

## **Public Assessment Report**

### **Paclitaxel 6mg/ml, concentrate for solution for infusion**

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**PL 20140/0003**

**PL 20140/0004**

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### **Lay Summary**

Paclitaxel is derived from the bark and needles of the Pacific Yew Tree *Taxus brevifoli*. A number of anti-cancer drugs have been isolated from this source and are known as taxanes. Like many anti-cancer drugs Paclitaxel interferes with the processes of cell division and therefore cancer growth. Paclitaxel inhibits the normal dynamic reorganisation of the intracellular microtubule network that is essential for cell division. It does this by causing the tubules to bind together in pairs.

Paclitaxel is used to treat a number of cancers including ovarian, breast and lung cancer, either on its own or in combination with other anti-cancer drugs. This product was granted a Market Authorisation on 18<sup>th</sup> January 2006 on the legal basis of essential similarity to the reference product Taxol<sup>®</sup>. No new or unexpected safety concerns arose during the assessment of these products and in view of the positive risk/benefit for these products a Market Authorisation was granted.

## **Scientific Discussion**

Paclitaxel is a member of the taxane group of antineoplastic agents. It is derived from the bark and needles of the Pacific Yew Tree *Taxus brevifolia*, and is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. Paclitaxel therefore inhibits the normal dynamic reorganisation of the intracellular microtubule network essential for interphase and mitotic cellular functions.

This Public Assessment Report is based on the Assessment Reports for two National applications for Marketing Authorisations for Paclitaxel 6mg/ml Concentrate for Solution for Infusion, vial sizes 30mg (5ml vial, PL 21040/0003) and 100mg (16.7 ml vials, PL 21040/0004). These Marketing Authorisations were granted on 18<sup>th</sup> January 2006.

The applicant claimed essential similarity, under article 10.1(a) (iii), to Taxol 6mg/ml Concentrate for Infusion PL 11184/0026, 30mg (5 ml vials) and PL 11184 / 0058. PL 11184 / 0026 was originally submitted as a national application and granted a national licence in 1993 but has since become the subject of MR procedures NL/H/0047. PL 11184 / 0058 is for the 100mg (16.7ml vial) and 300mg (50 ml vials). The proposed products contain the same concentration of active substance in the same pharmaceutical form. For information, PL 11184 / 0058 was submitted using the MR procedure NL/H/047 and granted in November 1996.

## **USE**

The applicant has submitted for the following indications: First-line and second-line chemotherapy of ovarian cancer, the initial treatment of advanced or metastatic breast cancer in combination with trastuzumab, single agent treatment of metastatic breast cancer and advanced non-small cell lung carcinoma in combination with cisplatin, AIDS-related Kaposi's sarcoma. These indications are consistent with those for Taxol<sup>®</sup> the reference product.

## **PHARMACEUTICAL ASSESSMENT**

### **DRUG SUBSTANCE**

A single source of Paclitaxel was included in these applications and was supported by a European Drug Master File which was assessed and found to be satisfactory after clarification of a number of points. A satisfactory letter of access and applicant's part was provided.

#### **Description**

Paclitaxel is an odourless, white to almost white powder. It is insoluble in water, slightly soluble in octanol and soluble in macrogolglycerol ricinoleate, ethanol, macrogol, chloroform, acetone and methanol.

Molecular formula:  $C_{47}H_{51}NO_{14}$   
Molecular weight: 853.92  
Physical form: A white, crystalline powder.  
Chirality: There are 11 chiral centres.

### **TSE Statement**

None of the ingredients are of animal origin.

### **GMP statement**

The manufacturer was inspected by the appropriate Health Authority in July 2003 and the outcome was positive.

### **Characterisation**

Characterisation of paclitaxel is by European Pharmacopoeial methods and levels of impurities checked by HPLC. Satisfactory documentation on reference standards was submitted. Data on 5 batches was provided and was acceptable for process validation. The packaging and container closure system of the drug substance was acceptable. Satisfactory data on stability of the drug substance and was provided after discussion with the Pharmaceutical Assessor.

## **DRUG PRODUCT**

The qualitative composition of the product is as follows. Paclitaxel (mg/ml), macrogolglycerol ricinolate, citric acid anhydrous, ethanol, anhydrous. The two vial sizes contain the same bulk solution and are thus proportionally identical. The same composition is already on the EU market for almost a decade and marketed as Taxol®. The composition is therefore acceptable.

