Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Paclitaxel Nucleus 6mg/ml Concentrate for Solution for Infusion

UK/H/1000/001/DC
UK licence no: PL 24701/0011

Nucleus ehf

LAY SUMMARY

The MHRA granted Nucleus ehf a Marketing Authorisation (licence) for the medicinal product Paclitaxel 6mg/ml Concentrate for Solution for Infusion. This is a prescription-only medicine (POM) used to treat various types of cancer.

Paclitaxel 6mg/ml Concentrate for Solution for Infusion contains the active ingredient Paclitaxel. Paclitaxel is derived from the bark and needles of the European Yew Tree, *Taxus baccata*. A number of anti-cancer drugs have been isolated from this source and are known as taxanes. Paclitaxel is used either on its own, or in combination with other anti-caner agents, to treat a variety of cancers including ovarian cancer, breast cancer, advanced non-small-cell lung cancer and AIDS-related Kaposi's sarcoma.

Paclitaxel 6mg/ml Concentrate for Solution for Infusion works by stopping cell division and is used to prevent the growth of cancer cells.

The proposed product was considered to be a generic version of the reference product Taxol 6mg/ml Concentrate for Solution for Infusion (Bristol-Myers Squibb Pharmac Ltd).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Paclitaxel 6mg/ml Concentrate for Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Paclitaxel 6mg/ml Concentrate for Solution for Infusion
Type of Application	Generic, Article 10.1
Active Substance	Paclitaxel
Form	Concentrate For Solution For Infusion
Strength	6mg/ml
MA Holder	Nucleus ehf, Naustnanesi, 1 16 Reykjavik, Iceland
RMS	UK
CMS	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Portugal, Slovenia, Slovak Republic, Spain
Procedure Number	UK/H/1000/001/DC
Timetable	Day 210 – 14th December 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paclitaxel Nucleus 6 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 6 mg paclitaxel.
One vial of 5 ml contains 30 mg paclitaxel.
One vial of 16.7 ml contains 100 mg paclitaxel.
One vial of 25 ml contains 150 mg paclitaxel.
One vial of 50 ml contains 300 mg paclitaxel.
Excipients:
Macrogolglycerol ricinoleate (527 mg/ml)
Ethanol, anhydrous (385 mg/ml)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to pale yellow, slightly viscous solution with a pH of 3.3 to 4.3 and an osmolarity of > 4000 mOsm/l.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian carcinoma

In the first-line chemotherapy of ovarian cancer for patients with advanced carcinoma of the ovary or with residual disease (>1 cm) after initial laparotomy, in combination with cisplatin.
In the second-line chemotherapy of ovarian cancer for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum-containing therapy.

Breast carcinoma

In the adjuvant setting, Paclitaxel Nucleus is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Paclitaxel Nucleus should be regarded as an alternative to extended AC therapy.
Paclitaxel Nucleus is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable (see sections 4.4 and 5.1).
As a single agent, Paclitaxel Nucleus is indicated for the treatment of metastatic carcinoma of the breast in patients who have either failed or are not candidates for standard, anthracycline-containing therapy.

Advanced non-small cell lung carcinoma

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

AIDS-related Kaposi's sarcoma

Paclitaxel Nucleus 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

Posology

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

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

* 8-20 mg for KS patients

** or an equivalent antihistamine e.g. chlorphenamine

Paclitaxel should be administered through an in-line filter with a microporous membrane ≤ 0.22 µm (see section 6.6).

First-line chemotherapy of ovarian carcinoma

Although other dosage regimens are under investigation, a combination regimen of paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel are recommended: paclitaxel 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every three weeks or paclitaxel 135 mg/m², in a 24-hour infusion, followed by cisplatin 75 mg/m², with a 3 week interval between courses (see section 5.1).

Second-line chemotherapy of ovarian carcinoma

The recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3 week interval between courses.

Adjuvant chemotherapy in breast carcinoma

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

First-line chemotherapy of breast carcinoma

When used in combination with doxorubicin (50 mg/m²), Paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of Paclitaxel is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see sections 4.5 and 5.1).

When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses (see section 5.1). Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated (for detailed trastuzumab posology see the Summary of Product Characteristics of Herceptin).

Second-line chemotherapy of breast carcinoma

The recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3-week interval between courses.

Treatment of advanced NSCLC

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

Treatment of AIDS-related KS

The recommended dose of Paclitaxel Nucleus is 100 mg/m² administered as a 3-hour intravenous infusion every two weeks.

Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be re-administered until the neutrophil count is ≥1,500/mm³ (≥1,000/mm³ for KS patients) and the platelet count is ≥100,000/mm³ (≥75,000/mm³ for KS patients). Patients who experienced severe neutropenia (neutrophil count <500/mm³ for ≥7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (see section 4.4).

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

4.3 Contraindications

Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipient, especially macrogolglycerol ricinoleate (polyoxyethylated castor oil) (see section 4.4).
Paclitaxel is contraindicated during pregnancy and lactation (see section 4.6), and should not be used in patients with baseline neutrophils < 1,500/mm³ (<1,000/mm³ for KS patients).
In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

4.4 Special warnings and precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.
Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists (see section 4.2).
Paclitaxel should be given before cisplatin when used in combination (see section 4.5).
Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.
Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to ≥1,500/mm³ (≥1,000/mm³ for KS patients) and platelets recover to ≥100,000/mm³ (≥75,000/mm³ for KS patients).
In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).
Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel.
If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel. Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than in those with breast- or ovarian carcinoma.
A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.
When paclitaxel is used in combination with doxorubucin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram and/or MUGA scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m^2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles). For more details see Summary of Product Characteristics of Herceptin or doxorubucin.
Although the occurrence of *peripheral neuropathy* is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of paclitaxel. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of paclitaxel as a 3 hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by cisplatin.
Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression

(see section 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 5.2).
No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should not be treated with paclitaxel.
Since Paclitaxel Nucleus contains ethanol (385 mg/ml), consideration should be given to possible CNS and other effects.
Special care should be taken to avoid intra-arterial administration of paclitaxel, since in animal studies testing for local tolerance severe tissue reactions were observed following intra-arterial administration.
Pseudomembranous colitis has been reported rarely including cases in patients who have not been treated concomitantly with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.
Paclitaxel in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of *interstitial pneumonitis.*
Sexually active fertile female and male patients should use effective methods of contraception during treatment and up to six months after treatment for men, and one month after treatment for women (see section 4.6). Hormonal contraception is contraindicated in hormone receptor positive tumours.
In KS patients, *severe mucositis* is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

