IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0585/029/001
Case No: 2057324

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pliva Pharma Limited

Vision House, **Bedford Road**, **Petersfield**, **Hampshire GU32 3QB**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Paclitaxel 6 mg/ml concentrate for solution for infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/12/2008** until **08/11/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paclitaxel 6mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One vial of 5ml contains 30mg paclitaxel.
One vial of 16.7ml contains 100mg paclitaxel.
One vial of 50ml contains 300mg paclitaxel.

Excipients:
ethanol, anhydrous (395mg/ml)
macrogolglycerol ricinoleate (527mg/ml)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Paclitaxel is a clear yellow viscous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

Breast cancer:
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 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 overexpress 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 either failed or are not candidates for standard, anthracycline-containing therapy.

Advanced non-small cell lung cancer:
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 radiotherapy.

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

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

4.2 Posology and method of administration

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

Drug	*Dose*	*Administration prior to Paxitel*
dexamethasone	20mg oral* or IV	For oral administration: approximately 12 and 6 hours or for IV administration: 30 to 60 min
diphenhydramine**	50mg i.v.	30-60 minutes
cimetidine or ranitidine	300mg i.v. or 50mg i.v.	30-60 minutes

* 8-20mg 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 treatment 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 175mg/m2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75mg/m2 every three weeks or paclitaxel 135mg/m², in a 24-hour infusion, followed by cisplatin 75mg/m², with a 3 week interval between courses (see section 5.1).
Second-line treatment of ovarian carcinoma: The recommended dose of paclitaxel is 175mg/m2 administered intravenously over a period of 3 hours, with a 3 week interval between courses.

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

First-line treatment of breast carcinoma: When used in combination with doxorubicin (50mg/m²), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220mg/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 175mg/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 175mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses.

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

Treatment of AIDS-related KS: The recommended dose of paclitaxel is 100mg/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 re-administered until the neutrophil count is ≥1.5x10^9/l (≥ 1x10^9/l for KS patients) and the platelet count is ≥100x10^9/l (≥ 75x10^9/l for KS patients) . Patients who experienced severe neutropaenia (neutrophil count <0.5x10^9/l for ≥7 days or longer) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (see section 4.4).

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

4.3 Contraindications

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

Paclitaxel is contraindicated during pregnancy and lactation (see section 4.6), and should not be used in patients with baseline neutrophils < 1.5x109/l (< 1x109/l for KS patients).

In KS, Paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

4.4 Special warnings and precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

Patients must be pretreated with corticosteroids, antihistamines and H2 antagonists (see section 4.2).

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

Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment as well as 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 neutropaenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to ≥1.5x10^9/l (≥1x10^9/l for KS patients) and platelets recover to ≥100x10^9/l (≥75x10^9/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 in those with breast- or ovarian carcinoma.
A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When paclitaxel is used in combination with 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 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 asses the cumulative dose (mg/m2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles). For more details see Summary of Product Characteristics of Herceptin or doxorubucin.

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of paclitaxel. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of paclitaxel as a 3 hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by cisplatin.

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression (see section 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments
(see section 5.2).
No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should not be treated with paclitaxel.

Since Paxitel contains ethanol (396mg/ml), consideration should be given to potential CNS and other effects. The amount of alcohol in this medicine can also change the effect of other medicines.

Special care should be taken to avoid intra-arterial administration of paclitaxel. In animal studies investigating local tolerance, severe tissue reactions occurred following intra-arterial administration.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.
The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given *before* cisplatin. When paclitaxel is given *before* cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel was given *after* cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.
Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see 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 into 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 CYP3A4.

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

4.6 Pregnancy and lactation

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

There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm and is therefore contraindicated during pregnancy.
Women should be advised to avoid becoming pregnant during therapy with paclitaxel, and to inform the treating physician immediately should this occur.

Paclitaxel has shown to be teratogenic, embryotoxic and mutagenic in many experimental systems. Therefore female and male patients of fertile age, and/or their partners, should use contraceptives for at least 6 months after treatment with paclitaxel.

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

4.7 Effects on ability to drive and use machines

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that the medicinal product contains alcohol (see sections 4.4 and 6.1).
The ability to drive or to use machines may be decreased due to alcohol content of this medicinal product.

4.8 Undesirable effects

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent paclitaxel in clinical studies. 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. Non of the observed toxicities were clearly influenced by age.

The most frequent clinically significant undesirable effect was *bone marrow suppression*. Severe neutropaenia (<0.5 x 10^9/l) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropaenia for 7 days or longer. Thrombocytopaenia was reported in 11% of patients. Three percent of patients had a platelet count nadir <50 x 10^9/l at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb <80 g/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 175mg/m^2 3-hour infusion (85% neurotoxicity; 15% severe) than with a 135mg/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 minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration, and on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discolouration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

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

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

very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000 < 1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000).