No clinical trials have been carried out. This is a parenteral product containing the same active substance in the same concentration and comparable excipients as the currently marketed product Taxol. A bioequivalence study is not required according to the CPMP guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98).

There are no novel or unusual excipients in the formulation. The excipients have been chosen based on the reference product and accepted.

The composition of Paclitaxel 6mg/ml, concentrate for solution for infusion is based on the innovator's product Taxol 6mg/ml. The stability of the solution is improved by adjustment of the pH with citric acid (anhydrous). Citric acid is used in this present formulation to provide equivalent stability to the innovator's formulation.

### **Manufacturing Process**

The product is manufactured using normal manufacturing methods and processes for parenteral products.

### **Container Closure System**

It is stated that the primary packaging materials are standard packaging materials used routinely for injectables within the proposed manufacturer and throughout the pharmaceutical industry. It is also stated that the stability studies have proven that the selected quality is suitable for the intended use. This is accepted. The stability data includes inverted vial position storage. Satisfactory stability data gives an assurance of protection from moisture and product compatibility.

### **Microbiological Attributes**

It is stated that investigations were carried out to demonstrate the microbiological stability of the drug product and were found to be acceptable.

### **Administration**

The vials are multidose containers. The product is a non-aqueous solution and alcohol acts as an antimicrobial and the undiluted product meets the requirements of antimicrobial preservative efficacy tests (see above). This is in-line with the reference product and the USP monograph for paclitaxel injections mentions multiple-dose containers, preferably of type I glass. This is accepted.

Section 6.6 of the SPC states the following for administration:

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.

Solutions prepared for infusion are stable for at least 27 hours at 25°C and light exposure. Following multiple needle entries and product withdrawals, Paclitaxel multi-dose 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. Diluted solutions should not be refrigerated.

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  $\leq 0.22 \mu\text{m}$ . 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 infusions, usually towards the end of a 24 hours 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 minimize 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.

These statements are in-line with the reference product.

The diluted product should not be refrigerated, (as the solubility of the active substance may be adversely affected).

The following in-use stability statements are found in the SPC:

Paclitaxel multi-dose vials maintain microbial, chemical and physical stability for up to 28 days at 25°C.

### **Description of Manufacturing Process and Process Controls**

The production process is was described and is standard for parenteral preparations for which heat treatment is not possible.

### **Process description**

Paclitaxel 6 mg/ml, concentrate for solution for infusion is manufactured under GMP conditions. The sterilisation process by filtration is carried out in accordance with the instructions of the European Pharmacopoeia.

### **Control of Excipients**

Macroglycerol ricinoleate, citric acid, anhydrous ethanol and nitrogen comply with European Pharmacopoeial specification with additional European Pharmacopoeial microbiological contamination and endotoxin tests for macroglycerol ricinoleate. CoAs from the finished product manufacture and the supplier have been provided.

### **Excipients of Human or Animal Origin**

None of the ingredients are of animal origin.

### **Novel Excipients**

There are no novel excipients.

### **Control of Drug Product**

#### **Specification**

The specification complies with ICH guidelines and European Pharmacopoeial requirements for sterile concentrates for injection or infusion

The limits for the specified degradants are in line with the limits for these degradants stated as requirement in the USP 27, monograph for Paclitaxel injection and therefore acceptable.

The limits for sterility and bacterial endotoxin are in line with the USP monograph for paclitaxel injection and the European Pharmacopoeia requirements for injection products and accepted.

The release and shelf life limits of the active substance are in line with batch and stability data.

#### **Analytical Procedures and Validation**

Appropriate details of test methods were provided for assessment. Analytical methods for paclitaxel identification, assay and degradation products were provided with the calculations and calibration equations and were accepted. The standard European Pharmacopoeia tests for water determination, visible particles, clarity, pH and extractable volumes are stated to not require validation. This is accepted.

The HPLC method for the identification and assay of paclitaxel been suitably validated for specificity, linearity, sensitivity, precision (repeatability) and accuracy. Selectivity is satisfactory with no interference from the other constituents. This is confirmed by the provision of representative chromatograms. Linearity, repeatability, precision and accuracy were demonstrated to be within acceptable limits. The HPLC method for the related substances and degradants analysis of paclitaxel has been

suitably validated for specificity, linearity, sensitivity, precision (repeatability) and accuracy. Satisfactory validation data has been provided for the sterility testing and the bacterial endotoxin test (using the LAL test).