4.5 Interaction with other medicinal products and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.
The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given *before* cisplatin. When paclitaxel is given *before* cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel was given *after* cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.
Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see 5.2).
The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see section 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel into 6α-hydroxypaclitaxel is the major metabolic pathway in humans. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment.
Further data on the potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or CYP3A4.
Studies in KS patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

4.6 Pregnancy and lactation

Fertility:
Paclitaxel has been shown to decrease fertility in rats.
Pregnancy:
Paclitaxel has shown to be teratogenic, embryotoxic and mutagenic in many experimental systems. In particular, it has been shown to be embryotoxic and foetotoxic in rabbits.
There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm and is therefore contraindicated during pregnancy.
Women should be advised to avoid becoming pregnant during therapy with paclitaxel, and to inform the treating physician immediately should this occur. Pregnancy should be avoided for at least 6 months after treatment.
Lactation:
It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation (see section 4.3). Breastfeeding should be discontinued for the duration of paclitaxel therapy.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent paclitaxel in clinical studies. As the KS population is very specific, a special chapter based on a clinical study with 107 patients, is presented at the end of this section.
The frequency and severity of undesirable effects, unless otherwise mentioned, are generally similar between patients receiving paclitaxel for the treatment of ovarian carcinoma, breast carcinoma or NSCLC. None of the observed toxicities were clearly influenced by age.
The most frequent significant undesirable effect was bone marrow suppression. Severe neutropenia (<500 cells/mm³) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for ≥7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir < 50,000/mm³ at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb <5 mmol/l) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.
Neurotoxicity, mainly *peripheral neuropathy*, appeared to be more frequent and severe with a 175 mg/m^2 3-hour infusion (85% neurotoxicity; 15% severe) than with a 135 mg/m^2 24-hour infusion (25% peripheral neuropathy; 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.
Arthralgia or myalgia affected 60% of patients and was severe in 13% of patients.
A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) of patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.
Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration; and on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discolouration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. “recall”, has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.
The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three-hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the postmarketing surveillance* of paclitaxel.
The frequency of undesirable effects listed below is defined using the following convention:
very common (≥ 1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

Infections and infestations:	*Very common* : infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome *Uncommon:* septic shock *Rare*:* pneumonia, peritonitis, sepsis
Blood and the lymphatic system disorders:	*Very common* : myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding *Rare** : febrile neutropenia

	Very rare:* acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	*Very common* : minor hypersensitivity reactions (mainly flushing and rash) *Uncommon* : significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension) *Rare*:* anaphylactic reactions *Very rare** : anaphylactic shock
Metabolism and nutrition disorders:	*Very rare** : anorexia
Psychiatric disorders:	*Very rare **: confusional stage
Nervous system disorders:	*Very common* : neurotoxicity (mainly: peripheral neuropathy) *Rare*:* motor neuropathy (with resultant minor distal weakness) *Very rare** : autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders:	*Very rare*:* optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended
Ear and labyrinth disorders:	*Very rare** : ototoxicity, hearing loss, tinnitus, vertigo
Cardiac disorders:	*Common:* bradycardia *Uncommon* : cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction *Very rare** : atrial fibrillation, supraventricular tachycardia
Vascular disorders:	*Very common* : hypotension *Uncommon:* hypertension, thrombosis, thrombophlebitis *Very rare **: shock
Respiratory, thoracic and mediastinal disorders:	*Rare*:* dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure *Very rare** : cough

Gastrointestinal disorders:	*Very common* : nausea, vomiting, diarrhoea, mucosal inflammation *Rare*:* bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis *Very rare** : mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis
Hepato-biliary disorders:	*Very rare*:* hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	*Very common* : alopecia *Common:* transient and mild nail and skin changes *Rare*:* pruritus, rash, erythema *Very rare** : Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
Musculoskeletal, connective tissue and bone disorders:	*Very common:* arthralgia, myalgia
General disorders and administration site conditions:	*Common* : injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) *Rare*:* asthenia, pyrexia, dehydration, oedema, malaise
Investigations:	*Common* : severe elevation in AST (SGOT), severe elevation in alkaline phosphatase *Uncommon:* severe elevation in bilirubin *Rare** : increase in blood creatinine

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

Combination treatment

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

When administered as a three hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with paclitaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

For the first line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever, and diarrhoea were reported more frequently and with greater severity when paclitaxel (220 mg/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m²) / doxorubicin (50 mg/m²) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel /doxorubicin arm.
When paclitaxel was administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to paclitaxel or trastuzumab) were reported more frequently than with single agent paclitaxel: heart failure (8% vs 1%), infection (46% vs 27%), chills (42% vs 4%), fever (47% vs 23%), cough (42% vs 22%), rash (39% vs 18%), arthralgia (37% vs 21%), tachycardia (12% vs 4%), diarrhoea (45% vs 30%), hypertonia (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 3%), herpes simplex (12% vs 3%), accidental injury (13% vs 3%), insomnia (25% vs 13%), rhinitis (22% vs 5%), sinusitis (21% vs 7%), and injection site reaction (7% vs 1%). Some of these frequency differences may be due to the increased number and duration of treatments with paclitaxel/trastuzumab combination vs single agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single agent paclitaxel.
When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, *cardiac contraction abnormalities* (≥20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. *Congestive heart failure* was observed in < 1% in both paclitaxel/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of *cardiac dysfunction* in comparison with patients treated with paclitaxel single agent (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment.
Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.
AIDS-related Kaposi's sarcoma
Except for haematologic and hepatic undesirable effects (see below), the frequency and severity of undesirable effects are generally similar between KS patients and patients treated with paclitaxel monotherapy for other solid tumours, based on a clinical study including 107 patients.
Blood and the lymphatic system disorders: Bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia (< 500 cells/mm3) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for > 7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting ≥7 days was 22%.
Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal.
Thrombocytopenia was observed in 50% of patients, and was severe (< 50,000 cells/mm^3) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm^3, at least once while on treatment. Bleeding episodes related to paclitaxel were reported in < 3% of patients, but the haemorrhagic episodes were localised.
Anaemia (Hb < 11 g/dL) was observed in 61% of patients and was severe (Hb < 8 g/dL) in 10%. Red cell transfusions were required in 21% of patients.
Hepato-biliary disorders: Among patients (> 50% on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Plant alkaloids and other natural products, taxanes, ATC code: L01C D01
Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital

interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.
In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II_{b-c}, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m^2 over 3 hr) followed by cisplatin (75 mg/m^2) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either paclitaxel (135 mg/m² over 24 hrs) 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. While the two different paclitaxel posologies were not compared with each other directly, in both trials patients treated with paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.
In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant paclitaxel therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p = 0.0014), and a significant reduction of 19% in the risk of death (p = 0.0044) relative to patients receiving AC alone. Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/ unknown tumours, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95%CI: 0.78-1.07). However, the design of the study did not investigate the effect of extended AC therapy beyond 4 cycles. It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel 8 cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.
In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225 mg/m² following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006) ; paclitaxel treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumour had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumour the risk reduction of disease recurrence was 10% (95%CI: 0.7-1.11).
In the first-line treatment of metastatic breast cancer, the efficacy and safety of paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials.
In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m²) followed after 24 hours by paclitaxel (220 mg/m² by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), both administered every three weeks for eight courses. In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of paclitaxel /doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the paclitaxel /doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.
In the second pivotal study, the efficacy and safety of the paclitaxel and Herceptin combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of Herceptin in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and paclitaxel (175 mg/m²) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175 mg/m²) 3-hour infusion, every three weeks in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. Paclitaxel was administered every three weeks for at least six courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for the paclitaxel/trastuzumab

combination in terms of time to progression (6.9 vs. 3.0 months), response rate (41% vs. 17%), and duration of response (10.5 vs. 4.5 months) when compared to paclitaxel alone. The most significant toxicity observed with the paclitaxel/trastuzumab combination was cardiac dysfunction (see section 4.8).

In the treatment of advanced NSCLC, paclitaxel 175 mg/m^2 followed by cisplatin 80 mg/m^2 has been evaluated in two phase III trials (367 patients with NSCLC on paclitaxel 6mg/ml containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100 mg/m^2, the other used teniposide 100 mg/m^2 followed by cisplatin 80 mg/m^2 as comparator (367 patients on comparator). Results in each trial were similar. For the primary outcome of mortality, there was no significant difference between the paclitaxel containing regimen and the comparator (median survival times 8.1 and 9.5 months on paclitaxel containing regimens, 8.6 and 9.9 months on comparators). Similarly, for progression-free survival there was no significant difference between treatments. There was a significant benefit in terms of clinical response rate. Quality of life results are suggestive of a benefit on paclitaxel containing regimens in terms of appetite loss and provide clear evidence of the inferiority of paclitaxel containing regimens in terms of peripheral neuropathy ($p<0.008$).

In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in a non-comparative study in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was best tumour response. Of the 107 patients, 63 were considered resistant to liposomal anthracyclines. This subgroup is considered to constitute the core efficacy population. The overall success rate (complete/partial response) after 15 cycles of treatment was 57% (CI 44 - 70%) in liposomal anthracycline-resistant patients. Over 50% of the responses were apparent after the first 3 cycles. In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one at least 2 months prior to treatment with paclitaxel (60.9%). The median time to progression in the core population was 468 days (95% CI 257-NE). Median survival could not be computed, but the lower 95% bound was 617 days in core patients.

5.2 Pharmacokinetic properties

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. The pharmacokinetics of paclitaxel were determined following 3 and 24 hour infusions at doses of 135 and 175 mg/m^2. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hr/m^2; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m^2, indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m^2 to 175 mg/m^2, the C_{max} and $AUC_{0-\infty}$ values increased 75% and 81%, respectively.

Following an intravenous dose of 100 mg/ m² given as a 3-hour infusion to 19 KS patients, the mean Cmax was 1,530 ng/ml (range 761 - 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 - 9,428 ng.hr/ml). Clearance was 20.6 l/h/ m² (range 11-38) and the volume of distribution was 291 l/ m² (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

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

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

The disposition of paclitaxel has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome P450 enzymes. Following administration of radiolabeled paclitaxel, an average of 26%, 2% and 6% of the radioactivity was excreted in the faeces as 6α-hydroxypaclitaxel, 3'-p-hydroxypaclitaxel, and 6α-3'-p-dihydroxy-paclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, CYP3A4 and both CYP2C8 and CYP3A4 respectively. The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a 3-hour infusion of paclitaxel 135mg/m^2 were within the range of those defined in non-dialysis patients.

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Macrogolglycerol ricinoleate
Ethanol, anhydrous

6.2 Incompatibilities

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

6.3 Shelf life

Vial before opening
3 years.
After opening before dilution
From a microbiological point of view, once opened the product must be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.
After dilution
Chemical and phyical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in 5% glucose solution and 5% glucose in Ringer solution for injection, 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. Once diluted, for single use only.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted medicinal product, see section 6.3

6.5 Nature and contents of container

Glass vial (type I PhEur) with bromobutyl rubber stopper and metal cap (aluminium) with polypropylene disk.
Vial will be packed with or without a protective plastic overwrap.
Pack sizes:
1 x 5 ml vial (30 mg/5 ml)
1 x 16.7 ml vial (100 mg/16.7 ml)
1 x 25 ml vial (150 mg/25 ml)
1 x 50 ml vial (300 mg/50 ml)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling
As with all antineoplastic agents, caution should be exercised when handling Paclitaxel Nucleus. 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 erythema have been observed. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

If unopened vials are refrigerated, a precipitate may form which redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy, or an insoluble precipitate is noted, the vial should be discarded.
Following multiple needle entries and product withdrawals, the vials maintain microbial, chemical and physical stability for up to 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.
Preparation of infusion solution
So called "closed system", e.g. the Chemo-Dispensing Pin device or similar devices, should not be used for withdrawal of the doses from injection vial since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.
Prior to infusion, Paclitaxel Nucleus 6 mg/ml concentrate for solution for infusion must be diluted, using aseptic techniques. The following solutions for infusion can be used for dilution: 0.9% Sodium Chloride solution for infusion, or 5% Glucose solution for infusion, or 5% Glucose and 0.9% Sodium Chloride solution for infusion, or 5% Glucose in Ringer's solution for infusion, to a final concentration of 0.3 to 1.2 mg/ml.
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in a 5% glucose solution and 5% glucose in Ringer solution for injection and for 14 days when diluted in sodium chloride 0.9%. 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 usually should not be more than 24 hours at 2- 8 ºC, unless the dilution is performed in controlled and validated aseptic conditions.
After the dilution, the solution is for single use.
Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. In order to reduce the precipitation risk the diluted Paclitaxel Nucleus infusion should be used as soon as possible after dilution. Paclitaxel should be administered through an in-line filter with a microporous membrane ≤ 0.22 µm. No significant losses in potency have been noted following
simulated delivery of the solution through IV tubing containing an in-line filter.
There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24 hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, paclitaxel should be used as soon as possible after dilution and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regurlarly 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 paclitaxel solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Use of filter devices (e.g. IVEX-2 ®) which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP (see section 6.2).
Protection instructions for preparation of Paclitaxel Nucleus solution for infusion

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
2. Pregnant women or women who may become pregnant, should not handle this product.
3. Opened containers, like injection vials and infusion bottles and used canules, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
4. Follow the instructions below in case of spillage:
   - protective clothing should be worn
   - broken glass should be collected and placed in the container for HAZARDOUS WASTE
   - contaminated surfaces should be flushed properly with copious amounts of cold water
   - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
5. In the event of Paclitaxel Nucleus contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.

