Safeguarding public health

MHRA

Public Assessment Report

Decentralised

Paclitaxel 6mg/ml concentrate for solution for infusion

Paclitaxel

UK/H/1335/01//DC

Fresenius Kabi Limited

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Module 1

Product Name	Paclitaxel 6mg/ml concentrate for solution for infusion
Type of Application	Decentralised (Article 10.1)
Active Substance (INN)	Paclitaxel
Pharmacotherapeutic Classification (ATC)	L01CD01, plant alkaloids, taxane
Pharmaceuctical Form and Strength	Concentrate for solution for infusion, 6mg/ml
Procedure Numbers	**UK/H/1335/01/DC**
RMS	UK
CMS	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PT, RO, SE, SI, SK
Start Date	31/01/2008
End Date	17/03/2009
MA Number	PL 08828/0186
Name and address of MA holder	**Fresenius Kabi Lmited,** Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire WA7 1NT, United Kingdom

Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paclitaxel 6 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains paclitaxel 6 mg per 1 ml of concentrate for solution for infusion.

A vial contains 5 ml of paclitaxel (corresponding to 30 mg paclitaxel).

A vial contains 16.7 ml of paclitaxel (corresponding to 100 mg paclitaxel).

A vial contains 50 ml of paclitaxel (corresponding to 300 mg paclitaxel).

Excipients:

Ethanol, anhydrous, 393 mg/ml (49.7 % (v/v))

Macrogolglycerol ricinoleate, 530 mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, slightly yellowish 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 human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable (see section 4.4 and 5.1).

As a single agent, Paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy.

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

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

Limited efficacy data supports this indication, a summary of the relevant studies is shown in section 5.1.

4.2 Posology and method of administration

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel , e.g.

Paclitaxel concentrate for solution for infusion must be diluted before use (see section 6.6) and should only be administered intravenously.

Drug	Dose	Administration prior to Paclitaxel
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 Ranitidine	300 mg IV 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 ≤ 0.22 μm (see section 6.6).

First-line chemotherapy of ovarian carcinoma: although other dosage regimens are under investigation, a combination regimen of Paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of Paclitaxel are recommended: Paclitaxel 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every three weeks or Paclitaxel 135 mg/m², in a 24-hour infusion, followed by cisplatin 75 mg/m², with a 3-week interval between courses (see section 5.1).

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

Adjuvant chemotherapy in breast carcinoma: the recommended dose of Paclitaxel is 175 mg/m² administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.

First-line chemotherapy of breast carcinoma: when used in combination with doxorubicin (50 mg/m²), Paclitaxel should be administered 24 hours after doxorubicin. The recommended

dose of Paclitaxel is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see section 4.5 and 5.1).

When used in combination with trastuzumab, the recommended dose of Paclitaxel is 175 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see section 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®).

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

Treatment of advanced NSCLC: the recommended dose of Paclitaxel is 175 mg/m² administered over a period of 3 hours, followed by cisplatin 80 mg/m², with a 3 week interval between courses.

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

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

Paclitaxel should not be readministered until the neutrophil count is $\geq 1.5*10^9$/l ($\geq 1.0*10^9$/l for KS patients) and the platelet count is $\geq 100*10^9$/l ($\geq 75*10^9$/l for KS patients). Patients who experience severe neutropenia (neutrophil count $< 0.5*10^9$/l for ≥ 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (see section 4.4).

Paediatric patients:

Safety and efficacy in children (under 18 years) has not been established. Therefore, paclitaxel is not

recommended for paediatric use.

Hepatic impairment:

Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 4.4 and 5.2). Patients with severe hepatic impairment should not be treated with paclitaxel.

Renal impairment:

Studies in patients with impaired renal function have not been performed and there are insufficient

data to permit dosage recommendations (see section 5.2).

4.3 Contraindications

Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipient, especially macrogolglycerol ricinoleate (see section 4.4).

Paclitaxel should not be used in patients with baseline neutrophils $<1.5*10^9$/l ($< 1.0*10^9$/l for KS patients).

Paclitaxel is contraindicated during lactation (see section 4.6).

In KS patients, 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 H_2 antagonists (see section 4.2).

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

Significant hypersensitivity reactions (characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria) have occurred in < 1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, Paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to $\geq 1.5*10^9$/l ($\geq 1.0*10^9$/l for KS patients) and platelets recover to $\geq 100*10^9$/l ($\geq 75*10^9$/l 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 doxorubucin 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 Multiple Gated Acquisition (MUGA) scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m^2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles). 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-IV myelosuppression. There is no evidence that the toxicity of Paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When Paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of

profound myelosuppression (see section 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 5.2).

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

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***.

Sexually active female and male patients of fertile age, and/or their partners, should use contraceptives for at least 6 months after treatment with paclitaxel (see section 4.6).

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

This medicinal product contains 49.7 vol % ethanol (alcohol). Harmful for those suffering from alcoholism. To be taken into account in children and high-risk groups such as patients with liver disease, or epilepsy.

Since Paclitaxel contains ethanol (393 mg/ml), consideration should be given to possible CNS and other effects.

This medicinal product contains macrogolglycerol ricinoleate which may cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.

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

Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, Paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see section 5.2).

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see section 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6α-hydroxypaclitaxel, is the major metabolic pathway in humans. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment. Further data on the potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either

CYP2C8 or 3A4.

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

4.6 Pregnancy and lactation

Pregnancy

Paclitaxel has been shown to be teratogenic, embryotoxic and mutagenic in many experimental systems. 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 therefore should not be used during pregnancy unless clearly necessary.. Women should be advised to avoid becoming pregnant during therapy with Paclitaxel , and to inform the treating physician immediately should this occur. Sexually active female and male patients of fertile age, and/or their partners, should use contraceptives for at least 6 months after treatment with paclitaxel.

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

Lactation

It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation (see section 4.3). Breast-feeding should be discontinued for the duration of therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, it should be noted that Paclitaxel does contain alcohol (see section 4.4 and 6.1).

4.8 Undesirable effects

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent paclitaxel in clinical studies. As the KS population is very specific, a special chapter based on a clinical study with 107 patients, is presented at the end of this section.

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

The most frequent significant undesirable effect was ***bone marrow suppression***. Severe neutropenia ($< 0.5*10^9$ cells/l) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for ≥ 7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir $< 50*10^9$/l 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^2 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m^2 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 mild hypersensitivity reactions. These mild 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*.

The frequency of undesirable effects listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (frequency cannot be estimated from the available data).

