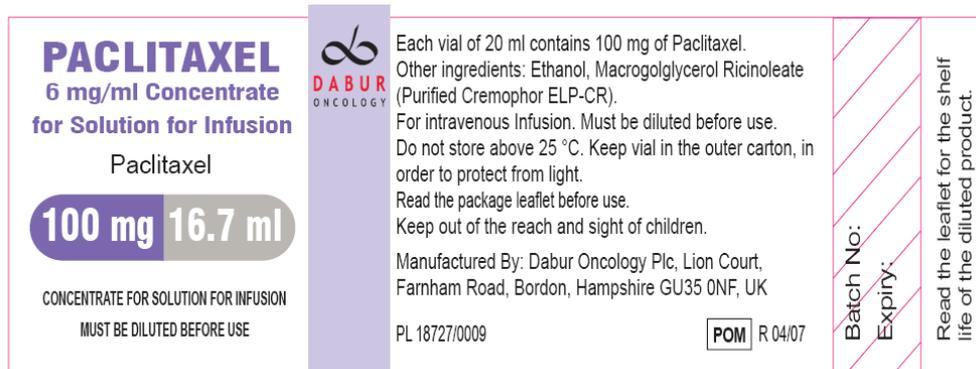
Label



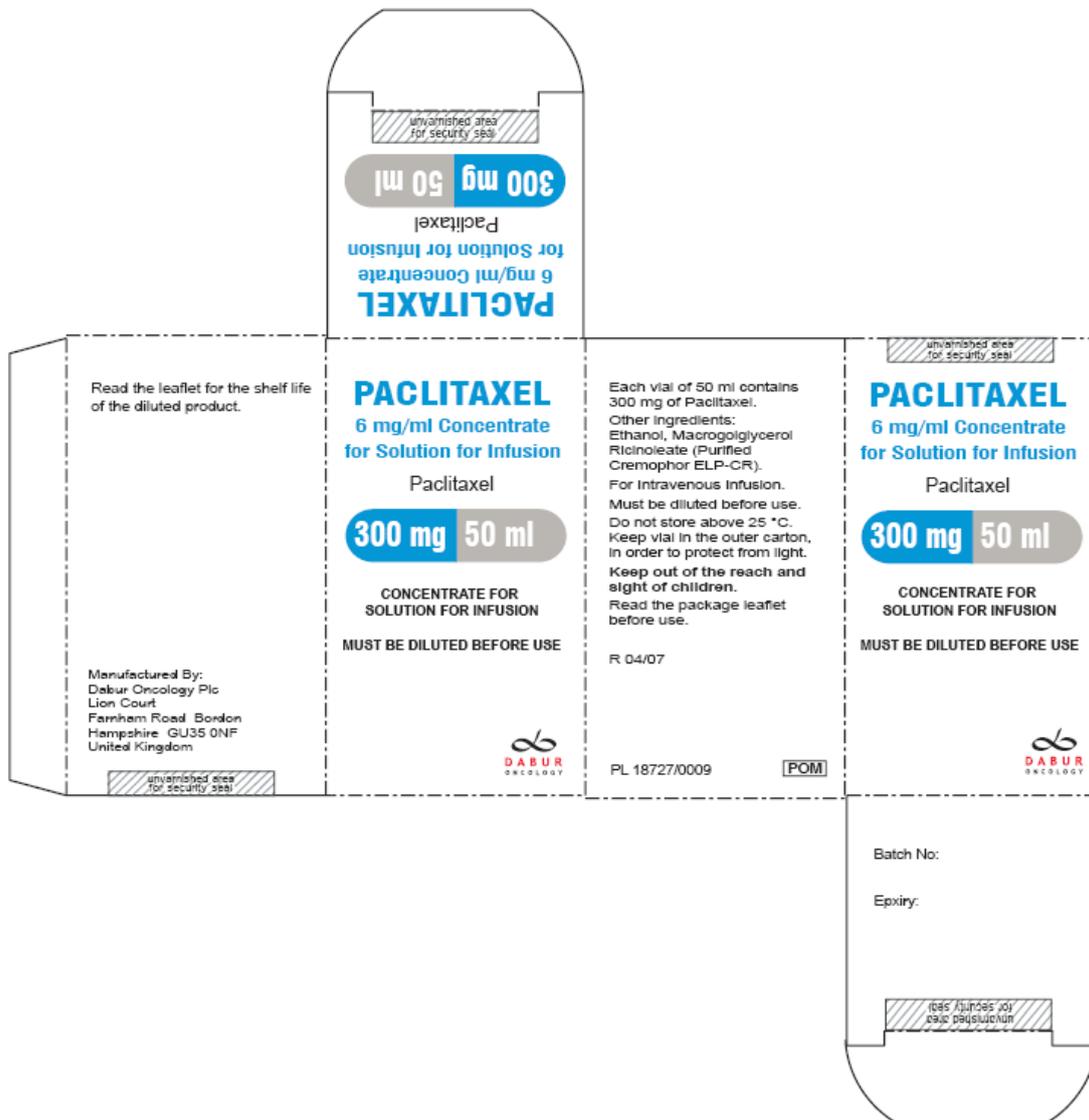
Carton for 100mg / 16.7ml pack



Label



Carton for 300mg / 50ml pack



Label