6. In case of contact of Paclitaxel Nucleus with eyes, wash them thouroughly with plenty of cold water. Contact an ophthalmologist immediately.

Disposal
All items used for preparation, administration or otherwise coming into contact with paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Nucleus ehf.
Naustanesi
116 Reykjavik
Iceland

8 MARKETING AUTHORISATION NUMBER(S)
PL 24701/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/01/2008

10 DATE OF REVISION OF THE TEXT
24/01/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3
Product Information Leaflet

Nucleus ehf.

Paclitaxel Nucleus 6mg/ml Concentrate For Solution For Infusion

Read all of this leaflet carefully before you start using this medicine.
- **Keep this leaflet. You may need to read it again.**
- **If you have any further questions, ask your doctor.**
- **This medicine has been prescribed for you. Do 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.**

In this leaflet:

Paclitaxel Nucleus concentrate for solution for infusion is given only by a doctor or nurse. They can answer any questions you may have after reading this package leaflet.

1. WHAT PACLITAXEL NUCLEUS IS AND WHAT IT IS USED FOR

This medicinal product is used for treatment of cancer. It can be cancer in the ovaries or breast cancer (advanced or spreading ovarian cancer, advanced or spreading breast cancer). This medicinal product may also be used for a special cancer in the lungs (advanced non-small-cell lung cancer, NSCLC) in patients who cannot be treated with surgery and/or radiotherapy. Paclitaxel may also be used for a special cancer, called Kaposi´s sarcoma, which may be associated with AIDS (Acquired Immuno-Deficiency Syndrome) caused by an HIV disease) where other treatments i.e. liposomal anthracyclines have not worked. Paclitaxel works by stopping cell division and is used to prevent the growth of cancer cells.

Special care should be observed if you are taking medicines which influence the metabolism of paclitaxel such as: erythromycin, fluoxetine, gemfibrozil, rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, and nevirapine and for HIV patients receiving protease inhibitors (ritonavir, nelfinavir) as concomitant therapy.

Driving and using machines
There is no reason why you cannot continue driving between courses of Paclitaxel Nucleus but you should remember that this medicine contains some alcohol and it may be unwise to drive or use machines immediately after a course of treatment. As in all cases, you should not drive or use machines if you feel dizzy or light-headed.

Important information about some of the ingredients of Paclitaxel Nucleus
Paclitaxel contains:
- Alcohol (ethanol) approximately 50% by volume, that is up to about 20 g per dose. This is equivalent to half a litre of beer per dose or a large glass (210ml) of wine per dose. This amount may be dangerous for patients suffering from alcoholism and for high risk patients including those with liver problems or epilepsy (fits). The amount of alcohol in this product may alter the effects of other medicines.
- Macrogolglycerol ricinoleate, which can cause severe allergic (hypersensitivity) reactions.

3. HOW TO USE PACLITAXEL NUCLEUS

- Your doctor will decide how much Paclitaxel Nucleus you will be given. It is given under the supervision of a doctor, who can give you more information. The dose will depend on the type and the extent of the cancer, and your body surface in square metres (m^2) which is calculated from your height and weight. The dose you receive will also depend on results of your blood tests.
- Paclitaxel solution has to be diluted before being given to you.

2. BEFORE YOU USE PACLITAXEL NUCLEUS

Do not use Paclitaxel Nucleus
- if you are allergic (hypersensitive) to paclitaxel or any of the other ingredients. One of the ingredients, macrogolglycerol ricinoleate, can cause severe allergic reactions
- if you are pregnant or breast-feeding
- if the number of white blood cells (neutrophils) is too low. This is measured by a doctor or nurse.
- In patients with Kaposi's sarcoma, this product should not be used if you have a serious uncontrolled infection.

If you are unsure about anything, ask your doctor or pharmacist.

Take special care with Paclitaxel Nucleus
- if you have heart disease or liver problems
- when diarrhoea occurs during or shortly after treatment with paclitaxel (pseudomembranous colitis)
- if you have Kaposi's sarcoma and severe inflammation of the mucous membrane (membranes lining the passages of the body that open to the outside) occurs
- if you have had nerve problems in your hands or in feet, such as numbness, tingling or burning (peripheral neuropathy)
- if you have blood problems, such as changes in the number of some cells
- if Paclitaxel Nucleus is given to you in combination with radiotherapy of the lung.

Pregnancy and breast-feeding
Pregnancy
- **Do not use Paclitaxel Nucleus** if you think you are pregnant or you are trying to become pregnant. **Paclitaxel can damage the unborn baby**
- Pregnancy must be avoided and both partners should use reliable contraception during treatment with Paclitaxel Nucleus and for at least 6 months after treatment.
  Tell your doctor immediately if you do become pregnant.

Breast-feeding
- Paclitaxel Nucleus should not be used when you are breast-feeding. You should stop breast feeding while you are being treated with Paclitaxel Nucleus. Do not restart breast feeding until your doctor tells you it is safe to do so.

Ask your doctor or pharmacist for advice before taking any medicine.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines you have obtained without a prescription.
When used in combination, Paclitaxel Nucleus should be given before cisplatin. Paclitaxel Nucleus should be given 24 hours after doxorubicin.

SINPL008

- Paclitaxel Nucleus is given by infusion (a drip) into a vein for 3 hours. Treatment is usually repeated every three weeks. Treatment of AIDS-related Kaposi's sarcoma is repeated every other week.
- Depending on the type and severity of the cancer you will receive Paclitaxel Nucleus either alone or in combination with another anticancer agent.
- Each time before you are given Paclitaxel Nucleus, you will be given other medicines (premedication) such as dexamethasone, diphenhydramine and cimetidine, or ranitidine.
  This is necessary to decrease the risk of severe allergic (hypersensitive) reactions (see section 4. Possible side effects, uncommon).

