Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Also includes excipients:
Ethanol anhydrous: 396 mg/ml
Macrogolglycerol ricinoleate: 527 mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

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

Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable *(see sections 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties).*

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

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

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

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

4.2 Posology and method of administration

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

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

*8-20 mg for KS patients
** or an equivalent antihistamine e.g. chlorpheniramine 10 mg IV

Appropriate supportive medications should be readily available in case of severe hypersensitivity reactions.

Paclitaxel should be administered through an in-line filter with a microporous membrane ≤ 0.22 µm *(see section6.6, 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 regimes are under investigation, a combination regimen of paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel are recommended: paclitaxel 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every three weeks or paclitaxel 135 mg/m^2, in a 24-hour infusion, followed by cisplatin 75 mg/m^2, with a 3-week interval between courses *(see section 5.1 Pharmacodynamic properties).*

Second-line chemotherapy of ovarian carcinoma
The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours, with a 3-week interval between courses.

Adjuvant chemotherapy in breast carcinoma
The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.

First-line chemotherapy of breast carcinoma
When used in combination with doxorubicin (50 mg/m^2), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses (*see sections 4.5, Interaction with other medicinal products and other forms of interactions and section 5.1, Pharmacodynamic properties).*

When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses (*see section 5.1, Pharmacodynamic properties)*. 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 trastuzumab).

Second-line chemotherapy of breast carcinoma
The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours, with a 3-week interval between courses.

Treatment of advanced NSCLC
The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours, followed by cisplatin 80 mg/m^2, with a 3-week interval between courses.

Treatment of AIDS-related KS
The recommended dose of paclitaxel is 100 mg/m^2 administered as a 3-hour intravenous infusion every two weeks.

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

Paclitaxel should not be readministered until the neutrophil count is ≥1,000/mm^3 and the platelet count is ≥75,000/mm^3. Patients who experience severe neutropenia (neutrophil count <500/mm^3 for ≥ 7 days), severe peripheral neuropathy or mucositis (grade 3 or worse) should receive a dose reduction of 25% to 75mg/m^2 for subsequent courses *(see section 4.4 Special warnings and precautions for use).*

Dosage adjustments during treatment

Metastatic breast carcinoma (MBC), ovarian cancer (MOC) and non-small cell lung carcinoma (NSCLC)
Courses of paclitaxel should not be repeated until the neutrophil count is at least 1, 500 cells/mm^3 and the platelet count is at least 100, 000 cells/ mm^3 . Patients who experience severe neutropenia (neutrophils <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during paclitaxel therapy should have their dosage reduced by 20% (NSCLC and first line treatment of ovarian cancer) or 25% (MBC and MOC) for subsequent courses of paclitaxel. Patients who experience mucositis (grade 2 or worse) during paclitaxel therapy should have their dosage reduced by 25% for subsequent courses of paclitaxel.

Patients with hepatic impairment
Studies in patients with impaired hepatic function have not been performed. 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 section 5.2, Pharmacokinetic Properties).*Patients with severe hepatic impairment should not be treated with paclitaxel.

Patients with impaired renal function
Studies in patients with impaired renal function have not been performed and there are insufficient data to permit dosage recommendations.

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

Method of administration
The concentrate for solution for infusion must be diluted before use *(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)* and should only be administered intravenously.

4.3 Contraindications

Paclitaxel is contraindicated in patients with a history of severe hypersensitivity to paclitaxel or to any excipient, especially macrogolglycerol ricinoleate (*see section 4.4, Special warnings and precautions for use*).

Paclitaxel is contraindicated in patients with severe hepatic impairment.

Paclitaxel is contraindicated during lactation (*See section 4.6, Pregnancy and lactation),* and should not be used in patients with baseline neutrophils <1,500/mm^3 (<1,000/mm^3 for KS patients).

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

4.4 Special warnings and precautions for use

Paclitaxel products contain macrogolglycerol ricinoleate, which can cause an allergic reaction.

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.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Patients must be routinely pretreated with corticosteroids, antihistamines and H_2 antagonists to prevent severe hypersensitivity reactions (see section 4.2).

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

Hypersensitivity reactions
Significant hypersensitivity reactions characterised by dyspnoea requiring brochodilators and hypotension requiring treatment, angioedema and generalised urticaria 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, aggressive symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.
Minor symptoms such as flushing or skin reaction do not require interruption of therapy.

Patients should be observed closely during the initial cycles of treatment. Appropriate supportive therapies should be readily available in case of a severe hypersensitivity reaction.