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
Blood and the lymphatic system disorders:	*Very common* : myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding *Rare** : febrile neutropenia *Very rare*:* acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	*Very common* : minor 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** : anaphylactic shock
Metabolism and nutrition disorders:	*Very rare** : anorexia
Psychiatric disorders:	*Very rare **: confusional stage
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

Cardiac disorders:	*Common:* bradycardia *Uncommon* : cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction *Very rare** : atrial fibrillation, supraventricular tachycardia
Vascular disorders:	*Very common* : hypotension *Uncommon:* hypertension, thrombosis, thrombophlebitis *Very rare* *: shock
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
Hepato-biliary disorders:	*Very rare*:* hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
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 (patients on therapy should wear sun protection on hands and feet)
Musculoskeletal, connective tissue and bone disorders:	*Very common:* arthralgia, myalgia
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
Investigations:	*Common* : severe elevation in AST (SGOT), severe elevation in alkaline phosphatase *Uncommon:* severe elevation in bilirubin *Rare** : increase in blood creatinine

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

Combination treatment

The following discussion refers to two major trials for the first-line chemotherapy of ovarian carcinoma (paclitaxel + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients), another one investigating the combination with trastuzumab (planned subgroup analysis paclitaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (paclitaxel + cisplatin; over 360 patients) (see 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 (220mg/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50mg/m²) when compared to standard FAC therapy (5-FU 500mg/m², doxorubicin 50mg/m², cyclophosphamide 500mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220mg/m²) / doxorubicin (50mg/m²) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel /doxorubicin arm.

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

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, *cardiac contraction abnormalities (*≥20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. *Congestive heart failure* was observed in < 1% in both paclitaxel/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of *cardiac dysfunction* in comparison with patients treated with paclitaxel single agent (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma

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

Blood and the lymphatic system disorders: Bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia (< 500 cells/mm3) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for > 7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting ≥7 days was 22%.

Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal.

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

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

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

4.9 Overdose

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plant alkaloids and other natural products, taxanes.

ATC code: L01C D01

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

In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750mg/m^2 plus cisplatin 75mg/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 (175mg/m^2 over 3 hr) followed by cisplatin (75mg/m^2) or control.

The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either paclitaxel (135mg/m² over 24 hrs) followed by cisplatin (75mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a >1 cm residual disease after staging laparotomy, or with distant metastases.

While the two different paclitaxel posologies were not compared with each other directly, in both trials patients treated with paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

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

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225mg/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 favoured 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 (50mg/m²) followed after 24 hours by paclitaxel (220mg/m² by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500mg/m², doxorubicin 50mg/m², cyclophosphamide 500mg/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 (4mg/kg loading dose then 2mg/kg weekly) and paclitaxel (175mg/m²) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175mg/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 175mg/m^2 followed by cisplatin 80mg/m^2 has been evaluated in two phase III trials (367 patients with NSCLC on paclitaxel 6mg/ml containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100mg/m^2, the other used teniposide 100mg/m^2 followed by cisplatin 80mg/m^2 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 175mg/m^2. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hr/m^2; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m^2, 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 135mg/m^2 to 175mg/m^2, the C_{max} and $AUC_{0-\infty}$ values increased 75% and 81%, respectively.

Following an intravenous dose of 100mg/ m² given as a 3-hour infusion to 19 KS patients, the mean Cmax 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 of 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 radiolabeled 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 135mg/m^2 were within the range of those defined in non-dialysis patients.

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous
Macrogolglycerol ricinoleate

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.

6.3 Shelf Life

Vial before opening:
2 years

After opening before dilution:
From a microbiological point of view, the opened vial can be stored for up to 28 days at 25°C.
Other storage times and storage conditions after opening are the responsibility of the user.

After dilution:
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated for 27 hours at 25° C.
From a microbiological point of view, diluted solution should be used immediately. The prepared infusion should not be stored in a refrigerator.

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

Glas vial with butyl rubber stopper

Vials of :
1 x 5ml (30mg)
1 x 16.7ml (100mg) – multidose vial
10 x 16.7ml (10 x 100mg) – multidose vial
1 x 50ml (300mg) - multidose vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Handling: as with all antineoplastic agents, caution should be exercised when handling paclitaxel.
Pregnant women or women of childbearing potential must be warned to avoid handling cytotoxic agents.

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

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

Devices for withdrawal of doses from the vial according to so called “closed system”, e.g. types of Chemo-Dispensing Pin devices, should not be used since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.

Preparation for IV administration: Prior to infusion, paclitaxel 6mg/ml concentrate for solution for infusion must be diluted, using aseptic techniques, in 0.9% Sodium Chloride Injection, or 50mg/ml Dextrose Injection, or 5% Dextrose and 0.9% Sodium Chloride Injection, or 50mg/ml Dextrose in Ringer's Injection, to a final concentration of 0.3 to 1.2mg/ml.

The prepared infusion solution has a shelf-life of up to 27 hours at 25°C. Following repeated withdrawl of doses with a withdrawal cannula, Paxitel in multidose vials retains its microbial and chemical/physical integrity for up to 28 days at 25°C. Other storage times and storae conditions after opening are the responsibility of the user. Diluted solutions must not be stored in a refrigerator.

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 ≤0.22μm. 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 inspected regularly and the infusion should be stopped if precipitation is present.

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

Disposal: All items used for preparation, administration or otherwise coming into contact with Paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7 MARKETING AUTHORISATION HOLDER

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10 DATE OF REVISION OF THE TEXT