#### **Batch Data**

Batch data were provided. They were manufactured at the proposed site and are considered to adequately represent the product to be marketed. The data comply with the proposed specification and demonstrate consistent manufacture.

#### **Reference Standards Materials**

Satisfactory certificates of analysis are provided for analytical reference standards.

#### **Container Closure System**

The glass vials and the rubber stoppers comply with the requirements of the European Pharmacopoeia. Schematics of the packaging components have been provided. It is stated that testing are routinely carried out on the delivered materials on receipt. The material supplied will be checked for the prescribed quality determining parameters of the specifications. This is accepted.

#### **Stability**

##### **Parameters tested, methods and validation**

Appearance, clarity, colour, pH, assay, impurities, ethanol content, water content, extractable volume, endotoxins, and sterility were investigated according to standard methods. The range of tests is considered acceptable. The container was the same as that proposed for marketing.

The stability programme was considered acceptable.

##### **Stability and shelf-life**

After assessment of the stability data a shelf-life of two years was judged to be acceptable for this product.

The applicant is continuing the long term stability studies to 36 months (longer than the stability protocol) and adding one commercial scale batch yearly thereafter into the stability programme after approval. One batch will also be studied at the 3 years time point for stability after dilution in the recommended diluents. This is accepted.

##### **In-use shelf life**

Prior to infusion Paclitaxel, concentrate for solution for infusion 6mg/ml must be diluted in appropriate intravenous solutions to an appropriate concentration in the range of 0.3 to 1.2 mg/ml. A study was carried out to show compatibility and stability of Paclitaxel, concentrate for solution for infusion 6mg/ml after dilution with 0.9% sodium chloride, 5% glucose solution and mixture of 5% glucose and Ringer's solution. The data provided showed that the diluted product at the initial time point (of the stability study) was chemically and physically stable for 27 hours at 25°C when stored in polyolefin bags or glass bottles. The product should be administered through polyethylene-lined administration sets containing an in-line filter with a microporous membrane.

### **Essential Similarity**

The following data are provided to support the claim for essential similarity

- a) Satisfactory comparative impurity profiles are provided for the test and reference products
- b) The active substance complies with the USP generally.
- c) The Finished Product Specification complies with ICH and European Pharmacopoeial general requirements and impurities are in line with the USP requirements for Paclitaxel Injections. It is also generally in line with that approved for the reference product.

### **CONCLUSION**

Marketing Authorisations were granted for these products.

## ***PRE-CLINICAL ASSESSMENT***

No new pre-clinical data were submitted for this product which given the nature of the application was acceptable.

## ***CLINICAL ASSESSMENT***

### **1. INTRODUCTION**

This Public Assessment Report is based on the Assessment Reports for Paclitaxel 6 mg/ ml, concentrate for solution for infusion (5ml vial) (PL 21040/003) and Paclitaxel 6 mg/ ml, concentrate for solution for infusion (16.7 ml vial) (PL 21040/0004). These products were granted a UK National Marketing Authorisation on January 18<sup>th</sup> 2006. These products were presented as an essentially similar product to Taxol<sup>®</sup>, 6mg/ml concentrate for solution for infusion currently licensed to Bristol-Myers Squibb.

### **2. BACKGROUND**

Bristol-Myers Squibb was granted a product licence (11184/0026) for their Taxol<sup>®</sup>, 6mg/ml concentrate for solution for infusion on 20 Sept 1993. Thus the 10-year rule has been fulfilled.

### **3. INDICATIONS**

The applicant has submitted the following:

#### Ovarian carcinoma:

The first-line chemotherapy of carcinoma of the ovary, in combination with cisplatin, in patients with advanced carcinoma of the ovary or with residual disease (over 1 cm) after initial laparotomy.

The second-line chemotherapy of metastatic carcinoma of the ovary after failure of standard platinum containing therapy.

Breast carcinoma:

The initial treatment of advanced or metastatic breast cancer 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)

Single agent 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:

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

AIDS-related Kaposi's sarcoma (KS):

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

**4. DOSE & DOSE SCHEDULE**

See the SPC for full details. The recommended dosages and dose schedules are consistent with those for Taxol<sup>®</sup>.