Investigations:

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

Uncommon: severe elevation in bilirubin

*Rare** : increase in blood creatinine

Cardiac disorders:

Common: bradycardia

Uncommon : cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction

*Very rare** : atrial fibrillation, supraventricular tachycardia

Blood and the lymphatic system disorders:

Very common : myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding

*Rare** : febrile neutropenia

Very rare:* acute myeloid leukaemia, myelodysplastic syndrome

Nervous system disorders:

Very common : neurotoxicity (mainly: peripheral neuropathy)

Rare:* motor neuropathy (with resultant minor distal weakness)

*Very rare** : autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia

Eye disorders:

Very rare:* optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended

Ear and labyrinth disorders:

*Very rare** : ototoxicity, hearing loss, tinnitus, vertigo

Respiratory, thoracic and mediastinal disorders:

Rare:* dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure

*Very rare** : cough

Gastrointestinal disorders:

Very common : nausea, vomiting, diarrhoea, mucosal inflammation

Rare:* bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis

*Very rare** : mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis

Skin and subcutaneous tissue disorders:

Very common : alopecia

Common: transient and mild nail and skin changes

Rare:* pruritus, rash, erythema

*Very rare** : Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis

Musculoskeletal and connective tissue disorders:

Very common: arthralgia, myalgia

Metabolism and nutrition disorders:

*Very rare** : anorexia

Infections and infestations:

Very common: infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome

Uncommon: septic shock

Rare:* pneumonia, peritonitis, sepsis

Vascular disorders:

Very common : hypotension

Uncommon: hypertension, thrombosis, thrombophlebitis

*Very rare **: shock

General disorders and administration site conditions:

Common : injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)

Rare:* asthenia, pyrexia, dehydration, oedema, malaise

Immune system disorders:

Very common : mild hypersensitivity reactions (mainly flushing and rash)

Uncommon : 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)

Rare:* anaphylactic reactions

*Very rare** : anaphylatic shock

Hepatobiliary disorders:

Very rare:* hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)

Psychiatric disorders:

*Very rare **: confusional stage

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

Combination treatment

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

When administered as a three hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with paclitaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

For the first line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever, and diarrhoea were reported more frequently and with greater severity when paclitaxel (220 mg/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m²) / doxorubicin (50 mg/m²) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel/doxorubicin arm

When paclitaxel was administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to paclitaxel or trastuzumab) were reported more frequently than with single agent paclitaxel: heart failure (8% vs 1%), infection (46% vs 27%), chills (42% vs 4%), fever (47% vs 23%), cough (42% vs 22%), rash (39% vs 18%), arthralgia (37% vs 21%), tachycardia (12% vs 4%), diarrhoea (45% vs 30%), hypertension (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 3%), herpes simplex (12% vs 3%), accidental injury (13% vs 3%), insomnia (25% vs 13%), rhinitis (22% vs 5%), sinusitis (21% vs 7%), and injection site reaction (7% vs 1%). Some of these frequency differences may be due to the increased number and duration of treatments with paclitaxel/trastuzumab combination vs single agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single agent paclitaxel

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, **cardiac contraction abnormalities** (≥ 20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. **Congestive heart failure** was observed in < 1% in both paclitaxel/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of **cardiac dysfunction** in comparison with patients treated with paclitaxel single agent (NYHA Class I/II 10% vs. 0%;

NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma

Except for haematological 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 ($< 0.5*10^9$ cells/l) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for > 7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting ≥ 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 ($< 50*10^9$ cells/l) in 9%. Only 14% experienced a drop in their platelet count $< 75*10^9$ cells/l, 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.

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

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. In case of overdose, the patient should be closely monitored. Treatment should be directed to the major anticipated toxicities.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 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.

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^2/cisplatin 75 mg/m^2) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II_{b-c},

III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m^2 over 3 hr) followed by cisplatin (75 mg/m^2) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either paclitaxel (135 mg/m² over 24 hrs) followed by cisplatin (75 mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residual disease after staging laparotomy, or with distant metastases. While the two different paclitaxel posologies were not compared with each other directly, in both trials patients treated with paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

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

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomised to receive or not four courses of paclitaxel at a higher dose of 225 mg/m² following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006); paclitaxel treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumour had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumour 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/m²) followed after 24 hours by paclitaxel (220 mg/m² by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), both administered every three weeks for eight courses. In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of paclitaxel/doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the paclitaxel/doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

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

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

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

5.2 Pharmacokinetic properties

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

The pharmacokinetics of paclitaxel were determined following 3 and 24 hour infusions at doses of 135 and 175 mg/m². Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hr/m²; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m², indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m² to 175 mg/m², the C_{max} and $AUC_{-\infty}$ values increased 75% and 81%, respectively.

Following an intravenous dose of 100 mg/m² given as a 3-hour infusion to 19 KS patients, the mean C_{max} was 1,530 ng/ml (range 761 - 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 - 9,428 ng.hr/ml). Clearance was 20.6 l/h/ m² (range 11 - 38) and the volume of

distribution was 291 l/ m² (range 121 - 638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

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

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

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

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

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

5.3 Preclinical safety data

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

Paclitaxel has also been shown to be embryotoxic and foetotoxic in rabbits, and to decrease fertility in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous (see section 4.4).

Macrogolglycerol ricinoleate (see section 4.4)

Citric acid, anhydrous (for pH adjustment)

6.2 Incompatibilities

Macrogolglycerol ricinoleate 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

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C following multiple needle entries and product withdrawal. Other in-use storage times and conditions are the responsibility of the user.

After dilution

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 25°C for 24 hours when diluted in 5% Glucose solution, 0.9% Sodium Chloride solution, 5% Glucose solution in Ringer solution, and 5% Glucose solution/0.9% Sodium Chloride solution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

After dilution the solution is for single use only.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order 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 Teflon® coated chlorobutyl rubber stopper) contain 30 mg, 100 mg or 300 mg of paclitaxel in 5 ml, 16.7 ml or 50 ml solution respectively.

Packs containing 1 or 5 glass vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling:

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

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.

See also section 6.3 for shelf-life.

Pregnant women should not handle paclitaxel (see section 4.6)

Preparation for IV administration:

Prior to infusion, Paclitaxel must be diluted using aseptic techniques in 5% Glucose solution, 0.9% Sodium Chloride solution, 5% Glucose solution in Ringer solution, and 5% Glucose solution/0.9% Sodium Chloride solution to a final concentration of 0.3 to 1.2 mg/ml.

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

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

See also section 6.3 for shelf-life.

