ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paxene 6 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 6 mg/ml of paclitaxel (30 mg of paclitaxel in 5 ml or 100 mg of paclitaxel in 16.7 ml or 150 mg of paclitaxel in 25 ml or 300 mg of paclitaxel in 50 ml).

Excipients

One vial contains polyoxyl castor oil: 527 mg/ml and ethanol anhydrous; 49.7 v/v%

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

Paxene is indicated for the treatment of patients with:
- advanced AIDS-related Kaposi's sarcoma (AIDS-KS) who have failed prior liposomal anthracycline therapy;
- metastatic carcinoma of the breast (MBC) who have failed, or are not candidates for standard anthracycline-containing therapy;
- advanced carcinoma of the ovary (AOC) or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin as first-line treatment;
- metastatic carcinoma of the ovary (MOC) after failure of platinum-containing combination therapy without taxanes as second-line treatment;
- non-small cell lung carcinoma (NSCLC) who are not candidates for potentially curative surgery and/or radiation therapy, in combination with cisplatin. Limited efficacy data supports this indication (see section 5.1).

4.2 Posology and method of administration

Paxene should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents (see section 6.6).

All patients must be pre-medicated with corticosteroids, antihistamines and H_2 antagonists prior to Paxene. The following is a recommended pre-medication regimen: dexamethasone (8 - 20 mg) given orally (12 and 6 hours) or intravenously (30 - 60 mins) prior to Paxene, chlorpheniramine 10 mg intravenously or an equivalent antihistamine 30 to 60 minutes before Paxene and cimetidine (300 mg) or ranitidine (50 mg) intravenously 30 to 60 minutes before Paxene. Appropriate supportive medicinal products should be readily available in case of severe hypersensitivity reactions.

For use of cisplatin in treatment of advanced ovarian carcinoma and non-small cell lung carcinoma, please consult the cisplatin Summary of Product Characteristics for information.

AIDS-related Kaposi's sarcoma
The recommended dose of Paxene is 100 mg/m^2 administered as a 3-hour intravenous infusion every two weeks.

Metastatic breast and ovarian cancer (second-line treatment)
The recommended dose of Paxene is 175 mg/m^2 administered as a 3-hour intravenous infusion every three weeks.

Advanced ovarian carcinoma (first-line treatment)
Although other dose regimens/combinations are under investigation, a combination regimen of Paxene and cisplatin is recommended. According to the duration of infusion, two dose regimes of Paxene are recommended: Paxene 175 mg/m^2 administered as a 3-hour intravenous infusion, followed by cisplatin 75 mg/m^2 every three weeks or Paxene 135 mg/m^2 as a 24-hour infusion, followed by cisplatin 75 mg/m^2 every three weeks.

Advanced non-small cell lung carcinoma
The recommended dose of Paxene is 175 mg/m^2 administered as a 3-hour intravenous infusion, followed by cisplatin at a dose of 80 mg/m^2 every three weeks.

Dose adjustments during treatment

Metastatic breast carcinoma, ovarian cancer and non-small cell lung carcinoma:
Courses of Paxene 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 Paxene therapy should have their dose reduced by 20 % (NSCLC and first-line treatment of ovarian cancer) or 25 % (MBC and MOC) for subsequent courses of Paxene. Patients who experience mucositis (Grade 2 or worse) during Paxene therapy should have their dose reduced by 25 % for subsequent courses of Paxene.

AIDS-related Kaposi's sarcoma
Courses of Paxene should not be repeated until the neutrophil count is at least 1,000 cells/mm^3 and the platelet count is at least 75,000 cells/mm^3. Patients who experience severe neutropenia (neutrophils < 500 cells/mm^3 for a week or longer), severe peripheral neuropathy or mucositis (Grade 3 or worse) during Paxene therapy should have their dose reduced by 25 % to 75 mg/m^2 for subsequent courses of Paxene.

Special populations

Patients with impaired hepatic function:
Adequate data are not available to recommend dose alterations in patients with mild to moderate hepatic impairment (see sections 4.4 and 5.2). Patients with severe hepatic dysfunction 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 dose recommendations (see section 5.2).

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

Paxene should be administered via an infusion control device (pump) using non-PVC tubing and connectors. An in-line filter with a microporous membrane not greater than 0.22 µm should be attached to the intravenous tubing during infusion of Paxene (see section 6.6).

4.3 Contraindications

Hypersensitivity to paclitaxel or to any of the excipients.

Severe hepatic impairment.

Baseline neutrophil count < 1,500 cells/mm^3 (< 1,000 cells/mm^3 for AIDS-KS).

Concurrent, serious, uncontrolled infections.

Pregnancy and lactation.

4.4 Special warnings and special precautions for use

Patients must be routinely premedicated with a corticosteroid, an antihistamine, and an H_2-receptor antagonist prior to Paxene to prevent severe hypersensitivity reactions (see section 4.2).

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

Hypersensitivity reactions

Minor symptoms such as flushing or skin reactions do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angio-oedema or generalised urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients experiencing severe reactions should not be rechallenged with the product.

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

Paclitaxel causes bone marrow suppression (particularly neutropenia). Therefore, frequent complete blood counts should be performed on all patients during treatment. Patients with baseline neutrophil counts < 1,500 cells/mm^3 (< 1,000 cells/mm^3 for AIDS-KS) should not receive paclitaxel.

Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophil counts recover to ≥ 1,500 cells/mm^3 (≥ 1,000 cells/mm^3 for AIDS-KS patients) and platelets recover to a level of ≥ 100,000 cells/mm^3 (≥ 75,000 cells/mm^3 for AIDS-KS patients).

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 Paxene therapy (see section 4.2).

Mucositis

Moderate to severe mucositis is uncommon with the recommended dose and schedule of Paxene. 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 Paxene (see section 4.2).