**5. TOXICOLOGY**

No formal data is provided under this heading and none are required for this application.

**6. CLINICAL PHARMACOLOGY**

This application does not require the inclusion of a bioequivalence study as it is an application claiming essential similarity for a parenteral drug containing the same active substance in the same concentration as the reference product.

**7. EFFICACY**

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

**8. SAFETY**

No formal safety data are presented. The adverse events that can be expected are listed in the SPC and are consistent with those for the reference product.

**9. CLINICAL OVERVIEW**

There is a satisfactory clinical overview which concludes that paclitaxel 6mg/ml concentrate for solution for infusion has a positive balance of benefits and risk for the proposed indications.

**10. SUMMARY OF PRODUCT CHARACTERISTICS**

The summary of product characteristics, which is on page of this Public Assessment Report, was amended during the assessment process with changes to the Special Warnings and Precautions and Undesirable Effects and other minor changes.

**11. PATIENT INFORMATION LEAFLET**

The Patient Information Leaflet was rewritten to reflect changes in the SPC and to improve the clarity of the language for patients. A colour mock-up of the leaflet was provided prior to the granting of the Marketing Authorisation and was satisfactory.

**12. LABELLING**

Minor changes were made to the Outer Label and the Ampoule Label

**13. MARKETING AUTHORISATION APPLICATION FORM**

The marketing authorisation application was completed satisfactorily.

**14. DISCUSSION**

The data presented has shown that paclitaxel 6mg/ml sterile concentrate for solution for infusion is essentially similar to Taxol.

**15. CONCLUSIONS**

A Marketing Authorisation was granted for both products.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The quality characteristics of Paclitaxel 6mg/ml 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**

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

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and the product is essentially similar to the reference product the product has a positive risk/benefit assessment.

### Steps Taken During Assessment

|   |  |
|---|--|
| 1 | The MHRA received the application on 18 <sup>th</sup> March 2004.  |
| 2 | Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 2 <sup>nd</sup> February 2005, 19 <sup>th</sup> July 2005, 23 <sup>rd</sup> December 2005 and 10 <sup>th</sup> January 2006. Further information on the clinical assessment was requested on 22 <sup>nd</sup> October 2004, 14 <sup>th</sup> July 2005 and 14 <sup>th</sup> December 2005. |
| 3 | The applicant provided further information in regard to the quality assessment on 11 <sup>th</sup> April 2004 and 10 <sup>th</sup> January 2005. Further information in regard of the clinical assessment was received on 19 <sup>th</sup> November 2004, 1 <sup>st</sup> July 2005 and 23 <sup>rd</sup> December 2005.  |
| 4 | The application was determined on 18 <sup>th</sup> January 2005.   |

## **Summary of Product Characteristics**

### **1. NAME OF THE MEDICINAL PRODUCT**

PACLITAXEL 6 mg/ ml, concentrate for solution for infusion.

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Paclitaxel: 6 mg per 1 ml of concentrate for solution for infusion.

A vial of 5 ml contains 30 mg of paclitaxel.

A vial of 16.7 ml contains 100 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:**

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

**Aids-related Kaposi's sarcoma (KS):**

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.

| <b>1 DRUG</b> | <b>2 DOSE</b>     | <b>Administration prior to PACLITAXEL</b>             |
|---------------|-------------------|---|
| dexamethasone | 20 mg oral* or iv | For oral administration: approximately 12 and 6 hours |

|                             |                       |  |
|-----------------------------|-----------------------|--|
|                             |                       | or for iv administration: 30 to 60 min |
| diphenhydramine**           | 50 mg iv              | 30 to 60 min                           |
| cimetidine or<br>ranitidine | 300 mg iv<br>50 mg iv | 30 to 60 min                           |

\*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  $\leq 0.22 \mu\text{m}$  (see 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  $175\text{mg}/\text{m}^2$  administered intravenously over 3 hours, followed by cisplatin at a dose of  $75\text{mg}/\text{m}^2$  every three weeks, or PACLITAXEL  $135 \text{ mg}/\text{m}^2$  in a 24-hour infusion followed by cisplatin  $75 \text{ mg}/\text{m}^2$ , with a 3-week interval between courses.

**Second-line chemotherapy of ovarian carcinoma:** the recommended dose of PACLITAXEL is  $175 \text{ mg}/\text{m}^2$  administered over a period of 3 hours, with a 3 week interval between courses.

