IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0002/059/001A
Case No: 2060347

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

Bristol-Myers Squibb Pharmaceuticals Ltd

Swords, **Co. Dublin**, **Ireland**

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

TAXOL 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 **22/05/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 6 mg/ml of paclitaxel (6 mg per 1 ml of concentrate for solution for infusion).
A vial of 5 ml contains 30 mg of paclitaxel
A vial of 16.7 ml contains 100 mg of paclitaxel
A vial of 25 ml contains 150 mg of paclitaxel
A vial of 50 ml contains 300 mg of paclitaxel.

Excipients: ethanol anhydrous 396 mg/ml and castor oil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to slightly yellow viscous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ovarian carcinoma: in the first-line chemotherapy of ovarian cancer, TAXOL 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, TAXOL is indicated for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy.

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

TAXOL 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, Special warnings and precautions for use and 5.1, Pharmacodynamic properties).*

As a single agent, TAXOL 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: TAXOL, 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: TAXOL 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, Pharmacodynamic properties.*

4.2 Posology and method of administration

TAXOL should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents *(see section 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).*

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

Medicinal Product	Dose	Administration prior to TAXOL
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

For instructions on dilution of the product before administration, see section 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.* TAXOL should be administered intravenously through an in-line filter with a microporous membrane ≤ 0.22 µm *(see section 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).*

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

Second-line chemotherapy of ovarian carcinoma: the recommended dose of TAXOL 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 TAXOL 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), TAXOL should be administered 24 hours after doxorubicin. The recommended dose of TAXOL is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses *(see sections 4.5, Interaction withother medicinal products and other forms of interaction and 5.1, Pharmacodynamic properties).*
When used in combination with trastuzumab, the recommended dose of TAXOL is 175 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses *(see section 5.1, Pharamcodynamic properties).* TAXOL 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 TAXOL 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 TAXOL 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 TAXOL is 100 mg/m^2 administered as a 3-hour intravenous infusion every two weeks.

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

TAXOL 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, Special warnings and precautions for use)*.

Patients with hepatic impairment: inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments *(see section 4.4, Special warnings and precautions for use and 5.2, pharmacokinetic properties).* Patients with severe hepatic impairment should not be treated with paclitaxel.

Paediatric use: TAXOL is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to paclitaxel or to any excipient, especially polyoxyethylated castor oil *(see section 4.4, Special warnings and precautions for use).*

TAXOL should not be used in patients with baseline neutrophils <1, 500/mm^3 (<1, 000/mm^3 for KS patients).

TAXOL is contraindicated during lactation *(see section 4.6, Pregnancy and Lactation).*

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

4.4 Special warnings and precautions for use

TAXOL 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, Posology and administration).*

TAXOL should be given before cisplatin when used in combination *(see section 4.5, Interaction with other medicinal products and other forms of interaction).*

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

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to ≥ 1,500/mm³ (≥ 1,000/mm³ for KS patients) and platelets recover to ≥ 100,000/mm³ (≥ 75,000/mm³ for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3-4 myelosuppression. There is no evidence that the toxicity of TAXOL is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When TAXOL 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, Posology and method of administration).* Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments *(see section 5.2, pharmacokinetic properties).*
No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment must not be treated with paclitaxel.

Severe cardiac conduction abnormalities have been reported rarely with single agent TAXOL. If patients develop significant conduction abnormalities during TAXOL administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with TAXOL. Hypotension, hypertension, and bradycardia have been observed during TAXOL administration, patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of TAXOL 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 TAXOL is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function.

When patients are candidates for treatment with TAXOL in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/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 TAXOL is recommended. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of TAXOL as a three hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent TAXOL and cyclophosphamide followed by cisplatin.

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

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

Since TAXOL contains *ethanol* (396 mg/ml), consideration should be given to possible CNS and other effects.

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.

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

The recommended regimen of TAXOL administration for the first-line chemotherapy of ovarian carcinoma is for TAXOL to be given before cisplatin. When TAXOL is given before cisplatin, the safety profile of TAXOL is consistent with that reported for single-agent use. When TAXOL was given after cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance.

Patients treated with TAXOL 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, TAXOL for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin *(see section 5.2, Pharmacokinetic properties).*

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 *(see section 5.2, pharmacokinetic properties).* 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.

Paclitaxel clearance is not affected by cimetidine premedication.

Studies in KS patients, who were taking multiple concomitant medicinal products, 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

There is no adequate data from the use of paclitaxel in pregnant women. Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits, and to reduce fertility in rats. As with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women. Therefore, paclitaxel should not be used during pregnancy unless clearly necessary. Women of childbearing potential receiving paclitaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraceptions 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.

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

4.7 Effects on ability to drive and use machines

TAXOL has not been demonstrated to interfere with the ability to drive and use machines. However, it should be noted that TAXOL does contain alcohol *(see sections 4.4, Special warnings and Precautions for use and 6.1, Excipients).*

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 TAXOL 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 adverse reactions, unless otherwise mentioned, are generally similar between patients receiving TAXOL for the treatment of ovarian carcinoma, breast carcinoma, or NSCLC. None of the observed toxicities were clearly influenced by age.

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%) 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 TAXOL therapy.

The most frequent significant adverse event was *bone marrow suppression*. Severe neutropenia (< 500 cells/mm³) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for ≥ 7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir < 50,000/mm³ at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb < 5 mmol/l) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.