Disposal:

Any unused product or waste material and 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

Fresenius Kabi Limited,

Cestrian Court, Eastgate Way

Manor Park, Runcorn

Cheshire WA7 1NT

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0186

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2009

10 DATE OF REVISION OF THE TEXT

17/03/2009

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Paclitaxel 6 mg/ml
concentrate for solution for infusion

Fresenius Kabi

Paditaxel

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. WHAT PACLITAXEL IS AND WHAT IT IS USED FOR

Paclitaxel belongs to a group of medicines known as cytotoxics, which are used in the treatment of cancer. Paclitaxel may be used to treat cancer:

- advanced ovarian cancer or remaining tumour (> 1 cm) after initial surgery, in combination with cisplatin as initial (first-line) treatment.
- advanced ovarian cancer when certain other treatments (platinum-containing combination therapy without taxanes) have been tried but have not worked (as second-line treatment).
- advanced breast cancer when other treatments are unsuitable (as first line treatment).
- advanced breast cancer when certain other treatments (standard anthracycline-containing therapy) have been tried but have not worked (as second line treatment).
- advanced non-small cell lung cancer if surgery and/or radiation therapy are not possible, in combination with cisplatin.
- AIDS-related Kaposi's sarcoma when certain other treatments (liposomal anthracyclines) have been tried but have not worked. This is a tumour that arises from blood vessels in the skin or internal organs and typically appears as flat or raised, purple to dark brown patches on the skin. There is limited information to support treatment of this condition.

Paclitaxel is a medicine that will be given to you by a doctor or health care professional.

2. BEFORE YOU USE PACLITAXEL

Do not use Paclitaxel

- if you are allergic (hypersensitive) to paclitaxel, macrogolglycerol ricinoleate or any of the other ingredients of Paditaxel .
- if you have a very low level of certain white blood cells in your blood
- if you have a serious infection
- if you are breast-feeding

Take special care with Paclitaxel

- if you have liver problems
- if you are also receiving radiotherapy
- if you are taking other medicinal products which could interact with Paditaxel (see "Using other medicines")
- if you develop severe or prolonged or bloody diarrhoea during or after treatment with Paclitaxel
- if you develop peripheral neuropathy (numbness or abnormal sensations in your arms and legs)

For certain types of treatment you may need to have your heart monitored before, during and after treatment with paditaxel. 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.

Sexually active women and men of childbearing potential, and/or their partners should use contraceptives for at least 6 months after treatment with paclitaxel.

Using other medicines
Paclitaxel is often used in combination with another drug, cisplatin. It is important that Paditaxel is administered before cisplatin.

If you have breast cancer you may be treated with another drug called doxorubicin. It is important that doxorubicin is given 24 hours prior your treatment with Paditaxel .

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. nelfinavir, ritonavir),
- erythromycin and rifampicin (drugs used to treat infections),
- fluoxetine (a drug used to treat depression),
- gemfibrozil (a drug used to treat heart disease),
- carbamazepine, phenytoin and phenobarbital which are used for epilepsy,
- efavirenz and nevirapine (drugs used to treat HIV).

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Pregnancy
Tell your doctor if you are pregnant or think you may be pregnant before receiving treatment with Paclitaxel. If there is a chance that you could become pregnant, use an effective and safe method of contraception during treatment. Paditaxel should not be used during pregnancy unless clearly necessary. Female and male patients of fertile age, and/or their partners should use contraceptions for at least 6 months after treatment with paditaxel.
Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Breast-feeding
Paditaxel must not be given to you if you are breast-feeding, as paclitaxel might pass into breast milk and affect the baby.

Children
Paditaxel is not recommended for use in children and adolescents (under 18 years).

Driving and using machines
Paditaxel contains alcohol. Each treatment this will be about the equivalent of taking one glass of wine (à 250 ml) or 3 glasses of beer (à 200 ml). The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

Important information about some of the ingredients of Paclitaxel
This medicinal product contains 49.7 vol % ethanol (alcohol), i.e. up to 23 g per dose, equivalent to approximately 600 ml beer, approximately 250 ml wine per dose.
Harmful for those suffering from alcoholism.
To be taken into account in high risk groups such as patients with liver disease or epilepsy.

This medicinal product contains macrogolglycerol ricinolate (Ph.Eur.) which may cause severe allergic reaction. If you know that you are allergic to this ingredient you should let your doctor know.

3. HOW TO USE PACLITAXEL

Paditaxel will only be given to you under the supervision of a doctor specialised in this type of treatment.

To help prevent allergic reactions occurring while you are receiving your infusion your doctor will treat you with other medicines called corticosteroids (such as dexamethasone), antihistamines (such as diphenhydramine) and H2-blocker (such as cimetidine) before starting Paditaxel .

The dosage of Paclitaxel depends on the condition you are being treated for, your response to the therapy and other medication you are being given. It depends on the body surface area which on average is 1.6 to 1.9 square metre in adults.

When receiving Paclitaxel for first-line treatment of ovarian cancer
The usual dosage of paditaxel 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 paditaxel is 175 mg per square metre of body surface area given over three hours, every three weeks.

When receiving Paclitaxel for first-line treatment of breast cancer
The usual dosage of paditaxel 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 of paclitaxel 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 (also as accompanying treatment)
The usual dosage of paditaxel is 175 mg per square metre of body surface area given over three hours. There is a three week interval between treatment courses. As accompanying treatment it is usually given in combination with another drug, trastuzumab.

When receiving Paclitaxel for treatment of advanced non-small cell lung cancer
The usual dosage of paditaxel 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.

When receiving Paclitaxel for treatment of AIDS related Kaposi's Sarcoma
The usual dosage of paditaxel is 100 mg per square metre given over three hours every two weeks.

Further treatments will depend on how well you react to the treatment. Your general condition and your response to the treatment will be closely observed before, during and after the Paclitaxel treatment.

Mode of administration
The paclitaxel concentrate must be diluted before use with a solution of sodium chloride or glucose and given as an infusion (drip) into a vein.

If you take more Paclitaxel than you should
If you think you have been given too much Paditaxel, tell your doctor straight away. There is no specific antidote. The expected symptoms of an overdosage are overall reduction of blood cells (bone marrow suppression), numbness or abnormal sensations in your arms and legs (peripheral neuropathy) and inflamation of the membranes lining the digestive tract (mucositis).

If you forget to use Paclitaxel
If you think you have missed an infusion, speak to your doctor or nurse.

If you stop using Paclitaxel
Do not stop treatment with Paclitaxel before consulting your doctor.

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

4. POSSIBLE SIDE EFFECTS

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

As well as killing the cancer cells, the medicine may also affect some of your own cells especially the cells in your blood. This makes you more prone to infections and to bleeding or bruising easily.

If you think you have an infection, a sore throat, mouth ulcers, fever, chills or achiness you should contact your doctor.

The evaluation of side effects is based on the following frequencies:

Very common:	more than 1 of 10 patients treated
Common:	1 to 10 out of 100 patients treated
Uncommon:	1 to 10 out of 1,000 patients treated
Rare:	1 to 10 out of 10,000 patients treated
Very rare:	less than 1 of 10,000 patients treated, including isolated reports

Very common:

- temporary hair loss,
- nausea, vomiting, diarrhoea,
- sore mouth,
- numbness and tingling in the hands and feet,
- aching muscles and joints,
- urinary tract and chest infections,
- mild allergic reactions along with flushing and rash,
- low blood pressure,
- blood problems.