**Adjuvant chemotherapy in breast carcinoma:** the recommended dose of Taxol is  $175 \text{ mg}/\text{m}^2$  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 ( $50 \text{ mg}/\text{m}^2$ ), PACLITAXEL should be administered 24 hours after doxorubicin. The recommended dose of PACLITAXEL is  $220 \text{ mg}/\text{m}^2$  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  $175 \text{ mg}/\text{m}^2$  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 80mg/m<sup>2</sup>, with a 3 week interval between courses.

**Treatment of AIDS-related Kaposi's sarcoma (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 alteration 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 (Cremophor<sup>®</sup> EL) (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** characterized by dyspnoea and hypotension requiring treatment, angioedema and generalized urticaria can occur 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  $\square 1500/\text{mm}^3$  ( $\geq 1,000/\text{mm}^3$  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 monotherapy. If patients develop significant conduction abnormalities during

administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. Hypotension, hypertension, and bradycardia has been observed during administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than in those with 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 combination, 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 physician should carefully assess the cumulative dose ( $\text{mg/ m}^2$ ) of anthracycline administered when making decision 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) is recommended for all subsequent courses of PACLITAXEL. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of PACLITAXEL as a three hour infusion in combination with cisplatin, can result 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 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 (385 mg/ml), consideration should be given to possible CNS and other effects.

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

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

PACLITAXEL in combination with radiation of the 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. Interactions 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 treatment 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 is given after cisplatin, patients may show 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 catalyzed, 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, 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 fetotoxic 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 fetal 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, the patients should be warned that the product contains 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 tumors 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 ( $< 1/10,000$ ).

|  |   |
|--|---|
| <b>Infections and infestations:</b>              | Very common: infection<br>Uncommon: septic shock<br>Rare*: pneumonia, sepsis  |
| <b>Blood and the lymphatic system disorders:</b> | Very common: myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia<br>Rare*: febrile neutropenia<br>Very rare*: acute myeloid leukaemia, myelodysplastic syndrome  |
| <b>Immune system disorders:</b>                  | Very common : minor hypersensitivity reactions (mainly flushing and rash)<br>Uncommon: significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills and back pain)<br>Rare*: anaphylactic reactions<br>Very rare* : anaphylatic shock |
| <b>Metabolism and nutrition disorders:</b>       | Very rare* : anorexia   |
| <b>Psychiatric disorders:</b>                    | Very rare* : confusional state  |
| <b>Nervous system disorders:</b>                 | Very common: neurotoxicity (mainly: peripheral neuropathy)<br>Rare*: motor neuropathy (with resultant minor distal weakness)<br>Very rare*: autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy,   |

|   |   |
|---|---|
|   | dizziness, headache, ataxia   |
| <b>Eye disorders:</b>                                   | Very rare*: optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended  |
| <b>Ear and labyrinth disorders:</b>                     | Very rare* : ototoxicity, hearing loss, tinnitus, vertigo   |
| <b>Cardiac disorders:</b>                               | Common: bradycardia<br>Uncommon: cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction<br>Very rare* : atrial fibrillation, supraventricular tachycardia           |
| <b>Vascular disorders:</b>                              | Very common: hypotension<br>Uncommon: hypertension, thrombosis, thrombophlebitis<br>Very rare *: shock  |
| <b>Respiratory, thoracic and mediastinal disorders:</b> | Rare*: dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure<br>Very rare* : cough   |
| <b>Gastrointestinal disorders:</b>                      | Very common: nausea, vomiting, diarrhoea, mucosal inflammation<br>Very rare*: bowel obstruction, bowel perforation, ischaemic colitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, pancreatitis |
| <b>Hepato-biliary disorders:</b>                        | Very rare*: hepatic necrosis, hepatic encephalopathy  |
| <b>Skin and subcutaneous tissue disorders:</b>          | Very common: alopecia<br>Common: transient and mild nail and skin changes   |

|  |  |
|--|--|
|  | Rare*: pruritus, rash, erythema<br>Very rare* : Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) |
| <b>Musculoskeletal, connective tissue and bone disorders :</b> | Very common: arthralgia, myalgia   |
| <b>General disorders and administration site conditions:</b>   | Common: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis)<br>Rare*: asthenia, pyrexia, dehydration, oedema   |
| <b>Investigations:</b>   | Common: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase<br>Uncommon: severe elevation in bilirubin<br>Rare*: increase in blood creatinine   |

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, anemia, 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 30-35 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/ATC code: cytostatic agent/ L01C D01.