Neurotoxicity, mainly *peripheral neuropathy*, appeared to be more frequent and severe with a 175 mg/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 TAXOL was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with TAXOL 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 TAXOL. Peripheral neuropathy was the cause of TAXOL discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of TAXOL discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for TAXOL therapy.

Arthralgia or myalgia affected 60% of patients and was severe in 13% of patients.

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 TAXOL 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 adverse reactions regardless of severity associated with the administration of single agent TAXOL administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the postmarketing surveillance* of Taxol.

The frequency of adverse reactions 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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*: myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy *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**: grand mal seizures, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, convulsions, dizziness, ataxia, headache
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**: hearing loss, ototoxicity, tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders:	*Rare*:* respiratory failure, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion *Very rare**: cough
Gastrointestinal disorders:	*Very common*: diarrhoea, vomiting, nausea, mucosal inflammation *Rare**: bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis *Very rare**: mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, ascites, oesophagitis, constipation,

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 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:* thrombosis, hypertension, 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*:* pyrexia, dehydration, asthenia, oedema, malaise
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
Hepatobiliary disorders:	*Very rare*:* hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Psychiatric disorders:	*Very rare**: confusional state

Breast cancer patients who received TAXOL 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 TAXOL, as reported above.

Combination treatment

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

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 TAXOL followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with TAXOL 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 TAXOL (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 TAXOL (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 TAXOL/doxorubicin arm.

When TAXOL 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 TAXOL or trastuzumab) were reported more frequently than with single agent TAXOL: 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 TAXOL/trastuzumab combination vs single agent TAXOL. Severe events were reported at similar rates for TAXOL/trastuzumab and single agent TAXOL.

When doxorubicin was administered in combination with TAXOL 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 TAXOL/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with TAXOL in patients previously treated with anthracyclines resulted in an increased frequency and severity of *cardiac dysfunction* in comparison with patients treated with TAXOL single agent (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma

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

Blood and the lymphatic system disorders: bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia (< 500 cells/mm^3) 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/mm^3) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm^3, 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 TAXOL overdose. In case of overdose, the patient should be closely monitored. Treatment should be directed at the primary anticipated toxicities which consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents (taxanes) / ATC code: L01C D01.

Paclitaxel is a 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.

<u>Ovarian carcinoma</u>
In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of TAXOL 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 TAXOL (175 mg/m^2 over 3 hours) 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 TAXOL (135 mg/m^2 over 24 hrs) followed by cisplatin (75 mg/m^2) 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 TAXOL posologies were not compared with each other directly, in both trials patients treated with TAXOL 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 TAXOL/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

Breast carcinoma

In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant TAXOL therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, TAXOL 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 + TAXOL 8 cycles). Therefore, adjuvant treatment with TAXOL 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 TAXOL 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, TAXOL patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006) ; TAXOL treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favored the TAXOL 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 TAXOL were evaluated in two pivotal, phase III, randomised and controlled open-label trials.

- In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m²) followed after 24 hours by TAXOL (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 TAXOL/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 TAXOL/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 TAXOL 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 TAXOL (175 mg/m²) 3-hour infusion, every three weeks was compared to single-agent TAXOL (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. TAXOL 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 TAXOL/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 TAXOL alone. The most significant toxicity observed with the TAXOL/trastuzumab combination was cardiac dysfunction *(see section 4.8, Undesirable effects).*

Advanced non-small cell lung carcinoma
In the treatment of advanced NSCLC, TAXOL 175 mg/m² followed by cisplatin 80 mg/m² has been evaluated in two phase III trials (367 patients on TAXOL 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 TAXOL containing regimen and the comparator (median survival times 8.1 and 9.5 months on TAXOL 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 TAXOL containing regimens in terms of appetite loss and provide clear evidence of the inferiority of TAXOL containing regimens in terms of peripheral neuropathy ($p < 0.008$).

AIDS-related Kaposi's sarcoma
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 $AUC_{0\rightarrow\infty}$ values increased 75% and 81%, respectively.

Following an intravenous dose of 100 mg/m^2 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/m^2 (range 11-38) and the volume of distribution was 291 l/m^2 (range 121-638). The terminal elimination half-life averaged 23.7 hours (range12 - 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 medicinal product 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 TAXOL 135 mg/m² were within the range of those defined in non-dialysis patients.

In clinical trials where TAXOL 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 medicinal products.

For use of TAXOL 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. TAXOL has been shown to be mutagenic in both *in vitro* and *in vivo* mammalian test systems. Paclitaxel has also been shown to be both embryotoxic and foetotoxic in rabbits, and to reduce fertility in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous.
Chromatographically purified polyoxyethylated castor oil.

6.2 Incompatibilities

Polyoxyethylated castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted TAXOL should be carried out using non-PVC–containing equipment. The medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf Life

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

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

6.4 Special precautions for storage

Store below 25°C.

Store in original package in order to protect from light.

Freezing does not adversely affect the unopened vials.

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

6.5 Nature and contents of container

Different pack sizes are available in vials (type I glass) with stopper (butyl rubber) packaged individually in a carton:
– a 5 ml vial containing 30 mg paclitaxel
– a 16.7 ml vial containing 100 mg paclitaxel
– a 25 ml vial containing 150 mg paclitaxel
– a 50 ml vial containing 300 mg paclitaxel
Boxes containing 10 cartons are also available.

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

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

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

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

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

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

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. TAXOL 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 TAXOL 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, TAXOL 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 TAXOL 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 should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Limited
Swords
County Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0002/059/001

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10 DATE OF REVISION OF THE TEXT

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