Haematology
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/mm^3 (≥1,000/mm^3 for KS patients) and platelets recover to ≥100,000/mm^3 (≥75,000/mm^3 for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

Patients with severe neutropenia (< 500 cells/mm^3 for 7 days or more) during a course of paclitaxel or neutropenic sepsis should have their dose of paclitaxel reduced for subsequent courses of paclitaxel (see section 4.2).

Mucositis
Moderate to severe mucositis is uncommon with the recommended dose and schedule of paclitaxel. However, if treatment is to be continued in the event of moderate or severe reactions, the dose of paclitaxel should be reduced for subsequent courses of paclitaxel therapy (see section 4.2). In KS patients, severe mucositis is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

Cardiac conduction abnormalities and arrhythmias
Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel. Mild electrocardiogram changes have been observed during administration of paclitaxel. Cardiac monitoring is not recommended except in patients with serious conduction abnormalities or arrhythmias. If patients develop significant conduction abnormalities or arrhythmias 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. Additionally, in paclitaxel MBC and MOC studies tachycardia, palpitation and syncope were observed. Therefore frequent vital sign monitoring, particularly during the first hour of Paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian carcinoma.
In de MBC and MOC studies a total of two patients experienced Grade 4 congestive heart failure. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When Paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with Paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or Multiple Gated Acquisition (MUGA) scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m^2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potential irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles). For more details see Summary of Product Characteristics of trastuzumab or doxorubicin.

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

Hepatic impairment
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.

Gastrointestinal
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.

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

Paclitaxel contains macrogolglycerol ricinoleate, which may cause severe allergic reactions.

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

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

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.
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

Formal clinical drug interaction studies have not been performed with paclitaxel.

Paclitaxel clearance is not affected by cimetidine premedication.

The recommended regimen of Paclitaxel administration in 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 approximate 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

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

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 *(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. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicinal products known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil, imidazole antifungals) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or CYP3A4 as the pharmacokinetics of paclitaxel may be affected.
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.

Studies in KS patients, who were taking paclitaxel and multiple concomitant medications, suggest that the systematic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir ($p<0.05$), 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 Fertility, pregnancy and lactation

Pregnancy
Paclitaxel at an intravenous dose of 0.6 mg/kg/day produced reproductive and foetal development toxicity in rats. Paclitaxel has been shown to be embroytoxic and foetotoxic in rabbits, and to decrease fertility in rats.

There is no adequate information on the use of paclitaxel in pregnant women. As with other cytotoxic medicinal products, Paclitaxel may cause foetal harm. Therefore paclitaxel must not be used during pregnancy unless clearly necessary. Women should be advised to use effective means of contraception to avoid becoming pregnant during therapy with Paclitaxel, and to inform the treating physician immediately should this occur.

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

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

4.7 Effects on ability to drive and use machines

Paclitaxel has no influence on the ability to drive and use machines. However, it should be noted that the formulation contains alcohol (*see section 4.4, Special warnings and precautions for use and 6.1, list of excipients).*

4.8 Undesirable effects

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

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

The most frequent significant undesirable effect was **bone marrow suppression**. Severe neutropenia (<500 cells/mm^3) 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/mm^3 at least once while on study. **Anaemia** was observed in 64% of patients, but was severe (Hb <5 mmol/l) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.

Neurotoxicity, mainly **peripheral neuropathy**, appeared to be more frequent and severe with a 175 mg/m^2 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m^2 24-hour infusion (25% peripheral neuropathy, 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

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

A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (<1%) of patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. “recall”, has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.
In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

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 (286 patients treated in paclitaxel clinical studies and 812 patients treated in other clinical studies) and those reported in the postmarketing surveillance (see*).