Neuropathy

Neuropathy, primarily peripheral sensory neuropathy, occurs very commonly and is usually of mild to moderate intensity. Severe peripheral neuropathy occurred in 3 % of patients treated with the recommended dose and schedule of Paxene. In the treatment of NSCLC and the first-line treatment of ovarian cancer, the administration of paclitaxel as a 3 hour infusion in combination with cisplatin

resulted in a greater incidence of severe neurotoxicity than both single-agent paclitaxel and cyclophosphamide followed by cisplatin.

If severe peripheral neuropathy occurs the benefit of continued treatment should be weighed against the risks. However, if treatment is to be continued, the dose of paclitaxel should be reduced for all subsequent courses of Paxene (see section 4.2).

Cardiac conduction abnormalities and arrhythmias

In patients treated with paclitaxel severe conduction abnormalities are rare. Mild electrocardiogram changes have been observed during administration of paclitaxel. Cardiac monitoring is not recommended except in patients with serious conduction abnormalities or arrhythmias. In the rare event of serious conduction abnormalities or arrhythmias, appropriate therapy and continuous cardiac monitoring is recommended during subsequent cycles of therapy. Hypotension, hypertension and bradycardia have been observed during administration of paclitaxel but patients are usually asymptomatic and do not require therapy.

Additionally, in Paxene MBC and MOC studies tachycardia, palpitation and syncope were observed. Therefore, frequent monitoring of vital signs during the first hours of Paxene infusion is recommended.

In the MBC and MOC studies a total of two patients experienced Grade 4 congestive heart failure. A single case of heart failure related to Paxene was seen in the AIDS-KS clinical study.

Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian carcinoma.

Hepatic impairment

Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3-4 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 given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be closely monitored for the development of profound myelosuppression (see section 4.2). Adequate data are not available to recommend dose alterations in patients with mild to moderate hepatic impairments (see section 4.2). 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

As Paxene contains ethanol (392 mg/ml), possible effects on the CNS and other effects should be considered (see section 4.7).

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

Like other genotoxic cytostatics, paclitaxel can have genotoxic effects. Male patients treated with Paxene are advised not to father a child during and up to six months after treatment.

Paxene contains polyoxyl castor oil, which can cause an allergic reaction.

Since Paxene contains ethanol, consideration should be given to possible central nervous system and other effects. The amount of alcohol in this medicinal product may alter the effects of other medicines.

4.5 Interaction with other medicinal products and other forms of interaction

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

When administered as part of a combination regimen with cisplatin, it is recommended that Paxene is given before cisplatin. When paclitaxel is given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel was given after cisplatin, patients showed a more profound myelosuppression and an approximately 20 % decrease in paclitaxel clearance.

Since elimination of doxorubicin and its active metabolites may be reduced when paclitaxel and doxorubicin are used in combination, paclitaxel should be administered 24 hours after doxorubicin.

Since paclitaxel is metabolised by cytochrome P450 isoenzymes CYP 3A4 and 2C8, caution should be exercised with other medicinal products known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil, imidazole antifungals) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) these enzymes as they may affect the pharmacokinetics of paclitaxel. Concurrent administration of ketoconazole, a known potent inhibitor of CYP 3A4, 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 CYP 3A4 substrates/inhibitors are limited.

Studies conducted in AIDS-KS patients who were taking Paxene and multiple concomitant medicinal products suggest that the systemic clearance of paclitaxel was significantly lower ($p < 0.05$) in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, Paxene should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

4.6 Pregnancy and lactation

Studies in animals have shown reproductive toxicity (see section 5.3).

Paxene should not be used in pregnancy. Women should be advised to use effective means of contraception to avoid becoming pregnant during therapy with Paxene and to inform the treating physician immediately should this occur.

Paxene is contraindicated during lactation. It is unknown whether paclitaxel is excreted in human milk. Therefore, breast-feeding should be discontinued for the duration of Paxene therapy.

4.7 Effects on ability to drive and use machines

Following an infusion of Paxene, the patients' performance at skilled tasks such as driving and operating machines may be impaired due to the alcohol content of Paxene (see section 4.4).

4.8 Undesirable effects

Monotherapy

The following adverse reactions relate to 166 MBC and 120 MOC patients treated with 175 mg/m^2 Paxene administered as a 3-hour infusion as second-line chemotherapy in two clinical studies and were considered possibly or probably related to Paxene. As the AIDS-KS population is very specific, safety data from a clinical study of 107 AIDS-KS patients are presented separately at the end of this section.

Bone marrow suppression was the major dose-limiting toxicity of Paxene. Severe neutropenia (< 500 cells/mm^3) occurred in 26 % of patients treated with Paxene during the entire treatment period. 19 % of patients had severe neutropenia for > 7 days. Thrombocytopenia was observed in 6 % of patients. Two percent of patients had a platelet count nadir < 50,000 cells/mm3. Anaemia (Hb< 11 g/dl) was observed in approximately 9 % of treated patients but was severe in less than 1 % (Hb< 8 g/dl).

Neuropathy occurred in 18 % of patients treated with Paxene. Paraesthesia was observed in 48 % of patients. Severe neuropathy and severe paraesthesia occurred in 3 % and 5 % of patients, respectively. 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 months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

The other most commonly reported nervous system disorder is somnolence, which affected 14 % of patients.

Arthralgia was reported in 32 % of all patients (5 % severe) and myalgia in 47 % (6 % severe).

Injection site reactions including reactions secondary to extravasation were usually mild and consisted of erythema, tenderness, skin discolouration, or swelling at the injection site but can result in cellulitis. 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. There is no known specific treatment for extravasation reactions.

The table below lists undesirable effects associated with the administration of single agent paclitaxel as a 3 hour infusion in the metastatic setting (286 patients treated in Paxene clinical studies and 812 patients treated in other paclitaxel clinical studies), and those reported in the postmarketing surveillance of paclitaxel*. Where event incidence differed between Paxene and other paclitaxel clinical studies, the most frequent incidence is presented.

