# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Pataxel 6mg/ml, concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paclitaxel: 6mg per ml concentrate for solution for infusion
5ml vial containing Paclitaxel 30mg
16.7ml vial containing Paclitaxel 100mg
50ml vial containing Paclitaxel 300mg

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Pataxel 6mg/ml is a clear, colorless to slightly yellow, viscous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

**Ovarian cancer:** As first line chemotherapy of ovarian cancer, Pataxel is indicated in patients with advanced or residual disease (> 1cm) after initial laparotamy, in combination with cisplatin.
As second-line chemotherapy of ovarian cancer, Pataxel is indicated in the treatment of metastatic ovarian cancer after failure of standard platinum based therapy.

**Breast cancer:** As an adjuvant treatment, Pataxel is indicated for the treatment of patients with node-positive breast cancer following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Pataxel should be considered as an alternative to prolonged AC therapy.

Pataxel 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 appropriate or in combination with trastuzumab, in patients with HER-2 over-expression at a 3+ level, as determined by immunohistochemistry and for whom anthracyclines are not appropriate (see section 4.4 and 5.1).

As a monotherapy, Pataxel is indicated for the treatment of metastatic breast cancer in patients who have failed or in whom the standard anthracycline therapy would not be appropriate.

**Advanced non-small cell lung cancer:** Pataxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for curative surgery and/or radiation therapy.

**AIDS-related Kaposi's sarcoma:** Pataxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS), who have failed prior liposomal anthracycline therapy.
Limited efficacy data supports this indication. A summary of the relevant studies is shown in section 5.1.

## 4.2 Posology and method of administration

Corticosteroids, antihistamines and H2-receptor antagonists should be given in all patients prior to Pataxel infusion, such as:

| **Pre-medication** | **Dosage** | **Administration prior to Pataxel** |
|---|---|---|
| Dexamethasone | 20 mg orally* or IV | Orally: Approximately,12 and 6 hours<br>IV: 30 to 60 minutes |
| Diphenhydramine ** | 50 mg IV | 30 to 60 minutes |
| Cimetidine or Ranitidine | 300 mg IV<br>50 mg IV | 30 to 60 minutes |

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

Pataxel should be administered via an in-line filter with a microporous membrane ≤ 0.22 μm attached to the infusion device (see section 6.6).

**First-line chemotherapy of ovarian cancer:** Although other dosage regimes are under investigation, a combination regimen of Pataxel and cisplatin is recommended. According to the duration of infusion, two dosage regimes of Pataxel are recommended: Pataxel 175mg/m$^2$ administered as a 3-hour intravenous infusion, followed by cisplatin 75mg/m$^2$ every 3 weeks, or Pataxel 135mg/m$^2$ as a 24-hour infusion, followed by cisplatin 75mg/m$^2$, with a 3-week interval between therapeutic regimes (see section 5.1).

**Second-line chemotherapy of ovarian cancer:** The recommended dose of Pataxel is 175mg/m$^2$ administered over a period of 3 hours, with a 3-week interval between therapeutic regimes.

**Adjuvant chemotherapy of breast cancer:** The recommended dose of Pataxel is 175mg/m$^2$ administered intravenously over a period of 3 hours every 3 weeks at four therapeutic regimes, following AC therapy.

**First-line chemotherapy of breast cancer**: When used in combination with doxorubicin (50mg/m$^2$), Pataxel should be administered 24 hours after doxorubicin. The recommended dose of Pataxel is 220mg/m$^2$ intravenously over a period of 3 hours, with a 3-week interval between the therapeutic regimes (see section 4.5 and 5.1). When used in combination with trastuzumab, the recommended dose of Pataxel is 175mg/m$^2$ intravenously over a period of 3 hours, with a 3-week interval between the therapeutic regimes (see section 5.1). Pataxel infusion may be initiated the day after the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the prior dose of trastuzumab was well tolerated (for trastuzumab detailed dosage, see SPC of Herceptin®).

**Second-line chemotherapy of breast cancer:** The recommended dose of Pataxel is 175mg/$m^2$ administered over a period of 3 hours, with a 3-week interval between the therapeutic regimes.