Common:

- sharp increase of certain liver enzymes
- slowing of the heart beat (bradycardia)
- temporary nail and skin discolouration
- swelling and pain (known as extravasation) at the injection site. If such symptoms occur, tell your doctor or nurse immediately.

Uncommon:

- heart attack, heart problems, rapid heart beat, high blood pressure, thrombosis (blood clot), inflammation of the vessel,
- sepsis (whole-body inflammatory state caused by infection) along with shock,
- severe allergic reaction requiring therapy- you may become breathless or have trouble breathing, you may notice chest pain, a speeding up of your heart, or your blood pressure may fall making you light-headed. Further symptoms of an allergic reaction:, chills, back pain, stomach pain, pain in fingers, toes, sweating, wheals (localised swellings on your skin), or swelling of your lips and/or your tongue. If any of these symptoms occur, contact your doctor immediately.

Rare:

- increased levels of creatinine in your blood ([likely] demonstrating a reduced kidney function)
- weakness or paralysis of the arms and legs (motor neuropathy),
- respiratory disorders such as shortness of breath (dyspnoea), scarring of the lung and fluid around the lungs (pleural effusion and lung fibrosis), inflammation of the lungs (interstitial pneumonia), blood clot in the lung vessels (pulmonary embolism), failure of the lungs to function properly. Paclitaxel , in combination with radiation therapy, can cause inflammation of the lung with breathlessness. If you develop a persistent cough, experience pain or difficulty breathing or become breathless, you should seek medical attention.
- bowel problems including constipation or perforation, inflammation of the pancreas and the abdominal membrane (peritoneum); all of which usually cause abdominal pain,
- dry skin, rash, itching (pruritus),
- general weakness (asthenia), fever, dehydration, fluid retention (oedema), severe tiredness (malaise)
- liver problems
- allergic reaction (known as anaphylactic reaction)

Very rare:

- heart rhythm problem known as atrial fibrillation,
- leukaemia,
- autonomic neuropathy along with intestinal blockage (ileus) and low blood pressure upon standing up,
- fits (convulsions) with dizziness and headache, uncontrolled movements (ataxia), damage of brain function (encephalopathy),
- problems with vision,
- loss of hearing and ringing in the ears,
- cough,
- mesenteric thrombosis (blood clot in the vessels of the intestine), pseudomembranous colitis (serious bowel inflammation with persistent or bloody diarrhoea associated with abdominal pain or fever), inflammation of the gullet (oesophagitis), abdominal swelling and water retention (ascites),

xxx xxx

- serious rash with reddening and flaking of the skin (Steven-Johnson syndrome, epidermal necrolysis), abnormal reddening, flaking, and thickening of the skin (exfoliative dermatitis), detachment of the nail plate from the nail bed (onycholysis),
- loss of appetite,
- shock,
- severe allergic reaction including fatal reactions (anaphylactic shock),
- severe liver problems along with damage of the brain,
- confusion.

Allergic reactions to macrogolglycerol ricinolate can occur, with wheezing, flushing, skin rash or swelling of your lips, eyes or tongue. You should contact your doctor immediately if you develop such symptoms.

Paclitaxel can harm unborn babies (see section 2 "Pregnancy and Lactation"). It may also affect fertility in men and women.

During the treatment with Paclitaxel your general condition will be closely monitored.

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

5. HOW TO STORE PACLITAXEL

Keep out of the reach and sight of children.

Do not store above 25°C.

Store vial in the original package in order to protect from light.

Do not use Paclitaxel after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of that month.

Do not use Paclitaxel if you notice any precipitation.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Paclitaxel contains

- The active substance is paditaxel 6 mg/ml. Each glass vial contains 30 mg, 100 mg or 300 mg of paclitaxel in 5 ml, 16.7 ml or 50 ml solution, respectively.
- The other ingredients are ethanol, anhydrous, macrogolglycerol ricinoleate (see section 2) and citric acid, anhydrous (for pH adjustment)

What Paclitaxel looks like and contents of the pack
Concentrate for solution for infusion
Paclitaxel is a clear, slightly yellowish solution.
Paclitaxel is available in glass vials. The glass vials are sealed with Teflon® coated rubber stoppers.

Pack sizes:
Packs containing 1 or 5 glass vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Fresenius Kabi Limited,
Cestrian Court, Eastgate Way
Manor Park, Runcorn
Cheshire WA7 1NT
United Kingdom

Manufacturer
Fresenius Kabi Deutschland GmbH
61346 Bad Homburg v.d.H.
Germany

MARKETING AUTHORISATION NUMBER(S):

PL 08828/0186
PA 0566/049/1

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Paditaxel Kabi 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Paditaxel Fresenius Kabi
Bulgaria	Paclitaxel Kabi 6 mg/ml Концентрат за инфузионен разтвор
Cyprus	Paclitaxel Kabi 6 mg/ml Πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Czech Republic	Paclitaxel Kabi 6 mg/ml koncentrát pro přípravuinfuzního roztoku
Danmark	Paditaxel Fresenius Kabi 6 mg/ koncentrat til infusionsvæske, opløsning
Estonia	Paditaxel Kabi 6 mg/ml infusioonilahuse kontsentraat
Germany	Paditaxel Kabi 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Greece	Paclitaxel Kabi 6 mg/ml Πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Finland	Paditaxel Fresenius Kabi 6 mg/ml infuusiokonsentraatti, liuosta varten
France	Paditaxel Kabi 6 mg/ml solution à diluer pour perfusion
Hungary	Paditaxel Kabi 6 mg/ml koncentrátum oldatos infúzióhoz
Ireland	Paditaxel 6 mg/ml concentrate for solution for infusion
Italy	Paditaxel Kabi 6 mg/ml concentrato per soluzione per infusione
Latvia	Paclitaxel Kabi 6 mg/ml koncentrāts infūziju šķīduma pagatavošanai
Lithuania	Paditaxel Kabi 6 mg/ml koncentratas infuziniam tirpalui
Luxemburg	Paditaxel Kabi 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Netherlands	Paditaxel Fresenius Kabi
Norway	Paditaxel Fresenius Kabi 6 mg/ml konsentrat til infusjonsvæske
Poland	Paditaxel Kabi
Portugal	Paclitaxel Kabi 6 mg/ml concentrado para solução para perfusão
Romania	Paclitaxel Kabi 6 mg/ml concentrat pentru soluţie perfuza
Slovakia	Paclitaxel Kabi 6 mg/ml
Slovenia	Paklitaksel Kabi 6 mg/ml koncentrat za raztopino za infundiranje
Spain	Paclitaxel Fresenius Kabi 6 mg/ml concentrado para solución para perfusión
Sweden	Paclitaxel Fresenius Kabi 6 mg/ml koncentrat till infusionsvätska, lösning
United Kingdom	Paclitaxel 6 mg/ml concentrate for solution for infusion

This leaflet was last approved in 03/2009

The following information is intended for medical or healthcare professionals only:

Practical information on preparation and/or handling of the medicinal product

Incompatibilities
Macrogolglycerol ricinoleate 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.