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

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (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 (including herpes simplex, oral candidiasis, pharyngitis, rhinitis) *Common:* flu syndrome *Uncommon:* severe infections, septic shock *Rare**: pneumonia
Blood and lymphatic system disorders	*Very common:* severe neutropenia, severe leucopenia, thrombocytopenia, anaemia, myelosuppression *Common:* neutropenic fever *Uncommon:* severe anaemia *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) *Rare**: anaphylactic reactions *Very rare*:* anaphylactic shock (including fatal hypersensitivity)
Metabolism and nutrition disorders	*Very common*: anorexia *Uncommon:* dehydration, weight loss and gain
Psychiatric disorders	*Very rare*:* confusional state
Nervous system disorders	*Very common*: neuropathy (mainly peripheral), paraesthesia, somnolence *Common:* severe neuropathy (mainly peripheral), dizziness, nervousness, insomnia, depression, abnormal thinking, hypokinesia, abnormal gait, hypaesthesia, taste perversion, headache *Rare**: motor neuropathy (with resultant minor distal weakness) *Very rare*:* acute encephalopathy, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), seizures
Eye disorders	*Uncommon*: dry eyes, amblyopia, visual field defect *Very rare**: optic nerve and/or visual disturbances (scintillating scotoma), particularly in patients who have received higher doses than recommended
Ear and labyrinth disorders	*Common:* tinnitus *Very rare**: sensorineural hearing loss, vertigo
Cardiac disorders	*Common:* tachycardia, palpitation, bradycardia, syncope *Uncommon*: congestive heart failure, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction *Very rare**: atrial fibrillation
Vascular disorders	*Very common:* hypotension *Common:* vasodilatation (flushing) *Uncommon:* thrombophlebitis, hypertension, thrombosis *Very rare*:* shock
Respiratory, thoracic and mediastinal disorders	*Common:* dyspnoea, epistaxis

	Rare: pleural effusion, lung fibrosis *Very rare**: cough, pulmonary hypertension
Gastrointestinal disorders	*Very common*: nausea, vomiting, diarrhoea, mucosal inflammation, constipation, stomatitis, abdominal pain *Common:* dry mouth, mouth ulceration, melaena, dyspepsia *Very rare*:* bowel obstruction, bowel perforation, pseudomembranous colitis, ischemic colitis, mesenteric thrombosis, necrotising enterocolitis, oesophagitis, ascites, acute pancreatitis
Hepatobiliary disorders	*Very rare**: hepatic necrosis, hepatic encephalopathy
Skin and subcutaneous tissue disorders	*Very common:* alopecia *Common*: transient skin change, dry skin, exfoliative dermatitis, pruritis, rash, acne, transient and mild nail changes *Uncommon:* changes in nail pigmentation or discolouration of nail bed *Rare**: erythema *Very rare**: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
Musculoskeletal and connective tissue disorders	*Very common*: arthralgia, myalgia *Common*: bone pain, leg cramps, myasthenia, back pain
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 reactions (erythema, tenderness, skin discolouration or swelling, pain, extravasation, can result in cellulitis and skin ulceration), malaise, chest pain, chills, pyrexia
Investigations	*Common:* severe elevation in transaminases, severe elevation in alkaline phosphatase *Uncommon:* severe elevation in bilirubin

* As reported in post-marketing surveillance of paclitaxel.

Combination therapy

The following discussion refers to two major trials for the first-line chemotherapy of ovarian cancer (paclitaxel plus cisplatin: over 1,050 patients) and two Phase III trials for the treatment of advanced NSCLC (paclitaxel plus cisplatin: over 360 patients) (see section 5.1).

When administered as a 3 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 ciclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a 3 hour infusion followed by cisplatin compared with ciclophosphamide followed by cisplatin.

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 and 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 months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

In eight published clinical trials (8 Phase III trials) including 4,735 patients with advanced ovarian cancer and in twelve published clinical trials (one large Phase II and eleven Phase III trials) including 4,315 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 and/or gemcitabine has been reported very rarely.

AIDS-related Kaposi's sarcoma

The following undesirable effects relate to 107 AIDS-KS patients treated with 100 mg/m^2 Paxene administered as a 3 hour infusion as second-line chemotherapy in a clinical study, and were considered possibly or probably related to Paxene. Except for haematological and hepatic events (see below), generally the frequency and severity of undesirable effects in AIDS-KS patients were similar to those noted in patients with other solid tumours treated with paclitaxel monotherapy.

Bone marrow suppression was the major dose-limiting toxicity of Paxene. Severe neutropenia (< 500 cells/mm^3) occurred in 20 % and 39% of patients during the first course of treatment and the entire treatment period, respectively. Neutropenia was present for > 7 days in 41 % and for 30 - 35 days in 8 % of patients. Neutropenia resolved in 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting 7 days or more was 22 %. Neutropenic fever related to Paxene was reported in 14 % of patients. There were three septic episodes (2.8 %) during Paxene 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 %. Bleeding episodes related to Paxene were reported in < 3% of patients and bleeding was 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.

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

No known antidote exists for Paxene overdose. 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, mucositis and peripheral neuropathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: taxanes, ATC code: L01CD01.

The active substance of Paxene is paclitaxel. The exact mechanism of the antitumour activity of paclitaxel is not known. It is generally believed that paclitaxel promotes the assembly of microtubules from tubulin dimer and prevents depolymerisation. Stabilisation results in the inhibition of the normal dynamic reorganisation of the microtubular network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Metastatic breast cancer

The efficacy and safety of Paxene (175 mg/m² over 3 hours at 3-week intervals) in refractory metastatic breast cancer were investigated in 172 women in a multicentre, open-label Phase III trial. The clinical response rate was 18.5 %, median time to progression was 2.8 months (CI: 2.1 - 3.3 months) and the median survival time was 9.9 months (CI: 7.8 - 13.1 months). The results obtained with Paxene are closely similar to those of published paclitaxel Phase III trials.