**Treatment of advanced non-small cell lung cancer**: The recommended dose of Pataxel is 175mg/$m^2$ administered over 3 hours, followed by cisplatin 80mg/$m^2$, every 3 weeks between the therapeutic regimes.

**Treatment of AIDS-related Kaposi's Sarcoma**: The recommended dose of Pataxel is 100mg/m² administered as a 3-hour intravenous infusion every two weeks.

Additional doses of Pataxel can be administered according to individual patient tolerance.

Pataxel should not be re-administered until the neutrophil count is ≥ 1500/$mm^3$ (≥ 1000/$mm^3$ for patients with KS) and the platelet count is ≥ 100000/$mm^3$ (≥ 75000/$mm^3$ for patients with KS). Patients who experience severe neutropenia (neutrophil count < 500/$mm^3$ for ≥ 7 days) or severe peripheral neuropathy, should have their dosage reduced by 20% (25% for patients with KS) for subsequent doses (see 4.4).

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

## 4.3 Contraindications

Pataxel is contraindicated in patients with severe hypersensitivity reaction to paclitaxel, or to any of the excipients, especially to polyethoxylated castor oil (see 4.4).
Pataxel is contraindicated during pregnancy and lactation (see 4.6) and should not be used in patients with baseline neutrophil count < 1500/$mm^3$ (< 1000/$mm^3$ for patients with KS).
In Kaposi's Sarcoma, Pataxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

## 4.4 Special warnings and precautions for use

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

Patients must be premedicated with corticosteroids, antihistamines and $H_2$-receptor antagonists (see 4.2).

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

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

**Bone marrow suppression** (particularly neutropenia) is a toxic manifestation limiting the dose level. Frequent complete blood counts should be performed. Patients should not be retreated until the neutrophil count is ≥ 1500/$mm^3$ (≥ 1000/$mm^3$ for patients with KS) and the platelets recover to ≥ 100000/$mm^3$ (≥ 75000/$mm^3$ for patients with KS). In the Kaposi's Sarcoma clinical study, the majority of patients was receiving granulocyte colony stimulating factor (G-CSF).

**Severe cardiac conduction abnormalities** have been rarely reported during Pataxel monotherapy. If patients develop significant conduction abnormalities during Pataxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Pataxel. Hypotension, hypertension, and bradycardia have been observed during Pataxel administration. Patients are usually asymptomatic and generally do not require treatment. Frequent monitoring of vital signs, particularly during the first hour of Pataxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian cancer. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

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

Although the occurrence of **peripheral neuropathy** is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction by 20% (25% for patients with KS) for all subsequent courses of Pataxel is recommended. In non-small cell lung cancer patients and in patients with ovarian cancer treated in the first-line setting, the administration of Pataxel as a 3-hour infusion in combination with cisplatin resulted in a greater incidence of neurotoxicity than it is observed in patients receiving either monotherapy with Pataxel or cyclophosphamide followed by cisplatin.

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

Since Pataxel contains ethanol (396mg/ml), consideration should be given to possible central nervous system and other effects.

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

**Pseudomembranous colitis** has been rarely reported including cases in patients who had not received concurrent antibiotic treatment. This reaction should be considered in the differential diagnosis of severe or persistent cases of diarrhea occurring during or shortly after treatment with paclitaxel.

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

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.

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

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

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel to 6α-hydroxypaclitaxel, is the major metabolic pathway in humans. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients. Thus,

both medicinal products may be administered together without dosage adjustment. Further data on the potential of interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

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

## 4.6 Pregnancy and lactation

Pataxel has been shown to be embryotoxic in rabbits and to decrease fertility in rats.

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

It is not known whether paclitaxel is excreted in human milk. Pataxel is contraindicated during lactation. Breast-feeding should be discontinued for the duration of therapy.

## 4.7 Effects on ability to drive and use machines

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that Pataxel does contain alcohol (see 4.4 and 6.1).

## 4.8 Undesirable effects

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with paclitaxel monotherapy in clinical studies. As the population with KS 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 cancer, breast cancer, or non-small cell lung cancer. None of the observed toxicities was clearly influenced by age.