Special precautions for storage
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.

Shelf life
Vial before opening
2 years

After opening before dilution
Chemical and physical in-use stability has been demonstrated for 28 days at 25°C following multiple needle entries and product withdrawal. Other in-use storage times and conditions are the responsibility of the user.

After dilution
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 25°C for 24 hours when diluted in 5% Glucose solution, 0.9% Sodium Chloride solution, 5% Glucose solution in Ringer solution, and 5% Glucose solution/0.9% Sodium Chloride solution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

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.
Pregnant women should not handle paclitaxel (see section 2 Before you use Paclitaxel – Pregnancy and breast feeding)"

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.

Instructions for reconstitution
After dilution the solution is for single use only.
Prior to infusion, Paditaxel must be diluted using aseptic techniques in 5% Glucose solution, 0.9% Sodium Chloride solution, 5% Glucose solution in Ringer solution, and 5% Glucose solution/0.9% Sodium Chloride solution to a final concentration of 0.3 to 1.2 mg/ml.

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

There have been rare reports of precipitation during paditaxel 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, Paditaxel should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

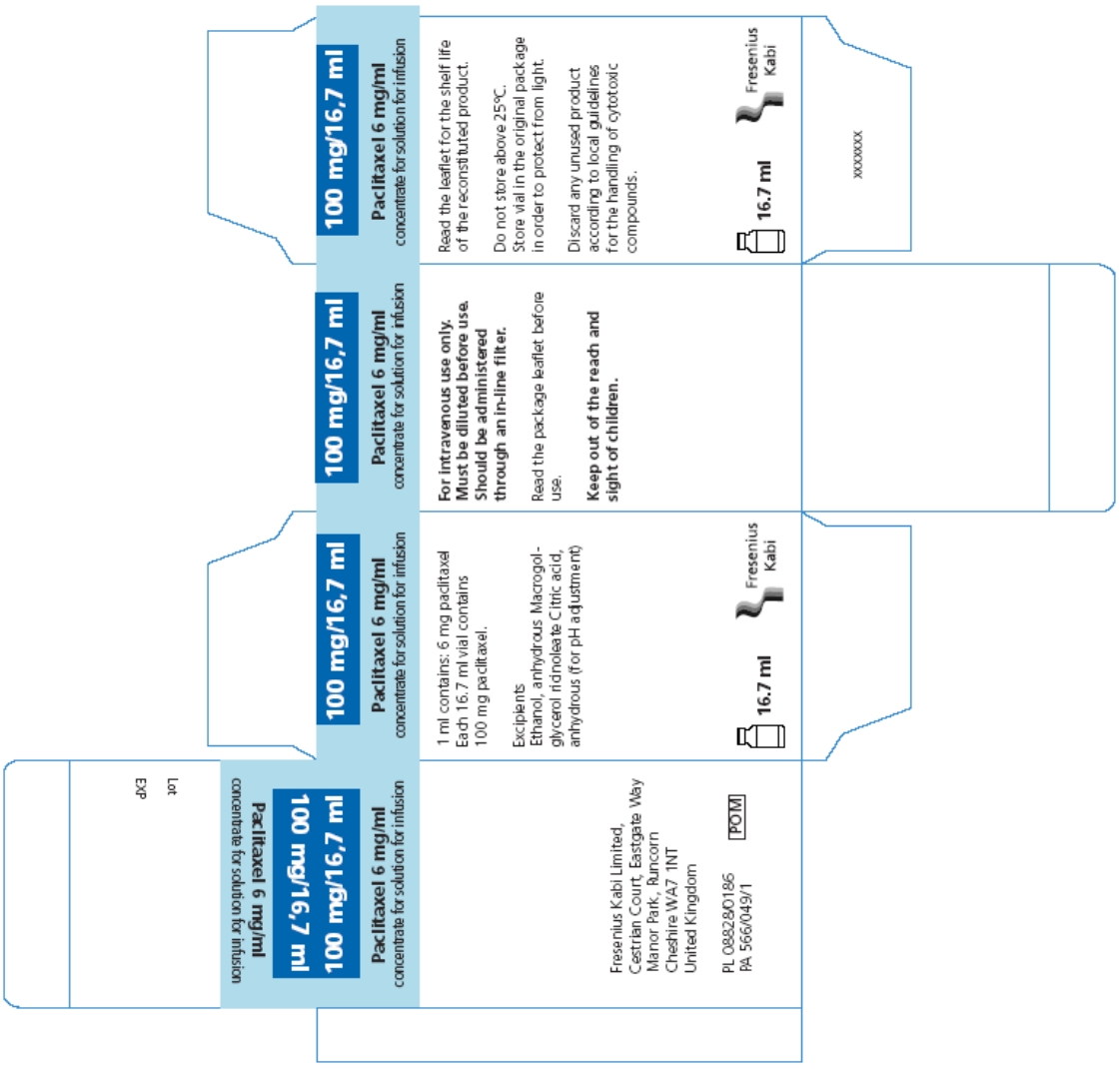
To minimise patient exposure to DEHP which may be leached from plasticised PVC infusion bags, sets, or other medical instruments, diluted Paclitaxel solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined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