Advanced ovarian cancer (first-line treatment)

The efficacy and safety of paclitaxel were evaluated in two major, randomised, controlled trials (vs. ciclophosphamide 750 mg/m^2/ cisplatin 75 mg/m^2). In the first trial, over 650 patients with stage IIb-c, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m^2 over 3 hours) followed by cisplatin (75 mg/m^2) or control. The second major trial evaluated a maximum of 6 courses of either paclitaxel (135 mg/m² over 24 hours) followed by cisplatin (75 mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residual disease after staging laparotomy, or with distant metastases. Although 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 longer time to progression (Study 1: median 15.3 months vs 11.5 months, p< 0.001; Study 2: median 17 months vs 13 months, p< 0.001), and longer survival time (Study 1: median 36 months vs 26 months, p= 0.0016; Study 2: median 36 months vs 24 months, p< 0.001), and in Study 1 a significantly higher response rate (Study 1: 59 % vs 45 %, p= 0.014; Study 2: 60 % vs 50 %, NS), 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 with patients who received ciclophosphamide/cisplatin.

Metastatic ovarian cancer (second-line treatment)

The efficacy and safety of Paxene (175 mg/m² over 3 hours repeated at 3-week intervals) in advanced metastatic ovarian cancer were investigated in 120 women in a multicentre, open-label extended Phase II trial. The clinical response rate was 21.7 % (CI: 14.7 - 31.1 %), median time to progression was 4.1 months (CI: 3.3 - 4.9 months) and the median survival time was 13.4 months (CI: 11.5 - 15.0 months). The results obtained with Paxene are closely similar to those of published paclitaxel Phase III trials.

Advanced non-small cell lung carcinoma

Efficacy of paclitaxel/cisplatin combination has been demonstrated in two randomised, controlled trials in patients with locally advanced or metastatic NSCLC.

In the first study, 332 patients with locally advanced or metastatic NSCLC were randomised to receive cisplatin (80 mg/m^2) in combination with teniposide (100 mg/m^2; n= 166), or cisplatin (80 mg/m^2) and paclitaxel (175 mg/m^2; n= 166). There was no advantage in survival (9.5 vs. 9.9 months) or progression free survival (5.1 vs. 5.0 months) with cisplatin/paclitaxel vs cisplatin/tenoposide. However, the higher response rates (37 % vs. 26 %), lesser overall side effects and improved short term QoL with cisplatin/paclitaxel vs cisplatin/tenoposide were considered important results in a palliative population. Grade 2 or 3 peripheral neurotoxicity was observed more commonly with cisplatin/paclitaxel (29 % vs. 6 %).

In the second study, 599 patients with stage IIIB or IV disease were randomised to receive cisplatin (75 mg/m^2) and etoposide (100 mg/m^2; n= 200), or cisplatin (75 mg/m^2) and low-dose paclitaxel (135 mg/m^2; n= 198), or cisplatin (75 mg/m^2) and high-dose paclitaxel (250 mg/m^2) with G-CSF (n= 201). Median survival for each paclitaxel-containing arm was not significantly different compared to etoposide/cisplatin (p= 0.097 and 0.090 for high-dose paclitaxel and low-dose paclitaxel, respectively). With respect to progression free survival, highly statistically significant results were noted for the high-dose paclitaxel arm compared with etoposide/cisplatin (p= 0.007). Response rates strongly favoured the paclitaxel-containing arms [13 %, 30 % and 26 % for the etoposide/cisplatin, high-dose paclitaxel (p< 0.001 vs etoposide/cisplatin) and low-dose paclitaxel regimens (p= 0.003 vs etoposide/cisplatin), respectively]. A greater proportion of paclitaxel-treated patients had improvements in short-term QoL.
However, Grade 3 neurotoxicity was significantly more common in the high-dose paclitaxel arm vs. etoposide/cisplatin (40 % vs. 21 %).

AIDS-related Kaposi's sarcoma

The efficacy and safety of Paxene were investigated in a single, non-comparative study in 107 patients with advanced KS, previously treated with systemic chemotherapy. In the study, the majority of patients were administered granulocyte colony stimulating factor (G-CSF). The primary endpoint was best tumour response. Patients were given a 3 hour infusion of Paxene 100 mg/m² administered every 14 days. Of the 107 patients, 63 patients were considered resistant to liposomal anthracyclines. This subgroup of patients is considered to constitute the core efficacy population.

The overall success rate (complete or partial response) after 15 cycles of treatment was 57 % (CI: 44 - 70 %) in liposomal anthracycline-resistant patients. More than half of the responses were apparent after the first three cycles of treatment. 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 Paxene (60.9 %).

The median time to progression in the core population was 468 days (95 % CI 257-NE). Median survival for Paxene could not be computed, but the lower 95 % bound was 617 days in core patients.

5.2 Pharmacokinetic properties

Following intravenous administration, plasma concentrations decline in a biphasic or triphasic manner. The disposition of paclitaxel is non-linear (concentration dependent) as the systemic exposure increases more than expected following an increase in dosage.

Based on *in vitro* studies, the degree of plasma protein binding has been reported to range from 88 to 98 %. In spite of this high protein binding, paclitaxel is widely distributed to tissues.

Metastatic breast cancer

Pharmacokinetic parameters of paclitaxel at 175 mg/m^2 given over 3 hours in 13 patients with breast cancer were as follows: maximum concentration (C_{max}) was 3,890 ng/ml, area under the plasma concentration vs. time curve (AUC_{last}) was 14,090 ng/h/ml and clearance (CL) was 13.3 l/h/m^2.

Metastatic breast or ovarian cancer

Pharmacokinetic parameters of paclitaxel at 175 mg/m^2 given over 3 hours in 5 patients with breast cancer and 3 patients with ovarian cancer were as follows: maximum concentration (C_{max}) was 4,213 ng/ml, area under the plasma concentration vs. time curve (AUC_{last}) was 12,603 ng·h/ml and clearance (CL) was 20.4 l/h/m^2.