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

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 (B-MS 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 tumors, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumors, 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/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: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumor had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumor the risk reduction of disease recurrence was 10% (95%CI: 0.7-1.11).

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 compared to the FAC 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 trastuzumab combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of trastuzumab 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 and 175 mg/m<sup>2</sup>. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 L/hr/m<sup>2</sup>; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 L/m<sup>2</sup>, indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m<sup>2</sup> to 175 mg/m<sup>2</sup>, the C<sub>MAX</sub> and AUC<sub>0→∞</sub> values increased 75% and 81%, respectively.

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

Inpatient variability in systemic paclitaxel exposure was minimal. There was no evidence 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 metabolized 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 feces as 6 $\alpha$ -hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6 $\alpha$ -3'-p-dihydroxypaclitaxel, respectively. The formation of these hydroxylated metabolites is catalyzed 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 hemodialysis who received a 3-hour infusion of PACLITAXEL 135mg/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 (385 mg/ml), macroglycerol ricinoleate, citric acid (anhydrous).

### **6.2. Incompatibilities**

Macroglycerol ricinoleate can result in DEHP [di-(2-ethylhexyl)phthalate] leaching from plasticized 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**

2 years.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated for 27 hours at 25°C. Diluted solutions should not be refrigerated. From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user. Once diluted, for single use only.

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

Do not store above 25°C.

Store in original package to protect from light.

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

Type I glass vials with bromobutyl rubber stoppers containing 30 mg paclitaxel in 5 ml or 100 mg paclitaxel in 16.67 ml solution. The vials are available individually packaged in a carton folding box.

## 6.6 Instructions for use and handling (and 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.

**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 stability has been demonstrated for 27 hours at 25°C. 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.

Following multiple needle entries and product withdrawals, PACLITAXEL multidose 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. Diluted solutions should not be refrigerated.

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.

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  $\leq 0.22$   $\mu\text{m}$ . 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 infusions, usually towards the end of a 24 hours 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 minimize patient exposure to DEHP, which may be leached from plasticized 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.

**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.

## **7. MARKETING AUTHORISATION HOLDER**

SINDAN S.à.r.l.  
16, Allée Marconi  
L-2112 Luxembourg

## **8. MARKETING AUTHORISATION NUMBER**

PL 21040/0003 –PACLITAXEL 30 mg/ 5 ml

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

18/01/2006

**10 DATE OF REVISION OF THE TEXT**

18/01/2006

PAR Paclitaxel 6mg/ml concentrate solution for infusion PL 21040/0003-4

## **Patient Information Leaflet**

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**Paclitaxel 6 mg/ml Concentrate for solution for infusion  
30 mg/5 ml and 100 mg/16.7 ml**

This leaflet gives a summary of information about your medicine. If you want to know more, or are not sure about anything, ask your doctor or pharmacist.

**WHAT IS IN PACLITAXEL?**

PACLITAXEL is available as vials containing 30 mg or 100 mg paclitaxel in a 6 mg/ml solution which has to be diluted before being given to you. The other ingredients are ethanol and macrogolglycerol ricinoleate. Paclitaxel is a member of a group of compounds referred to as the taxanes, which are anti-cancer agents.

**UK PRODUCT LICENCE HOLDER:**

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Tel: +352 453 154

**UK DISTRIBUTOR:**

hameln pharmaceuticals Ltd  
Gloucester, United Kingdom

**MANUFACTURER:**

S.C. SINDAN –PHARMA S.R.L.  
11<sup>o</sup> Ion Mihalache Blvd, 011171 Bucharest, Romania

**WHAT IS THIS MEDICINE FOR?**

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 node-positive following anthracycline and cyclophosphamide therapy (adjuvant treatment with PACLITAXEL should be regarded as an alternative to extended anthracycline and cyclophosphamide therapy); breast cancer as initial therapy 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 a medicine called trastuzumab, or on its own in patients who have not responded to standard treatments using a medicine belonging to the group known as 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. In AIDS-related Kaposi's sarcoma where other treatments i.e. liposomal anthracyclines have not

worked.