The most frequent significant undesirable effect was **bone marrow suppression**. Severe neutropenia (< 500cells/$mm^3$) 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. 3% of patients had a platelet count nadir < 50000/$mm^3$ 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 haemoglobulin status.

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

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

**A significant hypersensitivity reaction** with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) patients. 34% 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 paclitaxell therapy.

**Injection site reactions** during intravenous administration may lead to localised oedema, pain, erythema, and induration. Occasionally, 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 the site of a previous extravasation following administration of paclitaxel at a different site, i.e. “anamnestic reaction”, has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

The table below lists undesirable effects regardless of severity, associated with the administration of paclitaxel monotherapy administered as a 3-hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the post-marketing surveillance* of paclitaxel.

The frequency of undesirable effects listed below is defined using the following convention: Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥1/1.000, <1/100), rare (≥ 1/10.000, < 1/1.000), very rare (< 1/10000).

| | |
|---|---|
| **Infections and infestations**: | *Very common*: Infection (mainly urinary tract and upper respiratory infections), with reported cases of fatal outcome<br>*Uncommon*: Septic shock<br>*Rare**: Pneumonia, peritonitis, sepsis |
| **Blood and lymphatic system disorders**: | *Very common*: Myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding |

| | |
|---|---|
| | *Rare**: Febrile neutropenia<br>*Very rare**: Acute myeloid leukaemia, myelodysplastic syndrome |
| **Immune system disorders**: | *Very common*: Minor hypersensitivity reactions (mainly flushing and rash)<br>*Uncommon*: Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension)<br>*Rare**: Anaphylactic reactions<br>*Very rare**: Anaphylactic shock |
| **Metabolism and nutrition disorders**: | *Very rare**: Anorexia |
| **Psychiatric disorders**: | *Very rare**: Confusional stage |
| **Nervous system disorders**: | *Very common*: Neurotoxicity (mainly: peripheral neuropathy)<br>*Rare**: Motor neuropathy (with resultant minor distal weakness)<br>*Very rare**: Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia |
| **Eye disorders**: | *Very rare**: Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended |
| **Ear and labyrinth disorders**: | *Very rare**: Ototoxicity, hearing loss, tinnitus, vertigo |
| **Cardiac disorders**: | *Common*: Bradycardia<br>*Uncommon*: Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction<br>*Very rare**: Atrial fibrillation, supraventricular tachycardia |
| **Vascular disorders**: | *Very common*: Hypotension<br>*Uncommon*: Hypertension, thrombosis, thrombophlebitis |

| | |
|---|---|
| | *Very rare**: Shock |
| **Respiratory, thoracic and mediastinal disorders**: | *Rare**: Dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure<br>*Very rare**: Cough |
| **Gastrointestinal disorders**: | *Very common*: Nausea, vomiting, diarrhoea, mucosal inflammation<br>*Rare*:* Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis<br>*Very rare**: Mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis |
| **Hepato-biliary disorders**: | *Very rare**: Hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome) |
| **Skin and subcutaneous tissue disorders**: | *Very common*: Alopecia<br>*Common*: Transient and mild nail and skin changes<br>*Rare**: Pruritus, rash, erythema<br>*Very rare**: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) |
| **Musculoskeletal and connective tissue disorders**: | *Very common*: Arthralgia, myalgia |
| **General disorders and administration site conditions**: | *Common*: Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)<br>*Rare**: Asthenia, pyrexia, dehydration, oedema, malaise |
| **Investigations**: | *Common*: Severe elevation in AST (SGOT), severe elevation in alkaline phosphatase<br>*Uncommon*: Severe elevation in bilirubin<br>*Rare**: Increase in blood creatinine |

Breast cancer patients who received paclitaxel in the adjuvant setting following AC therapy, 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 paclitaxel monotherapy, as reported above.

**Combination treatment**

The following discussion refers to two major trials for the first-line chemotherapy of ovarian cancer (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), and another one investigating the combination with trastuzumab (planned subgroup analysis, paclitaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced non-small cell lung cancer (paclitaxel + cisplatin: over 360 patients) (see 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 by patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a 3-hour infusion followed by cisplatin compared to cyclophosphamide followed by cisplatin.