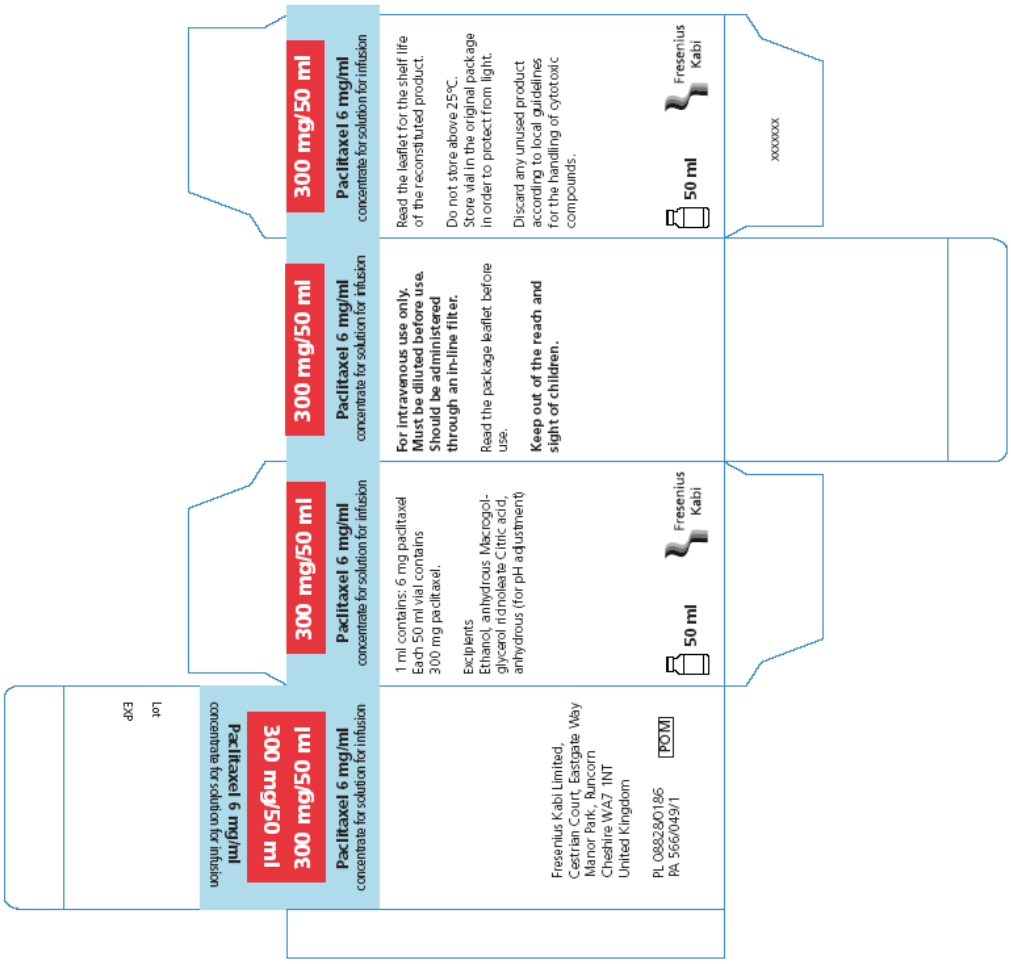
Disposal
Any unused product or waste material and all items used for preparation, administration or otherwise coming into contact with Paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