**BEFORE YOUR MEDICINE IS ADMINISTERED**

**What should my doctor know before I receive PACLITAXEL?**

Tell your doctor if you are allergic to any of the ingredients in PACLITAXEL or similar medicines as you should not receive PACLITAXEL if you are. Your doctor should have checked that the results of your last blood test mean that you can receive your course of treatment. Also, make sure that your doctor knows if you have any liver, heart or renal disease, serious, uncontrolled infection or if you are taking any other medicines.

**What if I am pregnant or think I might be pregnant?**

Make sure you tell your doctor immediately, as you should not receive PACLITAXEL during pregnancy.

**What if I am breast feeding?**

You should not breast feed while you are being treated with PACLITAXEL. Do not restart breast feeding until your doctor tells you it is safe to do so.

**Can I take other medicines?**

Not unless these have been discussed with your doctor or pharmacist. These include medicines bought at a pharmacy or elsewhere, e.g. supermarket.

**Is it all right to drive?**

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.

**Is it all right to drink alcohol?**

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

**ADMINISTRATION OF YOUR MEDICINE**

**How is PACLITAXEL given and what is the usual dose?**

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>,



Information for Health Professionals



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**PLEASE DETACH BEFORE HANDING ABOVE SECTION TO THE PATIENT 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.

**Preparation of Infusion**

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.

PACLITAXEL must be diluted under aseptic conditions to a concentration of 0.3 to 1.2 mg/ml with one of the following: 0.9% Sodium Chloride Intravenous Infusion, 5% Glucose Intravenous Infusion, 0.9% Sodium Chloride and 5% Glucose Intravenous Infusion, 5% Glucose in Ringer's Injection.

Chemical and physical in-use stability has been demonstrated for 27 hours at 25°C. 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. Diluted solutions should not be refrigerated.

Following multiple needle entries and product withdrawals, PACLITAXEL multidose 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.

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

body surface area, given over 3 hours, followed by the cisplatin for ovarian and lung cancer. The usual dose is 220 mg/m<sup>2</sup>, body surface area, given over 3 hours administered 24 hours after doxorubicin in breast cancer. The usual dose is 175 mg/m<sup>2</sup>, body surface area, given over 3 hours, administered after trastuzumab in breast cancer. The usual dose is 175 mg/m<sup>2</sup>, body surface area, given over 3 hours, administered after anthracycline and cyclophosphamide in breast cancer adjuvant therapy. For breast cancer the timing of PACLITAXEL administration after trastuzumab will depend on how you react to this medicine. In AIDS-related Kaposi's sarcoma the usual dose is 100 mg/m<sup>2</sup> given over 3 hours.

**Will I need to receive any other medicine?**

You will be asked to take a steroid tablet 12 hours and 6 hours or you may be given one steroid injection approximately 30 - 60 minutes before receiving PACLITAXEL. You will also be given two injections of different types of antihistamine approximately 30 - 60 minutes before you receive PACLITAXEL.

**How often will I receive PACLITAXEL?**

PACLITAXEL is usually given every 3 weeks. This may vary, depending on the results of regular blood tests.

**UNDESIRABLE EFFECTS**

**Are there any unwanted effects of PACLITAXEL?**

All medicines may cause some unwanted or "side" effects. Your doctor will discuss these with you.

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

Hair loss, nausea, vomiting and diarrhoea, allergic reactions such as flushing, skin rash and itching. Changes (decrease) in heart beat rate or rhythm, high or low blood pressure, 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. Liver disorders –increase of bilirubin (jaundice) and liver enzymes such as alkaline phosphatase and AST (SGOT) may appear. 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, discoloured skin and possibly skin peeling at the site of the injection. Inflammation of a vein occurs less commonly. On occasion, irritation around the injection site can result in cellulitis.

Chest pain and/or shortness of breath may occur if you are also receiving other chemotherapy agents and/or radiotherapy.

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

Infections, inflammation of the lungs (pneumonitis) in patients receiving radiotherapy, raised temperature,

dehydration and anaphylaxis -swelling of the face/throat, wheezing, feeling faint and shortness of breath, itching, rash and abnormal reddening. Weakness in the hands and/or feet have also been reported. Fewer neutrophils (a type of white blood cell) may be found in your blood. This could cause fever (high temperature) as you may be more likely to develop infections. Swelling due to accumulation of fluid in body tissue (oedema) and increase in blood creatinine have also been reported.