Renal excretion plays a minor role in the elimination of paclitaxel, less than 10 % of the dose has been reported to be excreted in the urine as unchanged drug. The major elimination pathway is metabolism followed by biliary excretion; in six patients 39 % to 87 % of an intravenous dose (175 mg/m^2) was excreted in faeces and, on average, only 10 % of the dose was excreted as unchanged paclitaxel. Several metabolites have been detected, but only three of them have been identified: 6 alpha-hydroxypaclitaxel, 3'-para-hydroxypaclitaxel and 6 alpha, 3'-para-dihydroxypaclitaxel. 6 alpha-hydroxypaclitaxel is the major component excreted in faeces. *In vitro* studies have shown that CYP 2C8 and 3A4 are involved in the formation of 6 alpha-hydroxypaclitaxel and 3'-para-dihydroxypaclitaxel, respectively.

AIDS-related Kaposi's sarcoma

Following an intravenous dose of 100 mg/m^2 given as a 3 hour infusion to 19 patients with AIDS-related Kaposi's sarcoma, the maximum concentrations ranged from 761 to 2,860 ng/ml (mean 1,530) and average area under the plasma concentration vs. time curve (AUC) was 5,619 ng/h/ml (range 2,609 - 9,428). 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).

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility
Paclitaxel has been shown to be genotoxic *in vivo* (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay. The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel belongs to a class of substances which are potentially carcinogenic based on their mechanism of action. Paclitaxel at low doses of 0.6 mg/kg/day was associated with low fertility and foetal toxicity in rats. Animal studies showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyoxyl castor oil
Citric acid (anhydrous)
Ethanol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Contact of the undiluted concentrate with plasticised PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted Paxene solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

6.3 Shelf life

Unopened vial: 2 years.

Chemical, physical and microbial stability of unused, undiluted product remaining in the vial has been demonstrated for up to 28 days when stored below 25 °C. Other in-use storage times and conditions are the responsibility of the user.

Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for 24 hours when stored below 25 ºC.

From a microbiological point of view, the diluted 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

Do not store above 25 °C.
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

5 ml clear glass (type I) vial fitted with a flip-off cap, containing 30 mg of concentrate.

20 ml clear glass (type I) vial fitted with a flip-off cap, containing 100 mg of concentrate.

30 ml clear glass (type I) vial fitted with a flip-off cap, containing 150 mg of concentrate.

50 ml clear glass (type I) vial fitted with a flip-off cap, containing 300 mg of concentrate.

Four pack sizes are available: 30 mg/5 ml vial, 100 mg/16.7 ml vial, 150 mg/25 ml vial and 300 mg/50 ml vial packaged in a carton.

Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

For single use only. Dispose of any remaining contents after first use.

Preparation and administration precautions
Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Paxene. The use of gloves, goggles and protective clothing is recommended. If Paxene solution contacts the skin, wash the skin immediately and thoroughly with

soap and water. If Paxene contacts mucous membranes, the membranes should be flushed thoroughly with water. Paxene should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Paxene.

Preparation for intravenous infusion
Paxene concentrate for solution for infusion must be diluted prior to infusion. Paxene should be diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for injection, or glucose 50 mg/ml (5%) in Ringer's solution for injection to a final concentration of 0.3 to 1.2 mg/ml. Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for at least 24 hours below 25 °C. From a microbiological point of view, the diluted 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.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle.

Paxene solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Paxene should be administered through an in-line filter with a microporous membrane not greater than 0.22 µm. Use of filter devices such as those which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Handling and disposa
Procedures for proper handling and disposal of cytotoxic medicinal products should be followed.

7. MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/113/001 for 30 mg/5 ml
EU/1/99/113/002 for 150 mg/25 ml
EU/1/99/113/003 for 100 mg/16.7 ml
EU/1/99/113/004 for 300 mg/50 ml

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th July 1999.
Date of latest renewal: 19th July 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

IVAX Pharmaceuticals UK
Aston Lane North
Preston Brook
Runcorn
Cheshire
United Kingdom

IVAX Pharmaceuticals s.r.o.
Ostravská 29/305
747 70 Opava
Komárov
Czech Republic

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT FOR PAXENE 30 mg/5 ml

1. NAME OF THE MEDICINAL PRODUCT

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 6 mg/ml of paclitaxel (30 mg of paclitaxel in 5 ml).

3. LIST OF EXCIPIENTS

Also contains: polyoxyl castor oil, citric acid (anhydrous) and 49.7 % (v/v) ethanol. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
30 mg/5 ml

5. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CAUTION: dilution required
For single use only.

8. EXPIRY DATE

Use by:

Chemical, physical and microbial stability of unused, undiluted product remaining in the vial has been demonstrated for up to 28 days when stored below 25 °C.

Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for 24 hours when stored below 25 ºC.

From a microbiological point of view, the diluted product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused contents according to standard practice for cytotoxic agents.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/113/001

13. MANUFACTURER'S BATCH NUMBER

Batch Number:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT FOR PAXENE 30 mg/5 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

Use by:

4. BATCH NUMBER

Batch Number:

5. OTHER

30 mg/5 ml
CAUTION: dilution required

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT FOR PAXENE 100 mg/16.7 ml

1. NAME OF THE MEDICINAL PRODUCT

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 6 mg/ml of paclitaxel (100 mg of paclitaxel in 16.7 ml)

3. LIST OF EXCIPIENTS

Also contains: polyoxyl castor oil, citric acid (anhydrous) and 49.7 % (v/v) ethanol. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
100 mg/16.7 ml

5. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CAUTION: dilution required
For single use only

8. EXPIRY DATE

Use by:

Chemical, physical and microbial stability of unused, undiluted product remaining in the vial has been demonstrated for up to 28 days when stored below 25 °C.

Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for 24 hours when stored below 25 ºC.

From a microbiological point of view, the diluted product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused contents according to standard practice for cytotoxic agents.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/113/003

13. MANUFACTURER'S BATCH NUMBER

Batch Number:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT FOR PAXENE 100 mg/16.7 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Use by:

4. BATCH NUMBER

Batch Number:

5. OTHER

100 mg/16.7 ml
CAUTION: dilution required

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT FOR PAXENE 150 mg/25 ml

1. NAME OF THE MEDICINAL PRODUCT

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 6 mg/ml of paclitaxel (150 mg of paclitaxel in 25 ml)

3. LIST OF EXCIPIENTS

Also contains: polyoxyl castor oil, citric acid (anhydrous) and 49.7 % (v/v) ethanol. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
150 mg/25 ml

5. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CAUTION: dilution required
For single use only

8. EXPIRY DATE

Use by:

Chemical, physical and microbial stability of unused, undiluted product remaining in the vial has been demonstrated for up to 28 days when stored below 25 °C.

Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for 24 hours when stored below 25 ºC.

From a microbiological point of view, the diluted product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused contents according to standard practice for cytotoxic agents.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/113/002

13. MANUFACTURER'S BATCH NUMBER

Batch Number:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT FOR PAXENE 150 mg/25 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Use by:

4. BATCH NUMBER

Batch Number:

5. OTHER

150 mg/25 ml
CAUTION: dilution required

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON TEXT FOR PAXENE 300 mg/50 ml

1. NAME OF THE MEDICINAL PRODUCT

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 6 mg/ml of paclitaxel (300 mg of paclitaxel in 50 ml)

3. LIST OF EXCIPIENTS

Also contains: polyoxyl castor oil, citric acid (anhydrous) and 49.7 % (v/v) ethanol. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
300 mg/50 ml

5. METHOD OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CAUTION: dilution required
For single use only

8. EXPIRY DATE

Use by::

Chemical, physical and microbial stability of unused, undiluted product remaining in the vial has been demonstrated for up to 28 days when stored below 25 °C.

Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for 24 hours when stored below 25 ºC.

From a microbiological point of view, the diluted product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Keep the vial in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused contents according to standard practice for cytotoxic agents.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/113/004

13. MANUFACTURER'S BATCH NUMBER

Batch Number:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL TEXT FOR PAXENE 300 mg/50 ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Paxene 6 mg/ml concentrate for solution for infusion
paclitaxel
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Use by:

4. BATCH NUMBER

Batch Number:

5. OTHER

300 mg/50 ml
CAUTION: dilution required

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Paxene 6 mg/ml concentrate for solution for infusion
Paclitaxel

Read all of this leaflet carefully before you start using this medicine:

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

In this leaflet:

1. WHAT PAXENE IS AND WHAT IT IS USED FOR

Paxene belongs to a group of medicines known as antineoplastic agents. These agents are used to treat cancer.

Paxene concentrate for solution for infusion is used to treat:

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

2. BEFORE YOU USE PAXENE

Do not use Paxene

- if you are hypersensitive (allergic) to paclitaxel or any of the other ingredients of Paxene,
- if you have ever had any problems with your liver,
- if you have been told that your white blood cell count is very low,
- if you have a serious, uncontrolled infection,
- if you are pregnant, may become pregnant or are breast-feeding.

Take special care with Paxene

- Before you start treatment with Paxene and during treatment, you will have regular blood tests to check that it is safe for you to continue with your treatment.
- Paxene is not recommended for use in children and adolescents under 18 years.
- Tell your doctor immediately if you develop severe or prolonged or bloody diarrhoea during or after treatment with Paxene. This may be a sign of a serious bowel inflammation (pseudomembranous colitis).
- If you experience an irregular heart beat, dizziness or faintness during treatment.
- If you previously had radiation treatment (radiotherapy) to your chest (see section 4: Possible side effects).
- If you are taking other medicines which could interact with paclitaxel (see Using other medicines).

Using other medicines

Please tell your doctor before you are given Paxene if you:

- are taking ritonavir, nelfinavir, efavirenz, nevirapine (for the treatment of AIDS) or any other prescribed medicines for your condition;
- are taking any other medicines prescribed by a physician for any condition (e.g. erythromycin, fluoxetine, gemfibrozil, imidazole antifungals, rifampicin, carbamazepine, phenytoin, phenobarbital);
- are taking other medicines that you have bought for yourself without a prescription.

If you are already being treated with doxorubicin for your condition, then your first dose of paclitaxel should be given 24 hours after doxorubicin.

Paxene may alter the effect of other medicines because of its high alcohol content. If you see another doctor or visit a hospital, remember to tell them what medicines you are taking.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, think you may be pregnant or are breast-feeding before you receive treatment with Paxene. Paxene cannot be used in pregnancy, and women receiving Paxene must not breast-feed. Adequate contraceptive precautions should be used when receiving Paxene.

Male patients treated with Paxene are advised not to father a child during and up to six months after the treatment.

Driving and using machines

Paxene contains alcohol. Thus it may not be safe for you to drive or to use machines for up to several hours after you have had your treatment. Check with your doctor. You should be able to drive and use machines between your treatments with Paxene, unless you feel tired or dizzy

Important information about some of the ingredients of Paxene

This medicine contains approximately 50 % by volume of alcohol. Each infusion contains up to 21 g of alcohol. The amount of alcohol in this medicine may alter the effects of other medicines and should be taken into account in patients with liver disease or epilepsy. Following an infusion of Paxene, the amount of alcohol may impair your ability to drive or use machines.

Paxene contains polyoxyl castor oil, which can cause an allergic reaction.