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

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 their relationship to paclitaxel or trastuzumab) were reported more frequently than with paclitaxel monotherapy: 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 paclitaxel monotherapy. Severe events were reported at similar rates for paclitaxel/trastuzumab combination and paclitaxel monotherapy.

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, cardiac contraction abnormalities (≥ 20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs 10% with standard FAC regimen. Congestive heart failure was observed in < 1% in both

paclitaxel/doxorubicin and standard FAC groups. 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 monotherapy (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 except these rare cases, patients responded to appropriate medical treatment.

**Radiation pneumonitis** has been reported in patients receiving concurrent radiotherapy.

**AIDS-related Kaposi's sarcoma:** Except for haematologic and hepatic undesirable effects (see below), the frequency and severity of undesirable effects are generally similar between patients with KS and patients treated with paclitaxel monotherapy for other solid tumors, based on a clinical study including 107 patients.

**Blood and the lymphatic system disorders**: Bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematologic toxicity. During the first course of treatment, severe neutropenia (< 500cells/$mm^3$) 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 up. 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 (< 50000 cells/$mm^3$) in 9% of patients. Only 14% of patients experienced a drop in their platelet count to < 75000 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% of cases. Red cell transfusions were required in 21% of patients.

**Hepato-biliary disorders**: Among patients (> 50% patients 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 overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neuropathy, and mucositis.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group / ATC Code: cytostatic agent, L01C D01

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic re-organization 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 first-line treatment of ovarian cancer, the safety and efficacy of paclitaxel were evaluated in two major randomized controlled trials (compared to cyclophosphamide 750mg/m$^2$ + cisplatin 75mg/m$^2$ therapy). In the trial (BMS CA 139-209), over 650 patients with stage $II_{b-c}$, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175mg/m$^2$ as a 3-hour infusion) followed by cisplatin (75mg/m$^2$) or control treatment. In another major study (GOG 111/B-MS CA 139-022), evaluated a maximum of 6 courses of either paclitaxel (135mg/m$^2$, as a 24-hour infusion) followed by cisplatin (75mg/m$^2$) or control treatment 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 dosages were not compared to 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 to standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion of paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

In the adjuvant treatment of breast cancer, 3121 patients with node positive breast cancer were treated with adjuvant paclitaxel therapy or no chemotherapy following 4 courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone ($p = 0.0014$), and a significant reduction of 19% in the risk of death 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 prolonged AC therapy.
In a second large clinical study in adjuvant node positive breast cancer therapy, with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225mg/m² following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who

received AC alone (p = 0.006). Paclitaxell treatment was associated with a reduction in the risk of death by 7% (95%CI: 0.78-1.12). All subset analyses favored paclitaxel arm. In this study patients with hormone receptor positive tumors had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92). In the patient subgroup with hormone receptor negative tumors 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, randomized, controlled open-label trials. In the first study (BMS CA 139-278), the combination of bolus doxorubicin (50mg/m²) followed after 24 hours by paclitaxel (220mg/m² by 3-hour infusion) (AT), was compared to standard FAC regimen (5-FU 500mg/m², doxorubicin 50mg/m², cyclophosphamide 500mg/m²), both administered every three weeks for eight courses. In this randomized 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 rate was in favour of paclitaxel/doxorubicin vs FAC (23.0 vs 18.3 months, p = 0.004). In the AT and FAC treatment 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT compared to the FAC (68% vs 55%). Complete responses were seen in 19% of paclitaxel/doxorubicin patients vs 8% of the FAC patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second pivotal study, the efficacy and safety of paclitaxel and Herceptin® combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of Herceptin® in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose and then 2 mg/kg weekly) and paclitaxel (175mg/m²) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175mg/m²) 3-hour infusion, every three weeks in 188 patients with metastatic breast cancer over-expressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. Paclitaxel was administered every three weeks for at least 6 courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for paclitaxel/trastuzumab combination in terms of time to disease 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 paclitaxel/trastuzumab combination was cardiac dysfunction (see 4.8).