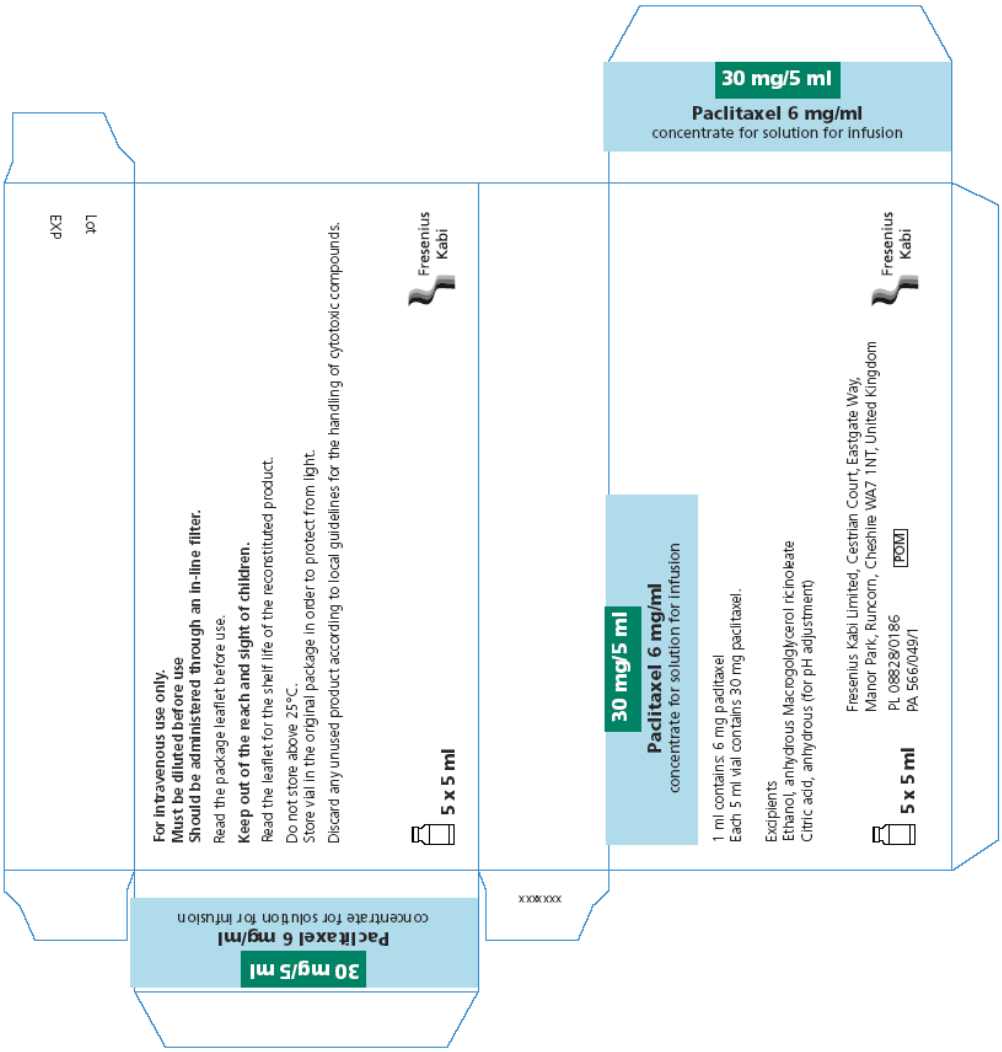
xxx xxx

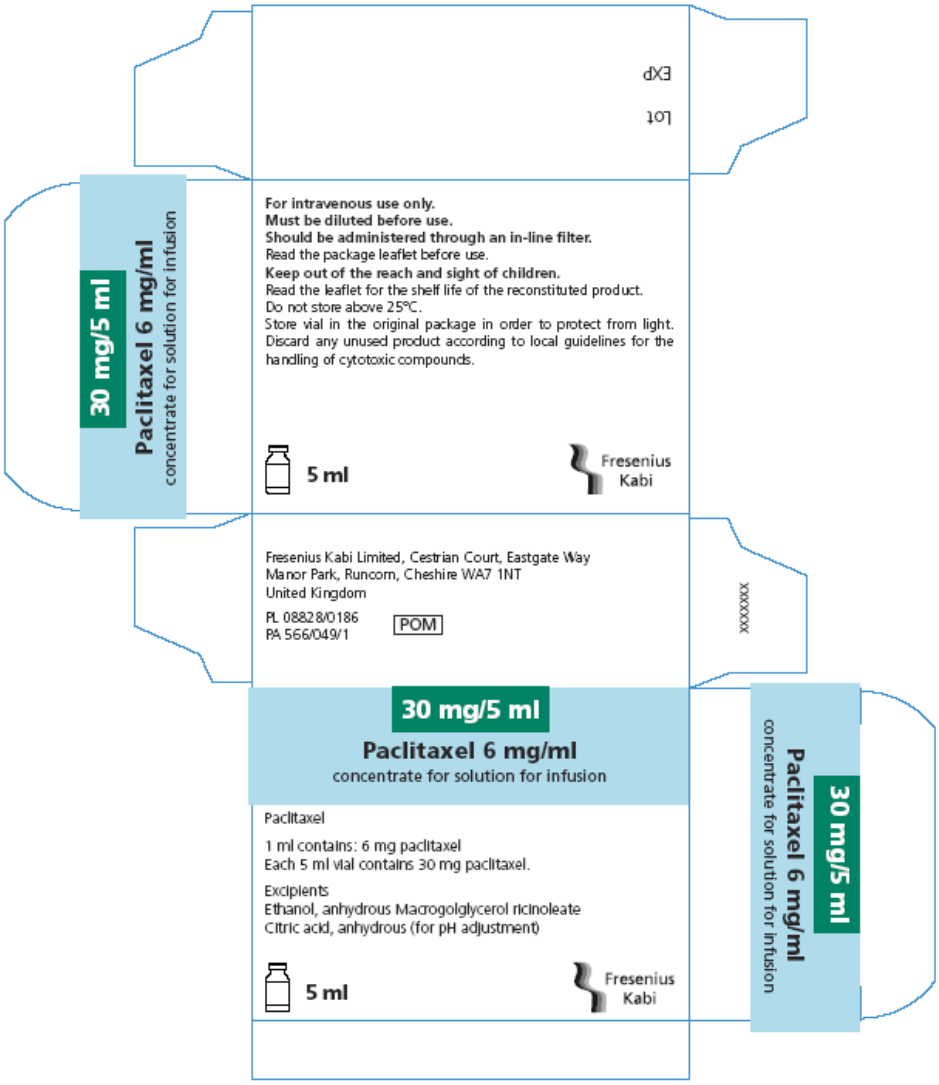
Module 4

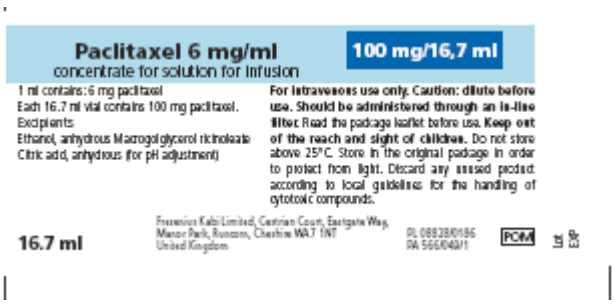
Labelling

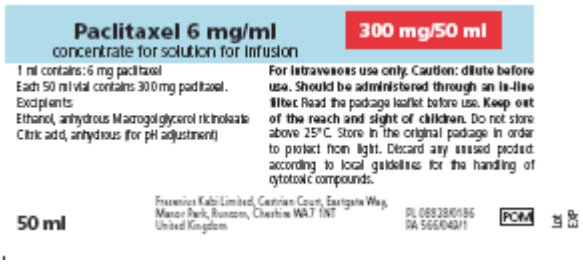


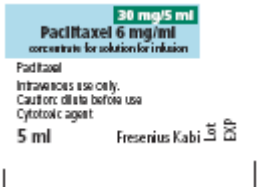

300 mg/50 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
EXP
Lot
300 mg/50 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
1 ml contains: 6 mg paclitaxel
Each 50 ml vial contains
300 mg paclitaxel.
Excipients
Ethanol, anhydrous Macrogol-glycerol ricinoleate Citric acid, anhydrous (for pH adjustment)
Fresenius Kabi Limited,
Cestrian Court, Eastgate Way
Manor Park, Runcorn
Cheshire WA7 1NT
United Kingdom
PL 08828/0186
PA 566/049/1
POM
50 ml
Fresenius Kabi
300 mg/50 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
For intravenous use only.
Must be diluted before use.
Should be administered through an in-line filter.
Read the package leaflet before use.
Keep out of the reach and sight of children.
300 mg/50 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
Read the leaflet for the shelf life of the reconstituted product.
Do not store above 25°C.
Store vial in the original package in order to protect from light.
Discard any unused product according to local guidelines for the handling of cytotoxic compounds.
50 ml
Fresenius Kabi
xxxxxx


30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
Fresenius Kabi
5 x 5 ml
For intravenous use only.
Must be diluted before use
Should be administered through an in-line filter.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Read the leaflet for the shelf life of the reconstituted product.
Do not store above 25°C.
Store vial in the original package in order to protect from light.
Discard any unused product according to local guidelines for the handling of cytotoxic compounds.
Lot
EXP
30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
1 ml contains: 6 mg paclitaxel
Each 5 ml vial contains 30 mg paclitaxel.
Excipients
Ethanol, anhydrous Macrogolglycerol ricinoleate
Citric acid, anhydrous (for pH adjustment)
Fresenius Kabi Limited, Cestrian Court, Eastgate Way,
Manor Park, Runcorn, Cheshire WA7 1NT, United Kingdom
PL 08828/0186
PA 566/049/1
POM
5 x 5 ml
Fresenius Kabi
xxxxxx
30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion


EXP
Lot
30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
For intravenous use only.
Must be diluted before use.
Should be administered through an in-line filter.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Read the leaflet for the shelf life of the reconstituted product.
Do not store above 25°C.
Store vial in the original package in order to protect from light.
Discard any unused product according to local guidelines for the handling of cytotoxic compounds.
5 ml
Fresenius Kabi
Fresenius Kabi Limited, Cestrian Court, Eastgate Way
Manor Park, Runcorn, Cheshire WA7 1NT
United Kingdom
PL 08828/0186
PA 566/049/1
POM
xxxxx
30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
Paclitaxel
1 ml contains: 6 mg paclitaxel
Each 5 ml vial contains 30 mg paclitaxel.
Excipients
Ethanol, anhydrous Macrogolglycerol ricinoleate
Citric acid, anhydrous (for pH adjustment)
5 ml
Fresenius Kabi
30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion


Paclitaxel 6 mg/ml
concentrate for solution for infusion
100 mg/16,7 ml
1 ml contains: 6 mg paclitaxel
Each 16.7 ml vial contains 100 mg paclitaxel.
Excipients
Ethanol, anhydrous Macrogolglycerol ricinoleate
Citric acid, anhydrous (for pH adjustment)
For intravenous use only. Caution: dilute before use. Should be administered through an in-line filter. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package in order to protect from light. Discard any unused product according to local guidelines for the handling of cytotoxic compounds.
16.7 ml
Fresenius Kabi Limited, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire WA7 1NT United Kingdom
PL 08828/0186
PA 566/049/1
POM


Paclitaxel 6 mg/ml
concentrate for solution for infusion
300 mg/50 ml
1 ml contains: 6 mg paclitaxel
Each 50 ml vial contains 300 mg paclitaxel.
Excipients:
Ethanol, anhydrous Macrogolglycerol richinoleate
Citric acid, anhydrous (for pH adjustment)
For intravenous use only. Caution: dilute before use. Should be administered through an in-line filter. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package in order to protect from light. Discard any unused product according to local guidelines for the handling of cytotoxic compounds.
50 ml
Fresenius Kabi Limited, Cestrian Court, Eastgate Way, Manor Park, Runcorn, Cheshire WA7 1NT United Kingdom
PL 08238/0186
PA 566/040/1
POM
Lot
EXP


30 mg/5 ml
Paclitaxel 6 mg/ml
concentrate for solution for infusion
Paclitaxel
Intravenous use only.
Caution: dilute before use
Cytotoxic agent
5 ml
Fresenius Kabi
Lot
EXP

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Paclitaxel 6 mg/ml concentrate for solution for infusion, for the treatment ovarian cancer, breast cancer, advanced non-small cell lung cancer and AIDS-related Kaposi's sarcoma, is approvable.

EXECUTIVE SUMMARY

Problem statement

This decentralised application concerns a generic version of paclitaxel, under the trade name Paclitaxel 6 mg/ml concentrate for solution for infusion. In this Assessment Report, the name Paclitaxel is used.

The originator product is Taxol 6 mg/l concentrate for solution for infusion held by Bristol Myers Squibb, registered since 18 November 1993.

With UK as the Reference Member State in this Decentralised Procedure Fresenius Kabi is applying for the Marketing Authorisations for Paclitaxel 6 mg/ml concentrate for solution for infusion in AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PT, RO, SE, SI, SK.

About the product

Paclitaxel is an anti-neoplastic agent (ATC L01CD01) belonging to the taxane group of anticancer drugs. It acts by promoting the assembly of microtubules from tubulin dimers and stabilising microtubules by inhibiting depolymerisation. This stability inhibits the normal dynamic reorganisation of the microtubule network essential for the vital interphase and cellular mitosis. In addition, paclitaxel causes the formation of abnormal microtubule fascicles throughout the cell cycle and formation of multiple asters of microtubules during mitosis.

Paclitaxel interferes with the normal function of microtubule growth. Whereas drugs like colchicine cause the depolymerization of microtubules in vivo, paclitaxel arrests their function by having the opposite effect; it hyper-stabilizes their structure.

The submitted indications are:

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

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

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

Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express HER-2 at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable (see section 4.4 and 5.1).

As a single agent, Paclitaxel is indicated for the treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for standard, anthracycline containing therapy.

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

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

Posology and method of administration:
The Applicant has submitted the following:
All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel, e.g.

Drug	Dose	Administration prior to Paclitaxel
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 Ranitidine	300 mg IV 50 mg IV	30 to 60 min

* 8 - 20 mg for KS patients
** or an equivalent antihistamine e.g. chlorpheniramine

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

First-line chemotherapy of ovarian carcinoma: although other dosage regimens are under investigation, a combination regimen of Paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of Paclitaxel are recommended: Paclitaxel 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every

three weeks or Paclitaxel 135 mg/m², in a 24-hour infusion, followed by cisplatin 75 mg/m², with a 3-week interval between courses (see section 5.1).

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

Adjuvant chemotherapy in breast carcinoma: the recommended dose of Paclitaxel is 175 mg/m² administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.

First-line chemotherapy of breast carcinoma: when used in combination with doxorubicin (50 mg/m²), Paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of Paclitaxel is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see section 4.5 and 5.1).

When used in combination with trastuzumab, the recommended dose of Paclitaxel is 175 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see section 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®).

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

Treatment of advanced NSCLC: the recommended dose of Paclitaxel is 175 mg/m² administered over a period of 3 hours, followed by cisplatin 80 mg/m², with a 3 week interval between courses.

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

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

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

Paediatric patients:
Safety and efficacy in children (under 18 years) has not been established. Therefore, paclitaxel is not recommended for paediatric use.

Hepatic impairment:
Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 4.4 and 5.2). Patients with severe hepatic impairment should not be treated with paclitaxel.

Renal impairment:
Studies in patients with impaired renal function have not been performed and there are insufficient data to permit dosage recommendations (see section 5.2).

General comments on the submitted dossier

The application is in accordance with Article 10(1) of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.

A Risk Management Plan has not been provided and is not required for this generic application.

Satisfactory documentation relating to a pharmacovigilance system has been provided.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

No new non-clinical studies have been submitted for this application.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to paclitaxel are of sufficient quality in view of the present European regulatory requirements.

The ASM has now been granted a CEP for the proposed drug substance. A copy of the relevant CEP for paclitaxel isolated from natural source: whole plant of Taxus x media has been provided. The re-test period of the drug substance is stated as four years on the CEP if stored in type III amber glass bottles closed with polyethylene undercaps and plastic screw cap.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches of each product presentation manufactured in 2004 and a single batch of each product

manufactured in 2007. The batch analysis results show that the finished products meet the specifications proposed and are concordant with one another.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The proposed shelf-life of 2 years when stored in the original packaging to be protected from light and not above 25 degrees C for the drug product is considered acceptable.

Non clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of paclitaxel are well known. As paclitaxel is a well known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate.

The non-clinical overview has been written by a suitably qualified expert. The overview is adequate.

Clinical aspects

Bioequivalence studies
No new data have been submitted and none are required for this application. According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

Pharmacodynamics
No novel pharmacodynamic data are supplied or required for this application. The pharmacodynamic claims in the SPC are appropriately consistent with the innovator product.

Clinical efficacy
No novel efficacy data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy of paclitaxel. Paclitaxel has an acceptable adverse event profile.

Clinical safety
No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of paclitaxel. No new safety issues have been identified.

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
No risk management plan has been submitted and one is not required for this application for a generic medicinal product on which no new safety issues have been identified.

BENEFIT RISK ASSESSMENT

The use of paclitaxel is well established. It has recognised efficacy and acceptable safety. With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. Overall the risk: benefit analysis for Paclitaxel 6mg/ml concentrate for solution for infusion is considered favourable and approval is recommended

Module 6

Steps taken after procedure

No non-confidential changes have been made to the marketing authorisation.