3. HOW TO USE PAXENE

Your concentrate for solution for infusion will be diluted and given slowly into a vein over about 3 hours unless otherwise stated. The amounts (dose) of Paxene you will be given will be worked out depending on your body surface area in square meters (m^2) and will also take into account the results of your blood tests and your medical condition. If necessary, your doctor will adjust the dosage during the treatment.

AIDS-related Kaposi's sarcoma

The usual dose of Paxene is 100 mg/m^2 of body surface area. You will be given Paxene every two weeks, as long as the results of your blood tests show that it is safe to carry on with your treatment.

Advanced breast cancer and ovarian cancer (second-line therapy)

The usual dose of Paxene is 175 mg/m^2 of body surface area. You will be given Paxene every three weeks, as long as the results of your blood tests show that it is safe to carry on with your treatment.

Advanced ovarian cancer (first-line therapy)

Two doses of Paxene may be given: Paxene 175 mg/m^2 of body surface area administrated as a 3 hour infusion into a vein, followed by another medicine, cisplatin, every three weeks; alternatively Paxene 135 mg/m^2 given as a 24 hour infusion, followed by cisplatin, every three weeks. Your continued treatment will depend on the results of your blood tests showing that it is safe to carry on with your treatment.

Advanced non-small cell lung cancer

The usual dose of Paxene is 175 mg/m^2 of body surface area, followed by cisplatin every three weeks. You will be given this therapy as long as the results of your blood tests show that it is safe to carry on with your treatment.

To help prevent allergic reactions occurring while you are receiving your infusion you will be given medication before your treatment starts. Twelve and then six hours before your infusion you will be given dexamethasone (a steroid), either as a tablet to swallow or as an injection. Half to one hour before your infusion you will be given two different types of injection (an antihistamine and an H_2 antagonist).

You will only be given your infusion under medical supervision, and you will be checked regularly while you are having your infusion to see how you are reacting to it. If you have a history of heart problems, your heart rate may be monitored. If any problems occur while you are having your infusion, the medical staff will be on hand to take any necessary action.

4. POSSIBLE SIDE EFFECTS

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

Side-effects may occur while you are receiving Paxene or following treatment. During treatment, you should tell the medical staff if you feel unwell. If you feel unwell between courses or after your treatment has finished, tell your doctor or pharmacist as soon as you can.

The frequency of possible side-effects listed below is defined using the following convention:
very common (affects more than 1 person in 10)
common (affects 1 to 10 persons in 100)
uncommon (affects 1 to 10 persons in 1,000)

rare (affects 1 to 10 persons in 10,000)
very rare (affects less than 1 person in 10,000)
not known (frequency cannot be estimated from the available data

Very common side-effects are listed below:

- Infections – this may be associated with feeling hot (fever) or cold (chills), sore throat and fungal infection in the mouth (oral candidiasis)
- Mild allergic reactions including flushing and skin rash
- Low blood pressure, which may make you feel light-headed upon standing
- Eating disorders including anorexia
- Nerve disorders including tingling sensation or pins and needles of the hands and feet
- Feeling or being sick
- Mild diarrhoea, constipation and stomach pain
- Hair loss
- Joint or muscle weakness, pain or loss of sensation in your legs
- Pain and swelling might occur around the injection site

Common side-effects are listed below:

- Flu-like symptoms
- Temporary low white blood cell count, which may make you develop an infection
- Low blood platelet counts that can cause unusual bleeding (e.g. nose bleeds) and unexplained bruising
- Painful sensation in the body
- Feeling dizzy
- Feeling agitated
- Lack of sleep
- Bad taste in your mouth
- Loss of balance or staggering
- Headache
- Ringing in your ears
- Abnormal heart rhythm
- Feeling faint
- Reddening or flushing of your skin
- Shortness of breath
- Nose bleeds
- Dry mouth and mouth ulcers
- Indigestion
- Discolouration of stool
- Changes in your skin and nails
- Mild flaking of skin associated with dryness, rash and acne
- Pain in the bones and back, as well as leg cramps
- Experiencing pain while passing urine
- Injection site reactions leading to pain, swelling and hardness of the skin around the injection site. Paxene might also leak from the vein and cause an infection or ulceration of the surrounding skin.
- The levels of some enzymes in your blood might rise

Uncommon side-effects are listed below:

- Severe infections such as pneumonia
- Severe anaemia
- Feeling tired
- Pale skin

- Dehydration, weight loss or weight gain
- Severe chest pains, irregular heart beat, feeling faint and heart attack
- High blood pressure, blood clots and inflammation in the veins
- Yellowing of the skin and nails

Rare side-effect are listed below:

- Infections such as pneumonia
- Localised swelling of the skin
- Severe allergic reactions (anaphylactic reaction) – you may experience localised itching and swelling of the hands, feet, ankles, face. lips, mouth, tongue or throat
- Effects on the nerves controlling your muscles resulting in weakness in the arms and legs
- Itching, red skin rash
- Problems with your lungs including swelling and fluid accumulation, which may cause breathing problems

Very rare side- effects are listed below:

- Acute leukaemia (blood cancer)
- Life-threatening allergic reaction (anaphylactic shock)
- Appearing and acting confused
- Brain disease
- Persistent diarrhoea
- Fits (convulsions, seizures)
- Vision disturbances
- Loss of hearing
- Balance problems
- Increase in heart beat
- Shock
- Constipation
- Abdominal pain caused by a build up of fluid in the abdomen (ascites), inflammation of the bowel, bowel obstruction, blood clots in the blood vessels to your bowel and perforation of your bowel wall
- Disease of the pancreas
- Disease in the oesophagus (the tube that carries food into your stomach)
- Loss of appetite
- Severe skin irritation, lesions and rash
- Loosening of finger and toe nails – you should wear protection on your feet and hands when exposed to the sun
- Liver damage – yellowing of the skin and abnormal levels of some liver enzymes

f you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

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

5. HOW TO STORE PAXENE

Keep out of the reach and sight of children.