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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations:	*Very common*: infection (mainly urinary tract and upper respiratory tract infections including herpes simplex, oral candidiasis, pharyngitis, rhinitis), with reported cases of fatal outcome *Common:* flu syndrome *Uncommon*: severe infection, septic shock *Rare**: sepsis, pneumonia, peritonitis
Blood and the lymphatic system disorders:	*Very common*: myelosuppression, severe neutropenia, anaemia, thrombocytopenia, severe leucopenia, bleeding *Common:* neutropenic fever *Uncommon:* severe anaemia *Rare*:* febrile neutropenia *Very rare**: acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	*Very common*: minor hypersensitivity reactions (mainly flushing and rash) *Uncommon*: (delayed) hypersensitivity, 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 (including fatal hypersensitivity)
Metabolism and nutrition disorders:	*Very common**: anorexia *Uncommon:* weight gain, weight loss *Not known*:* tumor lysis syndrome
Psychiatric disorders:	*Very rare**: confusional state
Nervous system disorders:	*Very common*: neuropathy (mainly: peripheral), paraesthesia, somnolence *Common*: depression, severe neuropathy (mainly peripheral), nervousness, insomnia, abnormal thinking, hypokinesia, abnormal gait, hypoaesthesia, taste perversion *Rare**: motor neuropathy (with resultant minor distal weakness) *Very rare**: autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, acute encephalopathy, dizziness, ataxia, headache
Eye disorders:	*Uncommon:* dry eyes, amblyopia, visual field defect *Very rare**: optic nerve disorder and/or visual disturbances (scintillating scotoma), particularly in patients who have received higher doses than recommended *Not known*:* macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders:	*Very rare**: ototoxicity**,** sensorineural hearing loss, tinnitus, vertigo
Cardiac disorders:	*Common*: bradycardia, tachycardia, palpitation, syncope *Uncommon*: congestive heart failure, myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy *Rare:* cardiac failure *Very rare**: atrial fibrillation, supraventricular tachycardia

Vascular disorders:	*Very common*: hypotension *Common:* vasodilatation (flushing) *Uncommon*: thrombosis, hypertension, thrombophlebitis *Very rare**: shock *Not known:* phlebitis
Respiratory, thoracic and mediastinal disorders:	*Common:* epistaxis *Rare**: respiratory failure pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion *Very rare**: cough, pulmonary hypertension
Gastrointestinal disorders:	*Very common*: diarrhoea, vomiting, nausea, mucosal inflammation, stomatitis, abdominal pain *Common:* dry mouth, mouth ulceration, melaena, dyspepsia *Rare*:* bowel obstruction, bowel perforation, ischemic colitis, acute pancreatitis *Very rare**: mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, necrotising enterocolitis, ascites, oesophagitis, constipation,
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 change, dry skin, acne *Uncommon:* changes in nail pigmentation or discoloration of nail bed *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), folliculitis *Not known:* scleroderma
Musculoskeletal, connective tissue and bone disorders:	*Very common*: arthralgia, myalgia *Common:* bone pain, leg cramps, myasthenia, back pain *Not known:* systemic lupus erythematosis
Renal and urinary disorders	*Common:* dysuria
General disorders and administration site conditions:	*Very common:* asthenia, pain, oedema including peripheral and face *Common*: mild injection site reaction (including localised oedema, pain, erythema, induration, tenderness, skin discoloration or swelling, on occasion extravasation, can result in cellulitis and skin fibrosis and skin necrosis), chest pain, chills *Rare*:* pyrexia, dehydration, asthenia, oedema, malaise
Investigations:	*Common*: severe elevation in transaminases 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 (220 mg/m^2) was administered as a 3 hour infusion 24 hours following doxorubicin (50 mg/m^2) when compared to standard FAC therapy (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m^2/ doxorubicin (50 mg/m^2) 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 administrated 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 <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.

In eight published clinical trials (8 Phase III trials) including 4735 patients with advanced ovarian cancer and in twelve published clinical trials (one large Phase II and eleven Phase III trials) including 4315 NSCLC patients treated with paclitaxel and platinum-containing regimens, similar undesirable effects were observed compared to single-agent paclitaxel treatment. Additionally ileus, effects on creatinine clearance, abnormal electrolytes (e.g. hyponatraemia, hypomagnesaemia), hyperglycaemia, cough and pneumonia occurred very rarely.

Pneumonitis in patients receiving concomitant radiotherapy has been reported.

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 treated with 100 mg/m^2 paclitaxel administered as a 3-hour infusion as second-line chemotherapy.

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.

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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. In the event of an overdose, the patient should be closely monitored. Treatment should be directed at the major anticipated toxicities which are bone marrow suppression, peripheral neuropathy and mucositis.
Overdoses in pediatric patients may be associated with acute ethanol toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents / taxanes
ATC code: L01CD01

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

In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750 mg/m^2 / cisplatin 75 mg/m^2) clinical trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II_{b-c}, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m^2 over 3 hr) followed by cisplatin (75 mg/m^2) or control. The second major trial (GOG-111/B-MS CA139-022) evaluated a maximum of 6 courses of either paclitaxel (135 mg/m^2 over 24 hours) 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 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 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 had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p=0.0014) and a significant reduction of 19% in the risk of death (p= 0.0044) relative to patients receiving AC alone.

Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/unknown tumors, reduction in risk of disease recurrence was 28% (95% CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumors, the risk reduction of disease recurrence was 9% (95 CI: 0.78-1.07). However, the design of the study did not investigate the effect of extended AC therapy beyond 4 cycles. It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel 8 cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.
In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225 mg/m^2 following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p=0.006); paclitaxel treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumor had a reduction in the risk of disease of 23% (95% CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumor the risk reduction of disease recurrence was 10% (95%CI: 0.7-1.11).

In the first-line treatment of metastatic breast cancer, the efficacy and safety of paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials.
In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m^2) followed after 24 hours by paclitaxel (220 mg/m^2 by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) both administered every three weeks for eight courses. In the 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 includes taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the paclitaxel/doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second pivotal study, the efficacy and safety of the paclitaxel and trastuzumab combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven.

The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and paclitaxel (175 mg/m^2) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175 mg/m^2) 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, Undesirable effects*).

In the treatment of advanced NSCLC, paclitaxel 175 mg/m^2 followed by cisplatin 80 mg/m^2 has been evaluated in two phase III trials (367 patients on paclitaxel containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100 mg/m^2, the other used teniposide 100 mg/m^2 followed by cisplatin 80 mg/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 after 3- and 24-hour infusions at doses of 135 mg/m^2 and 175 mg/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 135 mg/m^2 to 175 mg/m^2, there is a 75% increase in maximum serum concentration and an 81% increase in the AUC.

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 (range 12-33).

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

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

The disposition of paclitaxel has not yet 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-dihydroxypaclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, CYP3A4 and both CYP2C8 and CYP3A4 respectively.
The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally.

Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a 3-hour infusion of paclitaxel 135 mg/m^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 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 (396 mg/ml)
Citric acid, anhydrous
Macrogolglycerol ricinoleate (527 mg/ml).

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 solutions should be carried out using non-PVC-containing equipment.

6.3 Shelf life

Vial before opening:
2 years.

After opening before dilution
Chemical and physical in-use stability has been demonstrated for 28 days below 25°C following multiple needle entries and withdrawal.

From a microbiological point of view, after first opening the concentrated solution for infusion may be stored for a maximum of 28 days below 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 for 27 hours at 25 ° C when diluted in a mixture of 9 mg/ml (0.9 %) sodium chloride solution for infusion and 50 mg/ml (5 %) glucose solution for infusion, or Ringer's solution for infusion containing 50 mg/ml (5 %) glucose.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5 ºC and at 25 ºC for 14 days when diluted in 50 mg/ml (5 %) glucose solution for infusion or in 9 mg/ml (0.9 %) sodium chloride solution for infusion.

Microbiological in-use stability of the solution prepared for infusion has been demonstrated for 27 hours at 25°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

Diluted solutions: *see section 6.3, Shelf life.*

6.5 Nature and contents of container

Colourless, type I glass vial with bromobutylrubber stopper with Teflon coating, with aluminium seal and plastic snap-cap.
Vials of 5 ml, 16.7 ml, 25ml and 50 ml.

Not all pack sizes may be marketed in all member states.

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 should not handle cytotoxic agents (s*ee section 4.6, Pregnancy and lactation)*. 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 or mucous membranes. In the event of contact with the skin, the area should be washed with soap and water. Following topical exposure, tingling, burns 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 or frozen, a precipitation 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 intravenous administration
Prior to infusion, Paclitaxel must be diluted using aseptic techniques in 9 mg/ml (0.9%) sodium chloride solution for infusion, or 50 mg/ml (5%) glucose solution for infusion, or a mixture of 9 mg/ml (0.9%) sodium chloride solution for infusion and 50 mg/ml (5%) glucose solution for infusion**,** or Ringer’s solution for infusion containing 50 mg/ml (5%) glucose, to a final concentration of 0.3 to 1.2 mg/ml.

For microbial, chemical and physical in-use stability of the diluted solutions *see section 6.3., Shelf life.*

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

There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24-hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, Paclitaxel should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use.

During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

To minimise patient exposure to DEHP [di-(2-ethylhexyl)phthalate] which may be leached from plasticised PVC infusion materials, 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 which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Disposal
All items used for the 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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The Netherlands

8 MARKETING AUTHORISATION NUMBER

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