In the treatment of advanced non-small cell lung cancer, paclitaxel 175mg/m$^2$ followed by cisplatin 80mg/m$^2$ has been evaluated in two phase III trials (367 patients on paclitaxel containing regimes). Both were randomized trials. One compared treatment with cisplatin 100mg/m², the other used teniposide 100mg/m² followed by cisplatin 80mg/m² as comparator (367 patients on comparator). Results in each trial were similar. For the primary outcome, 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 regimes, 8.6 and 9.9 months on comparators). Similarly, for progression-free survival time 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 regimes in terms of appetite loss and provide clear evidence of the inferiority of paclitaxel containing regimes in terms of peripheral neuropathy ($p < 0.008$).

In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in non-comparative studies in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was the best tumor 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 results were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one protease inhibitor at least 2 months prior to treatment with paclitaxel (60.9%). The median time to disease progression in the core population was 468 days (95% CI 257-NE). Median survival could not be computed, but the lowest 95% bound was 617 days in core patients.

## 5.2 Pharmacokinetic properties

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

The pharmacokinetics of paclitaxel were determined following 3- and 24-hour infusions at doses of 135 and 175mg/m$^2$. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean non-compartmentally (partial) 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 paclitaxel plasma concentrations. Mean steady-state volume of distribution ranged from 198 to 688 l/m$^2$, indicating extensive extravascular distribution and/or paclitaxel tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m² to 175mg/m², the $C_{max}$ and $AUC_{0\rightarrow\infty}$ values increased 75% and 81%, respectively.

Following an intravenous dose of 100mg/m$^2$, given as a 3-hour infusion to 19 patients with KS, the mean $C_{max}$ was 1530ng/ml (range 761 - 2860 ng/ml) and the mean AUC 5619 ng.hr/ml (range 2609 - 9428 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).

Intra-patient variability in systemic paclitaxel exposure was minimal. There is no evidence for accumulation of paclitaxel with multiple administrations.

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

The disposition of paclitaxel has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome P450 enzymes. Following administration of a radiolabelled paclitaxel, an average of 26.2 and 6% of the radioactivity was excreted in the faeces as 6α-hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6α-3'-p-dihydroxy-paclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, -3A4, and both -2C8 and -3A4 respectively. The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a 3-hour infusion of paclitaxel 135mg/m² were within the range of those defined in non-dialysis patients.

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

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

### 5.3 Preclinical safety data

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Macrogolglycerol ricinoleate, Ethanol anhydrous, Citric acid anhydrous.

### 6.2 Incompatibilities

Polyoxyethylated castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted Pataxel should be carried out using non-PVC-containing equipment.

### 6.3 Shelf life

2 years

**Diluted solutions:**

At ≤ 25 °C or at 2° - 8 °C:
for 7 days when diluted in 5% Dextrose solution or
for 14 days when diluted in 0.9% Sodium Chloride Injection

## 6.4 Special precautions for storage

Store at 15-25 °C.
Store in original package to protect from light.
Freezing does not adversely affect the product.
**Diluted solutions:** see section 6.3.

## 6.5 Nature and contents of container

Type I glass vials (with rubber stopper) containing 30 mg, 100 mg or 300 mg of paclitaxel in 5 ml, 16.7 ml or 50 ml solution respectively.

## 6.6 Special precautions for disposal and other handling

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

If unopened vials are refrigerated, a precipitate may be formed that re-dissolves 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, Pataxel vials maintain microbial, chemical and physical stability for up to 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

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

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

Chemical and physical in-use stability of the solutions prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in 5% Dextrose solution, and for 14 days when diluted in 0.9% Sodium Chloride Injection.

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

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

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

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

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

## 7. MARKETING AUTHORIZATION HOLDER

VIANEX S.A. – Tatoiou str., 146 71 Nea Eryhtrea, Tel: 0030 210 8009111

## 8. MARKETING AUTHORIZATION NUMBER(S)

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

## 10. DATE OF REVISION OF THE TEXT