- If you are given too much Paclitaxel Nucleus
Your dose will be carefully calculated by the doctors, so overdose is unlikely. However, if too much is given this is likely to make the usual side effects worse, particularly blood disorders, numbness/tingling especially of the arms, hands, legs or feet, and stomach upsets including vomiting and diarrhoea.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Paclitaxel Nucleus can cause side effects, although not everybody gets them. The following side effects may occur after treatment with Paclitaxel Nucleus infusion.

The most frequent side effects are hair loss and decreased blood cell count. Your hair grows back and your blood cell count returns to normal after you have finished your paclitaxel treatment.

<u>If any of the following happens, tell your doctor immediately:</u>
- Any abnormal bruising, bleeding, or signs of infections such as a sore throat and high temperature.
- Severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint.
- Breathlessness and dry cough due to damage to the lung.
- Reaction at the injection site, e.g. local swelling, pain, redness

Very common (affects more than 1 out of 10 people):
- An effect on the bone marrow, which can cause decreased numbers of some blood cells. This may cause anaemia. It can also lead to infections, mainly urinary tract and upper respiratory tract infections (with reported cases of fatal outcome.

- Decreased number of blood platelets and bleeding.
- Milder allergic (hypersensitivity) reactions, such as flushing and rash.
- Nerve problems affecting the hands and/or feet (peripheral neuropathy), which can cause tingling feelings in the skin, numbness and/or pain.
- Low blood pressure.
- Feeling sick (nausea), being sick (vomiting) and diarrhoea.
- Hair loss.
- Muscle or joint pain.
- Inflammation of areas such as the lining of the mouth.

Common (affects more than 1 out of 100 people):
- Slow heart beat (pulse).
- Mild changes in nail and skin which soon disappear.
- Painful swelling and inflammation where the injection is given which may cause tissue hardening (occasionally cellulitis, thickening and scarring of the skin (skin fibrosis), death of skin cells (skin necrosis)).
- Changes in blood tests that check how the liver is working.

Uncommon (affects less than 1 out of 100 people):
- A state of shock resulting from blood poisoning.
- Serious allergic (hypersensitivity) reactions with e.g. decreased or increased blood pressure, swelling of the face, difficulty in breathing, skin rash, chills, back pain, chest pain, fast heart beat, abdominal pain, pain in arms and legs, sweating.
- Serious heart problems like heart muscle degeneration (cardiomyopathy), serious changes in your heart's rhythm even with fainting. Heart attack.
- Increased blood pressure.
- Blood clot (thrombosis), inflammation of a vein in connection with blood clots.
- Yellowing of the skin (jaundice).

Rare (affects less than 1 out of 1,000 people):
- Pneumonia
- Reduced number of a type of white blood cell with fever (febrile neutropenia)
- Serious allergic (anaphylactic) reaction.
- Effects on the nerves, which can cause muscle weakness in the arms and legs.
- Difficulty in breathing, fluid on the lungs, inflammation of the lungs and other lung problems (lung fibrosis, pulmonary embolism), markedly impaired pulmonary function (respiratory failure).

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 PACLITAXEL NUCLEUS

Keep out of the reach and sight of children.
Keep the vial in the outer carton in order to protect from light.
Do not use this medicinal product after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
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 Paclitaxel Nucleus contains

- The active substance is paclitaxel.
- 1ml of concentrate for solution for infusion contains 6mg paclitaxel.
- The other ingredients are citric acid, anhydrous, macrogolglycerol ricinoleate and ethanol, anhydrous.

What Paclitaxel Nucleus looks like and contents of the pack
Paclitaxel Nucleus 6mg/ml concentrate for solution for infusion is a clear, colourless to pale yellow, slightly viscous solution and is packed into glass vials.
Pack sizes:
1 x 5ml vial (30mg/5ml)
1 x 16.7ml vial (100mg/16.7ml)
1 x 25ml vial (150mg/25ml)
1 x 50ml vial (300mg/50ml)

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Nucleus ehf.
Naustanesi
116 Reykjavik
Iceland

Manufacturer
Actavis Nordic A/S
Ørnegårdsvej 16
DK-2820 Gentofte
Denmark
Or
S.C. Sindan- Pharma S.R.L.
11 Ion Mihalache Blvd
011171 Bucharest
Romania

- Itching, rash and reddened skin.
- Weakness, high temperature (fever), dehydration, oedema, feeling ill.
- Blood poisoning.
- Blockage of the intestines, penetration of the wall of the small intestine or large bowel, inflammation of the lining of the belly (peritoneum), inflammation of the intestine caused by inadequate blood supply, inflammation of the pancreas.
- Increased level of the substance creatinine in the blood

Very rare (occurs with less than 1 out of 10,000 of the users):

- Acute leukaemia (a type of blood cancer), myelodysplastic syndrome (a diverse collection of blood cell disorders).
- Life threatening allergic reaction (anaphylactic shock).
- Loss of appetite, shock due to decreased blood pressure, cough.
- Effects on the nervous system which can cause paralysis of the intestines (gut) and a decrease in blood pressure when standing up or sitting up from a lying down position, fits (epileptic seizures), cramps, confusion, dizziness, alteration in brain function or structure, headache, loss of the ability to coordinate muscular movement.
- Problems with eyesight and visual disturbances, usually in patients given larger doses.
- Reduction or loss of hearing, ringing in the ears (tinnitus), vertigo.
- Abnormal heart rhythm (atrial fibrillation, supraventricular tachycardia).
- A blood clot in the mesenteric artery, pseudomembranous colitis (an infection of the colon caused by specific bacteria), inflammation of the oesophagus, constipation. Collection of fluid in the abdomen (belly).
- Severe inflammation of the large bowel presenting with fever, watery or bloody diarrhoea, and crampy abdominal pain (neutropenic colitis).
- Death of liver cells (necrosis of the liver), confusion and other effects (hepatic encephalopathy) caused by changes in the way the liver works (both with reported cases of fatal outcome).
- Hives (urticaria), scaling and shedding of the skin usually accompanied by redness.
- Severe inflammatory eruption of the skin and mucous membranes (severity ranging from erythema multiforme to Stevens-Johnson syndrome to the most serious toxic epidermal necrolysis (TEN)).
- Disintegration of nails. Hands and feet should be protected against sunshine during the treatment time).