Do not use Paxene after the expiry date, which is stated on the vial label and outer carton after “use by”. The expiry date refers to the last day of that month.

Do not store above 25 ^{o}C.

Keep the vial in the outer carton in order to protect from light.

Your concentrate for solution for infusion will be kept in the pharmacy and they will prepare it, ready to be given by the doctor or nurse. Following dilution, chemical and physical in use stability has been demonstrated for at least 24 hours below 25 ^{o}C. From a microbiological point of view, once opened the product should be used immediately. Other in use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 ^{o}C.

Do not use Paxene if you notice any visible particles of discolouration of the solution. The prepared solution may appear hazy.

For single use only. Dispose of any remaining contents after first use.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Paxene contains

The active substance is paclitaxel 6 mg/ml (30 mg/5 ml, 100 mg/16.7 ml, 150 mg/25 ml or 300 mg/50 ml).
The other ingredients are polyoxyl castor oil, citric acid (anhydrous) and ethanol.

What Paxene looks like and contents of the pack

Paxene is a clear, colourless to slightly yellow, thickish solution that comes in vials containing 5 ml, 16.7 ml, 25 ml and 50 ml of concentrate.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Norton Healthcare Limited
Albert Basin
Royal Docks
London E16 2QJ
United Kingdom.

Manufacturer

IVAX Pharmaceuticals s.r.o.
Ostravská 29/305
747 70 Opava
Komárov
Czech Republic

IVAX Pharmaceuticals UK
Runcorn
Cheshire
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
S.A. Mayne Pharma (Benelux) N.V.
Tel: + 32 2 332 0315

България
IVAX Pharmaceuticals s.r.o
Tel: +420 553 641 111

Česká republika
IVAX Pharmaceuticals s.r.o
Tel: +420 553 641 111

Danmark
IVAX Scandinavia AB
Tlf.: +46 850 666 300

Luxembourg/Luxemburg
S.A. Mayne Pharma (Benelux) N.V.
Tel: + 32 2 332 0315

Magyarország
IVAX Drug Research Institute Ltd
Tel.: +36 1399 3343

Malta
Norton Healthcare Ltd t/a IVAX Pharmaceuticals UK
Tel.: +44 8705 02 03 04

Nederland
S.A. Mayne Pharma (Benelux) N.V.
Tel: + 32 2 332 0315

Deutschland
Mayne Pharma (Deutschland) GmbH
D-85540 Haar
Tel: +49 89 43 77 770

Eesti
IVAX Pharmaceuticals s.r.o
Tel: +420 553 641 111

Ελλάδα
Norton Healthcare Ltd t/a IVAX Pharmaceuticals
UK
Τηλ.: +44 8705 02 03 04

España
Combino Pharm, S.L.
Tel.: +34 93 480 88 33

France
Mayne Pharma (France) SAS.
Tel: + 33 1 41 11 28 50

Ireland
Mayne Pharma Plc
Tel: + 44 1926 821 010

Ísland
Norton Healthcare Ltd t/a IVAX Pharmaceuticals
UK
Tel.: +44 8705 02 03 04

Italia
Mayne Pharma (Italia) s.r.l.
Tel: +39 0 81 24 05 911

Κύπρος
Norton Healthcare Ltd t/a IVAX Pharmaceuticals
UK
Τηλ.: +44 8705 02 03 04

Latvija
IVAX Pharmaceuticals s.r.o
Tel: +420 553 641 111

Lietuva
IVAX Pharmaceuticals s.r.o
Tel: +370 525 26490

Norge
Mayne Pharma (Nordic) AB, Sverige
Tel: + 46 8 672 85 00

Österreich
Norton Healthcare Ltd t/a IVAX Pharmaceuticals
UK
Tel.: +44 8705 02 03 04

Polska
IVAX Pharma Poland Sp. z.o.o.
Tel: +48 22 742 04 25

Portugal
Mayne Pharma (Portugal) Lda
Tel: + 351 21 485 7430

România
IVAX Pharmaceuticals s.r.o
Tel: +420 553 641 111

Slovenija
Medis, d.o.o
Tel: + 386 1 589 69 00

Slovenská republika
IVAX Pharmaceuticals s.r.o
Tel: +420 553 641 111

Suomi/Finland
Mayne Pharma (Nordic) AB, Ruotsi/Sverige
Tel: + 46 8 672 85 00

Sverige
Mayne Pharma (Nordic) AB, Sverige
Tel: + 46 8 672 85 00

United Kingdom
Mayne Pharma Plc
Tel: + 44 1926 821 010

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.

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

Further instructions for preparation for infusion

Recommendations for handling

Paxene is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised in handling Paxene. The use of gloves, goggles and protective clothing is recommended. If Paxene solution comes into contact with the skin, wash the skin immediately and thoroughly with soap and water. If Paxene contacts mucous membranes, the membranes should be flushed thoroughly with water. Paxene should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Paxene.

Preparation of the infusion solution

Paxene must be diluted under aseptic conditions prior to infusion. Paxene should be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection, glucose 50 mg/ml (5%) solution for infusion, or glucose 50 mg/ml (5%) in Ringer's solution for injection to a final concentration of 0.3 to 1.2 mg/ml.

Following dilution, chemical and physical in-use stability in polypropylene infusion bags has been demonstrated for at least 24 hours when stored below 25 °C.

From a microbiological point of view, the diluted 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.

Chemical and physical and microbial stability of unused, undiluted product remaining in the vial has been demonstrated for up to 28 days when stored below 25 ºC. Other in-use storage times and conditions are the responsibility of the user.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle.

Levels of the extractable plasticiser DEHP [di-(2-ethylhexyl)phthalate] increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticised PVC containers and administration sets is not recommended.

Paxene solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Paxene should be administered through an in-line filter with a microporous membrane not greater than 0.22 µm. Use of filter devices which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Handling and disposal

Procedures for proper handling and disposal of cytotoxic medicinal products should be followed.