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), changes (increase) in normal heart rate, epileptic type fits, difficulty coordinating movement, confusion and other effects on the brain. Severe, persistent or bloody diarrhoea associated with abdominal pain or fever, which can be a sign of a serious bowel inflammation (pseudomembranous colitis), may occur rarely. Other bowel and liver disorders, loss of appetite, constipation, hearing and or balance effects, headache and weight loss (anorexia) have also been reported.

Discoloured nails and detachment of the nail plate from the nail bed (onycholysis) may occur. You should avoid exposing your hands and feet excessively to sunlight during the therapy.

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.

**LOOKING AFTER YOUR MEDICINE**

This medicine will be stored in the pharmacy and made up in a special area before the doctor or nurse gives it to you. It should be kept in the original package, out of the reach and sight of children.

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

**DATE OF LAST REVISION:**

December 2005

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dilution and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. If precipitation occurs during infusion, the infusion should be stopped.

**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>; or 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;

**Breast cancer adjuvant therapy:**

175 mg/m<sup>2</sup> over 3 hours, after anthracycline and cyclophosphamide.

**First-line breast cancer:**

175 mg/m<sup>2</sup> over 3 hours, after trastuzumab; 220 mg/m<sup>2</sup> over 3 hours, after doxorubicin;

**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 (KS)**

The recommended dose of PACLITAXEL is 100 mg/m<sup>2</sup>

administered as a 3-hour intravenous infusion every two weeks.

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**

Do not store above 25°C. Store in original package to protect from light.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated for 27 hours at 25°C. Diluted solutions should not be refrigerated. Once diluted, for single use only.

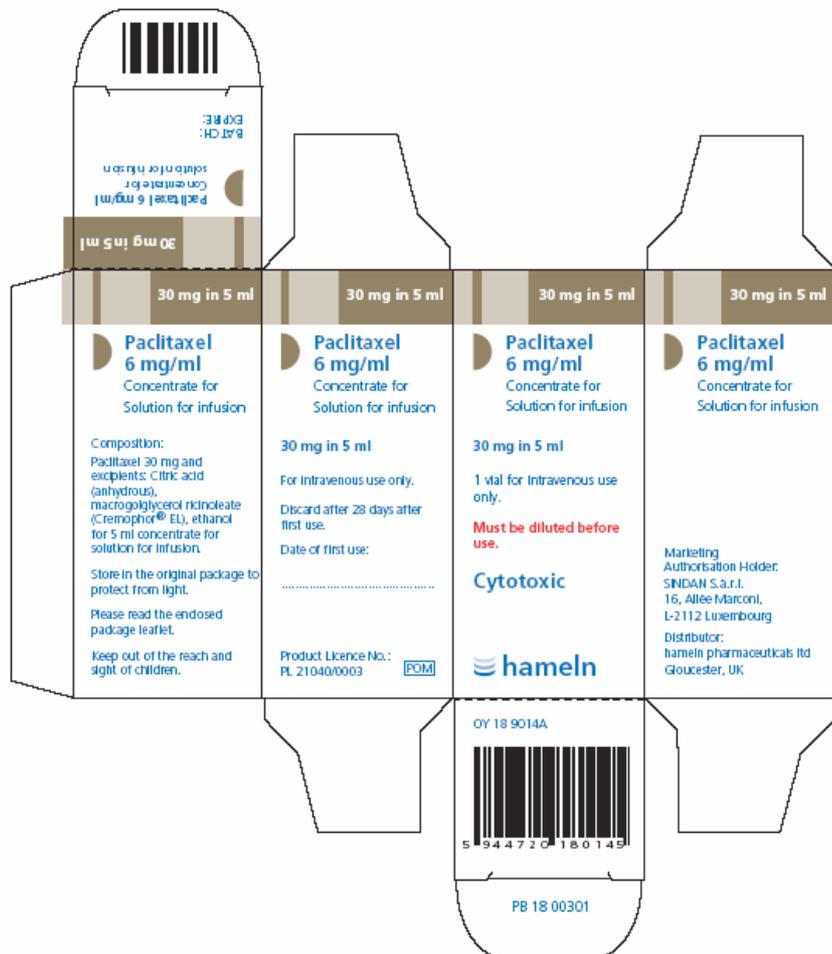
From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

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.

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## Labeling



Logo: 100%, 4.5%, 20%, P red 032 C