SINPL008

This medicinal product is authorised in the Member States of the EEA under the following names:

UK	Paclitaxel Nucleus 6mg/ml concentrate for solution for infusion
AT	Paclitaxel-Nucleus 6mg/ml Konzentrat zur Herstellung einer Infusionslösung
BE	PACLITAXEL NUCLEUS 6mg/ml, solution à diluer pour perfusion
CZ	Paclitaxel Nucleus 6mg/ml
DE	Paclitaxel-Nucleus 6mg/ml Konzentrat zur Herstellung einer Infusionslösung
DK	Paclitaxel Nucleus 6mg/ml
ES	Paclitaxel Nucleus 6mg/ml concentrado para solución para perfusión
EE	Paclitaxel Nucleus
FI	Paclitaxel Nucleus
FR	PACLITAXEL NUCLEUS 6mg/ml, solution à diluer pour perfusion
HU	Paclitaxel Nucleus
IE	Paclitaxel Nucleus 6mg/ml concentrate for solution for infusion
IS	Paclitaxel Nucleus
IT	Paclitaxel Nucleus
LT	Paclitaxel Nucleus
LV	Paclitaxel Nucleus
MT	Paclitaxel Nucleus 6mg/ml
NL	Paclitaxel Nucleus 6mg/ml
NO	Paclitaxel Nucleus
PT	Paclitaxel Nucleus
SE	Paclitaxel Nucleus
SI	PAKLITAKSEL Nucleus

This leaflet was last revised in
January 2008

If you would like a leaflet with larger text, please contact 01271 311257

Nucleus ehf.
Nucleus ehf., Naustanesi, 116 Reykjavik, Iceland

There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24 hour infusion period.
Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution.
To reduce the precipitation risk, paclitaxel should be used as soon as possible after dilution and excessive agitation, vibration or shaking should be avoided.
Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration.
In order to reduce the precipitation risk the diluted Paclitaxel Nucleus infusion should be used as soon as possible after dilution.

Infusion technique

Paclitaxel Nucleus infusion solution should be administered as intravenous infusion.
Paclitaxel Nucleus should be administered through an in-line filter with a microporous membrane ≤ 0.22 µm. (No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.)
The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regurlarly inspected and the infusion should be stopped if precipitation is present.

Stability and storage conditions

Store the vial in original package to protect from light. If refrigerated, a precipitate may form which redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy, or an insoluble precipitate is noted, the vial should be discarded. An expiry date is given on the outer carton and vial label of the product. It should not be used after this date.
After opening: From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in a 5% glucose solution and 5% glucose in Ringer solution for injection and for 14 days when diluted in sodium chloride 0.9%. 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 usually should not be more than 24 hours at 2- 8°C, unless the dilution is performed in controlled and validated aseptic conditions.
After the dilution, the solution is for single use.

Incompatibilities

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

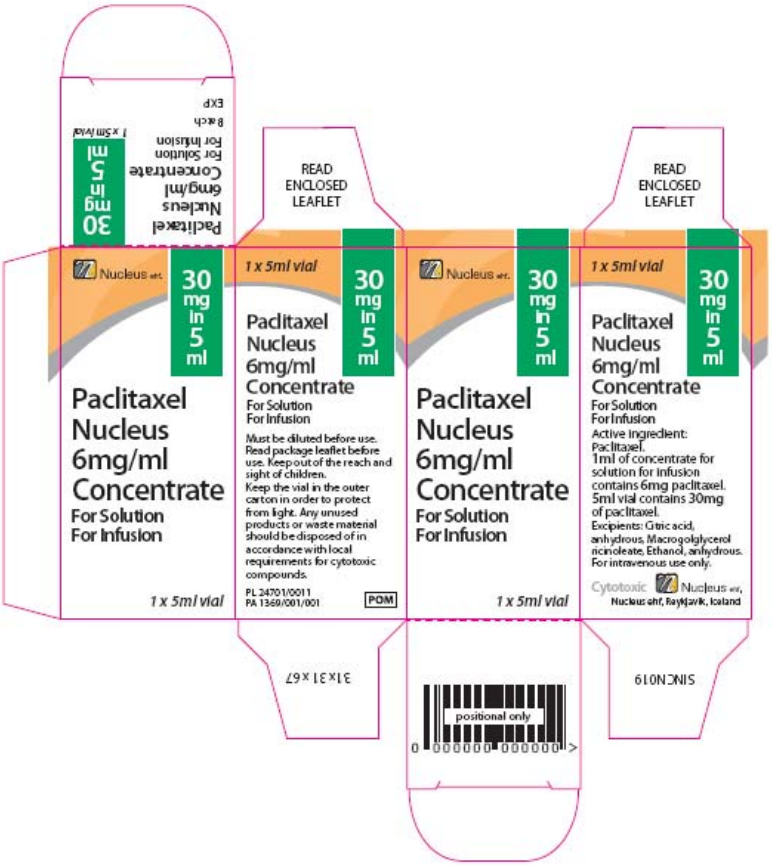
Disposal

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

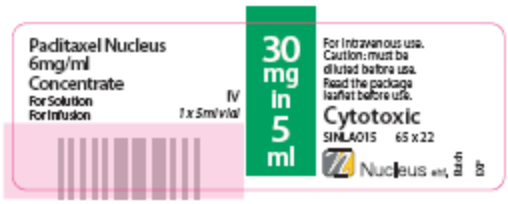
Module 4

Labelling

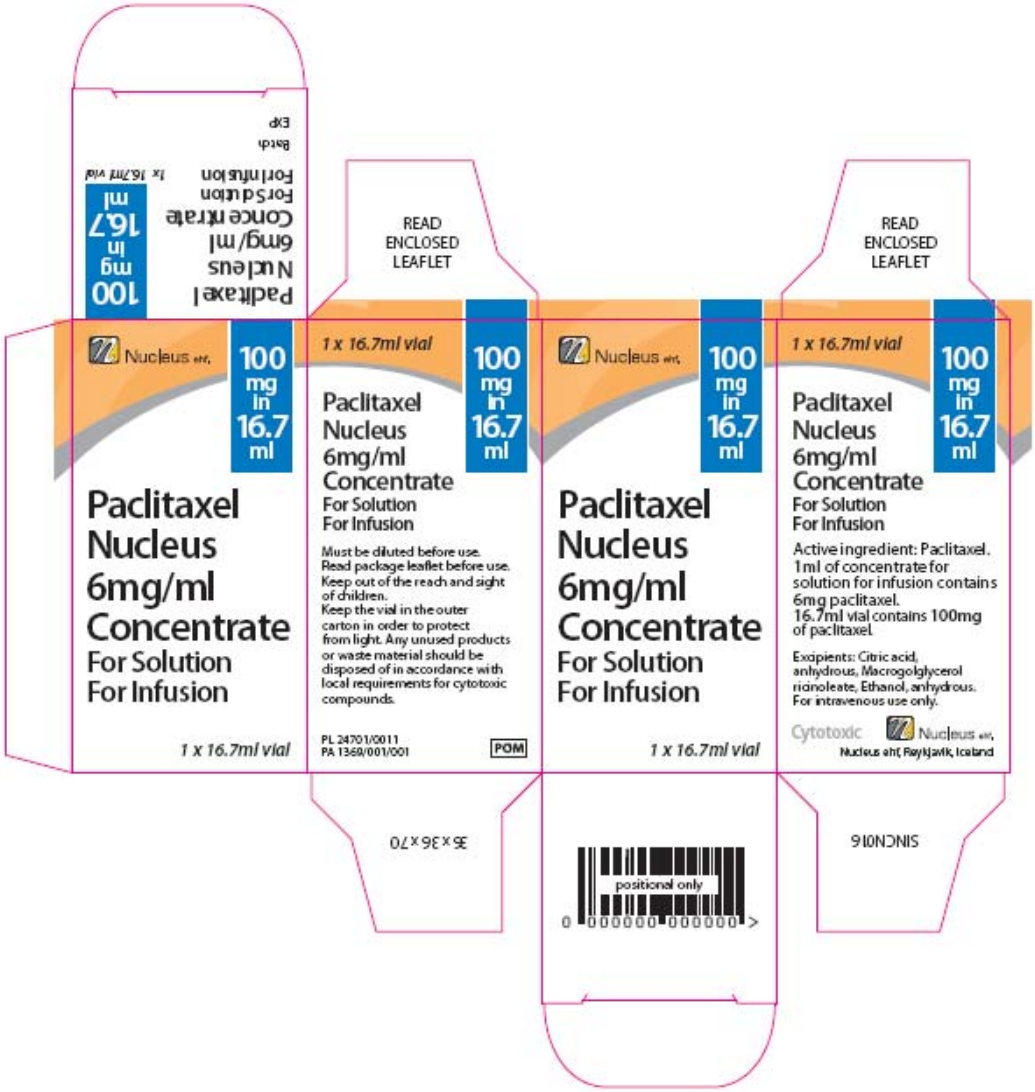
Paclitaxel Nucleus 6mg/ml Concentrate for Solution for Infusion Carton-1 x 5ml vial



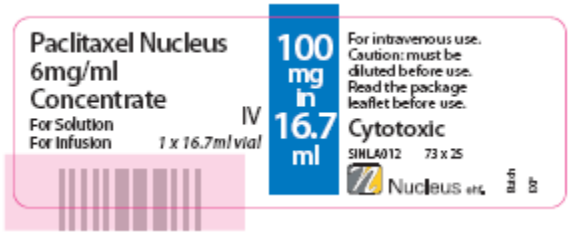
Label-1 x 5ml vial



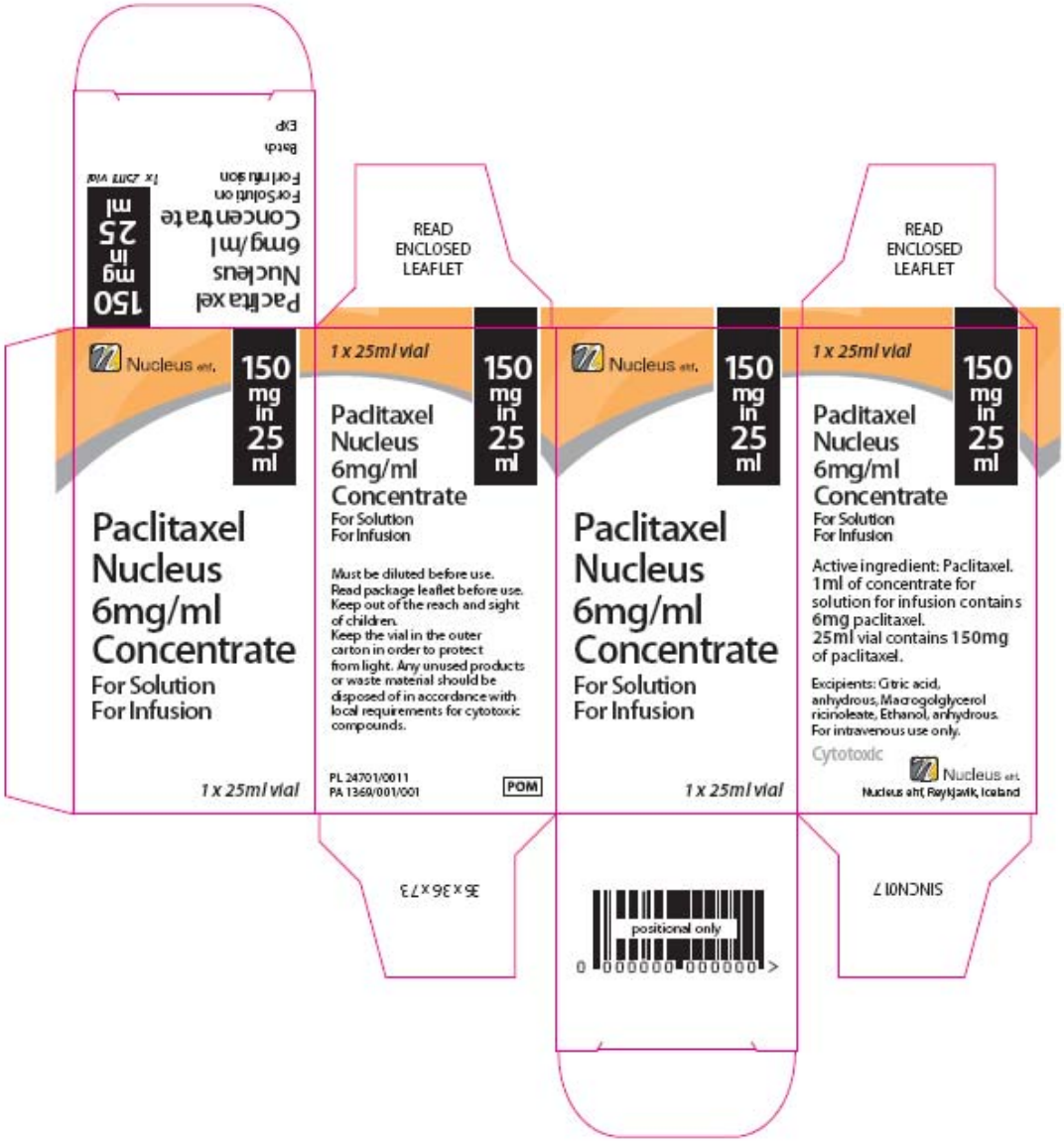
Paclitaxel Nucleus 6mg/ml Concentrate for Solution for Infusion
Carton-1 x 16.7ml vial



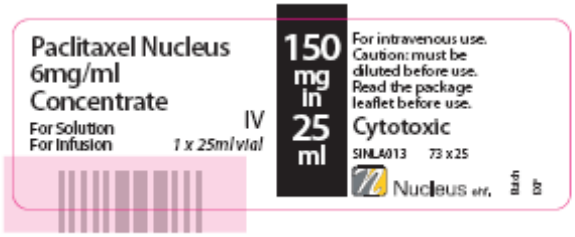
Label-1 x 16.7ml vial



Paclitaxel Nucleus 6mg/ml Concentrate for Solution for Infusion
Carton-1 x 25ml vial

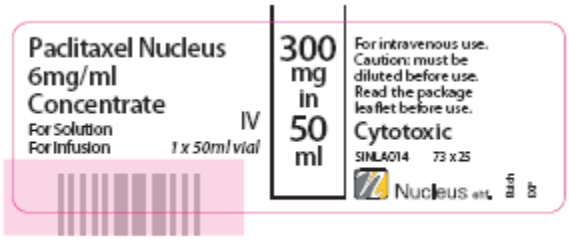


Label-1 x 25ml vial



Paclitaxel Nucleus 6mg/ml Concentrate for Solution for Infusion Carton-1 x 50ml vial

Label-1 x 50ml vial



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Paclitaxel 6mg/ml Concentrate for Solution for Infusion, in the treatment of ovarian, advanced breast cancer, non-small cell lung cancer and KS, is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, for Paclitaxel 6mg/ml Concentrate for Solution for Infusion, has been shown to be a generic product of Taxol 6 mg/ml concentrate for solution for infusion. The originator product is Taxol (6 mg/ml, concentrate for solution for infusion) by Bristol-Myers Squibb Pharmac. Ltd Netherlands has been registered in NL since the 20th of September, 1993.

Paclitaxel is a member of the Taxane group of drugs and is an alkaloid ester derived from the Western and European Yew trees. Paclitaxel enhances tubulin polymerization, acting as a mitotic spindle poison. The stabilization of polymerization results in mitotic disruption. Paclitaxel is used clinically in the treatment of ovarian, advanced breast cancer, non-small cell lung cancer and KS. Neutropenia, thrombocytopenia and peripheral neuropathy are dose limiting toxicities. Routine pre-medication with a corticosteroid, histamine H_1 and H_2-receptor antagonists is recommended to prevent severe hypersensitivity reactions

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Paclitaxel Nucleus (6mg/ml-concentrate for solution for infusion)
Name(s) of the active substance(s) (INN)	Paclitaxel
Pharmacotherapeutic classification (ATC code)	Cytostatic agent: L01C D01
Pharmaceutical form and strength(s)	6mg/ml-concentrate for solution for infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/1000/01/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Portugal, Slovenia, Slovak Republic, Spain
Marketing Authorisation Number(s)	PL 24701/0011
Name and address of the authorisation holder	Nucleus ehf, Box 55, Naustanes, 116 Reykjavik, Iceland.

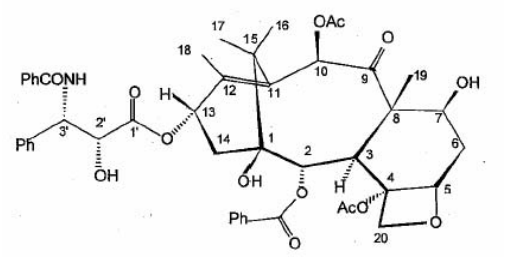
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Paclitaxel

INN: Paclitaxel



Molecular formula: $C_{47}H_{51}N_{14}$
Molecular weight: 853.92
CAS Registry Number: [33069-62-4]

Physical form: White to almost white, crystalline powder.
Solubility: Practically insoluble in water, freely soluble in methanol and in methylene dichloride.

The active substance paclitaxel is not reported in Ph Eur. EDMFs and relevant letters of access have been submitted to MHRA. An appropriate specification is provided for the active substance paclitaxel which is satisfactory.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active paclitaxel is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Satisfactory re-test periods have been stated based on the stability data provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely citric acid anhydrous, macrogolglycerolricinoleate and absolute ethanol. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph.Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

There were no novel excipients used and no overages.

Impurity profiles
Comparative impurity profiles between the innovator product and the test product are shown to be similar.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory validation batch data have been provided.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Product is packaged in clear type I glass vials (5ml, 20ml and 50ml) and sealed with bromobutyl rubber stoppers and aluminium flip-off caps. Specifications and satisfactory certificates of analysis are provided.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are "Store in original container".

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

Paclitaxel Nucleus 6mg/ml Concentrate for Solution for Infusion has been shown to be a generic medicinal product of the reference product Taxol 6mg/ml Concentrate for Solution for Infusion. The proposed drug product corresponds to the current EU definition of a generic product as it compiles with the criteria of having the same qualitative and quantitative content of the active substance and pharmaceutical form as the reference product.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of paclitaxel are well known. As paclitaxel is a widely used, well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is thus appropriate.

III.3 CLINICAL ASPECTS
Introduction
Paclitaxel 6 mg/ml concentrate for solution for infusion is the generic version of Taxol 6mg/ml Concentrate for solution for infusion (Bristol Myers Squibb). The use of the reference product is well-established in the EU. The product is essentially similar to Taxol 6mg/ml, concentrate for solution for infusion. Both products contain the same quantitative and qualitative composition of the active ingredient, paclitaxel.

No new data have been submitted and none are required for this application. In keeping with CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

Clinical Pharmacology

No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application. The pharmacodynamic and pharmacokinetic claims in the SPC are appropriately consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties of this combination have been extensively studied in the past.

Clinical efficacy

The clinical overview describes several clinical studies which have established Paclitaxel as an active drug in first and second line treatment of ovarian cancer, node positive and metastatic breast carcinoma, and advanced non-small lung carcinoma (Cohen *et al*., 2001; McGuire and Ozols., 1998; Conte *et al*., 2001; Perez., 1998; Gatzemeier et al., 2000; Von Pawel., 1996; Belani *et al*., 2003;). The clinical overview has been up dated to include a discussion of the use of Paclitaxel in patients with AIDS-related Kaposi's sarcoma (Gill *et al.*, 1999).

Clinical safety

No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of paclitaxel. No new safety data have been identified.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Paclitaxel 6mg/ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

Extensive clinical experience with paclitaxel is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome