ANNEX 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of paclitaxel.

After reconstitution, each ml of suspension contains 5 mg of paclitaxel.

Excipients
The reconstituted medicinal product contains approximately 425 mg sodium per dose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for infusion.

The reconstituted suspension has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg.

The powder is white to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abraxane monotherapy is indicated for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated (See also section 4.4).

4.2 Posology and method of administration

Abraxane should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents.

The procedure for reconstitution is described in section 6.6.

The recommended dose of Abraxane is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Dose adjustments during treatment:

Patients who experience severe neutropenia (neutrophil count < 0.50 x 10^9/l for a week or longer) or severe sensory neuropathy during Abraxane therapy should have the dose reduced to 220 mg/m^2 for subsequent courses. Following recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. Abraxane should not be administered until neutrophil counts recover to >1.5 x 10^9/l. For grade 3 sensory neuropathy withhold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses.

Patients with hepatic impairment:

Insufficient data are currently available to recommend dose modifications in patients with mild to moderate hepatic impairment (see sections 4.4. and 5.2). Patients with severe hepatic impairment should not be treated with paclitaxel.

Patients with impaired renal function:

Studies in patients with impaired renal function have not been performed and insufficient data are currently available to recommend dose modifications in patients with renal impairment (see section 5.2).

Paediatric patients:

Abraxane is not recommended for use in children below age 18 years due to insufficient data on safety and efficacy.

Elderly patients:

In the clinical studies, no toxicities occurred notably more frequently among elderly patients who received Abraxane.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Lactation.

Patients who have baseline neutrophil counts < 1.5 x 10^9/l.

4.4 Special warnings and precautions for use

Abraxane is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel (see sections 5.1 and 5.2)..

Hypersensitivity:

If hypersensitivity occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and that patient should not be rechallenged with paclitaxel.

Haematology:

Bone marrow suppression (primarily neutropenia) occurs frequently with Abraxane. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during Abraxane therapy. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to >1.5 x 10^9/l and platelets recover to >100 x 10^9/l.

Neuropathy:

Sensory neuropathy occurs frequently with Abraxane, although development of severe symptoms is less common. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose reduction. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of Abraxane is recommended (see section 4.2).

Hepatic Impairment:

Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. The use of Abraxane has not been formally studied in patients specifically with hepatic impairment. Patients with severe hepatic impairment (bilirubin > 5 x ULN or ASL/ALT > 10 x ULN) should not be treated with Abraxane. The appropriate dose regimen in patients with less severe hepatic impairment is unknown.

Cardiotoxicity:

While cardiotoxicity unequivocally related to Abraxane has not been demonstrated, cardiac events are not uncommon in the indicated population, especially in patients who have previously received anthracyclines or have underlying cardiac or pulmonary disease. Thus patients receiving Abraxane should be vigilantly monitored by physicians for the occurrence of cardiac events.

Sexually active men and women 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).

The effectiveness and safety of Abraxane in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy.

Gastrointestinal Symptoms:

If patients experience nausea, vomiting and diarrhoea following the administration of Abraxane, they may be treated with commonly used anti-emetics and constipating agents.

Excipients:

When reconstituted, Abraxane contains approximately 425 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, imidazole antifungals) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Abraxane is indicated for mono-therapy. Abraxane should not be used in combination with other anticancer agents.

4.6 Pregnancy and lactation

Pregnancy:

There are very limited data on the use of paclitaxel in human pregnancy. Paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). Abraxane should not be used in pregnancy, and in women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel.

Women of childbearing potential should use effective contraception during and up to 1 month after receiving treatment with Abraxane. Male patients treated with Abraxane are advised not to father a child during and up to six months after treatment.

Lactation:

It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breast-feeding infants, Abraxane is contraindicated during lactation. Breastfeeding must be discontinued for the duration of therapy.

Fertility:

Abraxane induced infertility in male rats (see section 5.3). Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Abraxane.

4.7 Effects on ability to drive and use machines

Abraxane has minor or moderate influence on the ability to drive and use machines. Abraxane may cause side effects such as tiredness (very common) and dizziness (common) that may affect the ability to drive and use machinery. Patients should be advised not to drive and use machines if they feel tired or dizzy.

4.8 Undesirable effects

The following are the most common and important incidences of adverse reactions related to 229 patients with metastatic breast cancer who were treated with 260 mg/m^2 Abraxane once every three weeks in the pivotal phase III clinical study.

Blood and lymphatic system disorders: Neutropenia was the most notable important haematological toxicity (reported in 79% of patients), and was rapidly reversible and dose dependent; leukopenia was reported in 71% of patients. Grade 4 neutropenia (< 0.5 x 10^9/l) occurred in 9% of patients treated with Abraxane. Febrile neutropenia occurred in four patients on Abraxane. Anaemia (Hb < 10 g/dl) was observed in 46% of patients on Abraxane, and was severe (Hb < 8 g/dl) in three cases. Lymphopenia was observed in 45% of the patients.

Nervous system disorders: In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving Abraxane. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on Abraxane with 10% being Grade 3, and no cases of Grade 4.

Gastrointestinal disorders: Nausea occurred in 29% of the patients and diarrhoea in 25% of the patients.

Skin and subcutaneous system disorders: Alopecia was observed in 90% of the patients treated with Abraxane.

Musculoskeletal and connective tissue disorders: Arthralgia occurred in 32% of patients on Abraxane and was severe in 6% of cases. Myalgia occurred in 24% of patients on Abraxane and was severe in 7% of cases. The symptoms were usually transient, typically occurred three days after Abraxane administration and resolved within a week.

General disorders and administration site disorders: Asthenia/Fatigue was reported in 40% of the patients.

Table 1 lists adverse reactions associated with the administration of Abraxane to patients from studies in which Abraxane has been administered as a single agent at any dose in any indication (N = 789).

The frequency of undesirable effects listed in table 1 is defined using the following convention:

Very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (< 1/10,000).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with Abraxane at any dose in clinical trials.

Investigations:	*Common*: Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase *Uncommon*: Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium
Cardiac disorders:	*Common*: Tachycardia
Blood and lymphatic system disorders:	*Very Common*: Neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia *Common*: Febrile neutropenia
Nervous system disorders:	*Very Common*: Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia. *Common*: Peripheral sensory neuropathy, headache, dysgeusia, dizziness, peripheral motor neuropathy, ataxia, sensory disturbance, somnolence. *Uncommon*: Polyneuropathy, areflexia, dyskinesia, hyporeflexia, neuralgia, sensory loss, syncope, postural dizziness, neuropathic pain, tremor
Eye disorders:	*Common:* Increased lacrimation, blurred vision, dry eye, keratoconjunctivitis sicca, madarosis *Uncommon*: Eye irritation, eye pain, abnormal vision, reduced visual acuity, conjunctivitis, visual disturbance, eye pruritus
Ear and labyrinth disorders:	*Common*: Vertigo *Uncommon*: Ear pain, tinnitus
Respiratory, thoracic and mediastinal disorder:	*Common*: Dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea *Uncommon*: Productive cough, exertional dyspnoea, sinus congestion, decreased breath sounds, pleural effusion, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing *Rare:* Interstitial pneumonitis
Gastrointestinal disorders:	*Very Common*: Nausea, diarrhoea, vomiting, constipation, stomatitis *Common*: Abdominal pain, abdominal distension, upper abdominal pain, dyspepsia, gastrooesophageal reflux disease, oral hypoaesthesia *Uncommon*: Dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, lower abdominal pain, mouth ulceration, oral pain, rectal haemorrhage
Renal and urinary disorders:	*Uncommon*: Dysuria, pollakiuria, haematuria, nocturia, polyuria, urinary incontinence

Table 1: Adverse reactions reported with Abraxane at any dose in clinical trials.

Skin and subcutaneous tissue disorders:	*Very Common*: Alopecia, rash *Common*: Nail disorder, pruritus, dry skin, erythema, nail discolouration, skin hyperpigmentation, onycholysis *Uncommon*: Nail bed tenderness, urticaria, skin pain, photosensitivity reaction, pigmentation disorder, pruritic rash, skin disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail discomfort, generalized pruritus, macular rash, papular rash, skin lesion, swollen face
Musculoskeletal and connective tissue disorders:	*Very Common*: Arthralgia, myalgia. *Common*: Pain in extremity, bone pain, back pain, muscle cramps, limb pain *Uncommon*: Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness
Metabolism and nutrition disorders:	*Very common:* Anorexia *Common:* Dehydration, decreased appetite, hypokalaemia *Uncommon:* Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia
Infections and infestations:	*Common*: Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis *Uncommon*: Oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, pneumonia, catheter-related infection, fungal infection, herpes zoster, injection site infection
Injury, poisoning and procedural complications:	*Uncommon*: Contusion *Rare:* Radiation recall phenomenon
Neoplasms benign, malignant and unspecified (including cysts and polyps):	*Uncommon:* Metastatic pain, tumour necrosis
Vascular disorders:	*Common*: Flushing, hot flushes, hypertension, lymphoedema *Uncommon*: Hypotension, peripheral coldness, orthostatic hypotension *Rare:* Thrombosis
General disorders and administration site conditions:	*Very Common*: Fatigue, asthenia, pyrexia. *Common*: Peripheral oedema, mucosal inflammation, pain, rigors, oedema, weakness, decreased performance status, chest pain, influenza-like illness, malaise, lethargy, hyperpyrexia *Uncommon*: Chest discomfort, abnormal gait, swelling, injection site reaction
Immune system disorders:	*Uncommon*[1]*:* Hypersensitivity
Hepatobiliary disorders	*Uncommon*: Hyperbilirubinaemia, hepatomegaly
Reproductive system and breast disorders:	*Uncommon*: Breast pain

Table 1: Adverse reactions reported with Abraxane at any dose in clinical trials.

Psychiatric disorders:	*Common*: Insomnia, depression, anxiety *Uncommon*: Restlessness

[1] The frequency of hypersensitivity reactions is calculated based on one definitely related case in a population of 789 patients

Post-marketing experience

Cranial nerve palsies, vocal cord paresis, and rare reports of severe hypersensitivity reactions have been reported during post-marketing surveillance of Abraxane.

In some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysaesthesiae have been reported as part of the continuing surveillance of Abraxane. Because these events have been reported voluntarily during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established.

4.9 Overdose

There is no known antidote for paclitaxel overdose. In the event of an overdose, the patient should be closely monitored. Treatment should be directed at the major anticipated toxicities, which are bone marrow suppression, mucositis and peripheral neuropathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Taxanes, ATC Code: L01CD01

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

Abraxane contains human serum albumin-paclitaxel nanoparticles. Albumin is known to mediate endothelial transcytosis of plasma constituents and *in vitro* studies demonstrated that the presence of albumin enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial transport is mediated by the gp-60 albumin receptor, and that there is accumulation of paclitaxel in the area of tumour due to the albumin-binding protein SPARC (secreted protein acidic rich in cysteine).

Breast carcinoma:

Data from 106 patients accrued in two single-arm open-label studies and from 454 patients treated in a randomised Phase III comparative study are available to support the use of Abraxane in metastatic breast cancer. This information is presented below.

Single-arm open-label studies

In one study, Abraxane was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilised a dose of 300 mg/m^2 as a 30 minute infusion in 63 patients with metastatic breast cancer. Patients were treated without steroid pre-treatment or planned G-CSF support. Cycles were administered at 3 week intervals. The response rates in all patients were 39.5% (95% CI: 24.9% - 54.2%) and 47.6%

(95% CI: 35.3% - 60.0%), respectively. The median time to disease progression was 5.3 months (175 mg/m^2; 95% CI: 4.6 – 6.2 months) and 6.1 months (300 mg/m^2; 95% CI: 4.2 – 9.8 months).

Randomised comparative study:

This multi-centre trial was conducted in patients with metastatic breast cancer, who were treated every 3 weeks with single-agent paclitaxel, either as solvent-based paclitaxel 175 mg/m^2 given as a 3-hour infusion with premedication to prevent hypersensitivity (N = 225), or as Abraxane 260 mg/m^2 given as a 30 minute infusion without premedication (N = 229).

Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting only, 40% in the metastatic setting only, and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study medicinal product as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

Results for overall response rate and time to disease progression, and progression-free survival and survival for patients receiving > 1st-line therapy, are shown below.

Table 2: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator

Efficacy variable	Abraxane (260 mg/m^2)	Solvent-based paclitaxel (175 mg/m^2)	p-value
Response rate [95% CI] (%)			
> 1st-line therapy	26.5 [18.98, 34.05] (n = 132)	13.2 [7.54, 18.93] (n = 136)	0.006[a]
**Median time to disease progression [95% CI] (weeks)*			
> 1st-line therapy	20.9 [15.7, 25.9] (n = 131)	16.1 [15.0, 19.3] (n = 135)	0.011[b]
**Median Progression Free Survival [95% CI] (weeks)*			
> 1st-line therapy	20.6 [15.6, 25.9] (n = 131)	16.1 [15.0, 18.3] (n = 135)	0.010[b]
**Survival [95% CI] (weeks)*			
> 1st-line therapy	56.4 [45.1, 76.9] (n = 131)	46.7 [39.0, 55.3] (n = 136)	0.020[b]

*This data is based on Clinical Study Report: CA012-0 Addendum dated Final (23 March-2005)
[a] Chi-squared test
[b] Log-rank test

229 patients treated with Abraxane in the randomized, controlled clinical trial were evaluated for safety. Neurotoxictiy to paclitaxel was evaluated through improvement by one grade for patients experiencing grade 3 peripheral neuropathy at any time during therapy. The natural course of peripheral neuropathy to resolution to baseline due to cumulative toxicity of Abraxane after > 6 courses of treatment was not evaluated and remains unknown.

5.2 Pharmacokinetic properties

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of Abraxane at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. The drug exposure (AUC) increased linearly from 2653 to 16736 ng.hr/ml following dosing from 80 to 300 mg/m^2.

Following intravenous administration of Abraxane to patients with metastatic breast cancer at the recommended clinical dose of 260 mg/m^2, paclitaxel plasma concentrations declined in a multiphasic manner. The mean C_{max} of paclitaxel, which occurred at the end of the infusion, was 18.7 µg/ml. The mean total clearance was 15 l/hr/m^2. The terminal half-life was about 27 hours. The mean volume of distribution was 632 l/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a study in patients with advanced solid tumours, the pharmacokinetic characteristics of paclitaxel following Abraxane administered intravenously at 260 mg/m^2 over 30 minutes were compared with those following 175 mg/m^2 of the solvent-based paclitaxel injection administered over 3 hours. The clearance of paclitaxel with Abraxane was larger (43%) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

The protein binding of paclitaxel following Abraxane administration is estimated at about 90%. Based on the published literature, *in vitro* studies of binding to human serum proteins, using paclitaxel at concentrations ranging from 0.03 to 1.2 µM, indicate that about 87% of paclitaxel is bound; the presence of ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Based on the published literature, *in vitro* studies with human liver microsomes and tissue slices show that paclitaxel is metabolised primarily to 6α-hydroxypaclitaxel; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α-3'-*p*-dihydroxypaclitaxel. 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 has not been formally investigated.

In patients with metastatic breast cancer, after a 30 minute infusion of Abraxane at 260 mg/m^2, the mean value for cumulative urinary excretion of unchanged active substance accounted for 4% of the total administered dose with less than 1% as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel, indicating extensive non-renal clearance. Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.
Pharmacokinetics of paclitaxel in patients aged over 65 years seems comparable to that in patients less than 65 years. However, little information in patients over 75 years is available as only 3 patients over 75 years of age where included in the pharmacokinetic analysis.

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, based on the published literature, paclitaxel is a potentially carcinogenic and genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel has been shown to be genotoxic *in vivo* (micronucleus test in mice), but it did not induce mutagenicity

in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay.

Paclitaxel at doses below the human therapeutic dose was associated with low fertility and foetal toxicity in rats. Animal studies with Abraxane showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 24 months

Stability of reconstituted suspension in the vial:

After first reconstitution, the suspension should be filled into an infusion bag immediately. However, chemical and physical in use stability has been demonstrated for 8 hours at 2°C - 8°C in the original carton, and protected from bright light.

Stability of the reconstituted suspension in the infusion bag:

After reconstitution, the reconstituted suspension in the infusion bag should be used immediately. However chemical and physical in use stability has been demonstrated for 8 hours not above 25°C.

6.4 Special precautions for storage

Unopened vials: 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

Vial 50ml (type 1 glass) with a stopper (butyl rubber), with an overseal (aluminium).
Pack size one vial of 100 mg paclitaxel.

6.6 Special precautions for disposal and other handling

Preparation and administration precautions:

Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Abraxane. The use of gloves, goggles and protective clothing is recommended. If the suspension contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. Abraxane should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Abraxane.

Reconstitution and administration of the product:

Abraxane is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of suspension contains 5 mg of paclitaxel.

Using a sterile syringe, 20 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into a vial of Abraxane over a minimum of 1 minute. The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming.

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete resuspension of any powder occurs. The generation of foam must be avoided. If foaming or clumping occurs, the solution must stand for at least 15 minutes until foam subsides.

The reconstituted suspension should be milky and homogenous without visible precipitates. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Some settling of the reconstituted suspension may occur. Complete resuspension should be ensured by mild agitation before use.

Discard the reconstituted suspension if precipitates are observed.

Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient and inject the appropriate amount of reconstituted Abraxane into an empty, sterile, PVC or non-PVC type intravenous bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Abraxane infusions. In-line filters should not be used.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Abraxis BioScience Limited
West Forest Gate
Wellington Road
Wokingham
Berkshire
RG40 2AQ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF LAST REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Catalent UK Packaging Ltd.
Lancaster Way
Wingates Industrial Park
Westhoughton BL5 3XX
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 of the Risk Management Plan (RMP) and presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
Carton and Vial

1. NAME OF THE MEDICINAL PRODUCT

Abraxane 5 mg/ml powder for suspension for infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg paclitaxel.

After reconstitution, each ml of suspension contains 5 mg of paclitaxel.

3. LIST OF EXCIPIENTS

Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate)

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for infusion
One vial of 100 mg paclitaxel

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Single use vial
Intravenous use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only to be prepared and administered by personnel appropriately trained in handling cytotoxics.

Abraxane may have substantially different pharmacological properties compared to other paclitaxel formulations.

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Unopened Vials: Keep the vial in the outer carton in order to protect from light.
After first reconstitution: 8 hours in a refrigerator in the vial when kept in the outer carton in order to protect from light.
In an infusion bag: up to 8 hours not above 25^{o}C

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abraxis BioScience Limited
West Forest Gate
Wellington Road
Wokingham
Berkshire
RG40 2AQ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Abraxane 5 mg/ml powder for suspension for infusion
Paclitaxel

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.
- 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:

1. WHAT ABRAXANE IS AND WHAT IT IS USED FOR

Abraxane is a medicine containing paclitaxel in human albumin (portion of blood). Paclitaxel belongs to a group of medicines called taxanes used to treat cancers.

Abraxane is used for the treatment of breast cancer when other therapies have been tried but have not worked and if you are unsuitable for anthracycline containing treatments.

2. BEFORE YOU USE ABRAXANE

Do not use Abraxane
- if you are allergic (hypersensitive) to paclitaxel or any of the other ingredients of Abraxane
- if you are breast feeding
- if you have a low white blood cell count (baseline neutrophil counts $<1.5 \times 10^9/l$ - your doctor will advise you on this)

Take special care with Abraxane
- if you have poor kidney function
- if you experience numbness, tingling, pricking sensations, sensitivity to touch, or muscle weakness
- if you have severe liver problems
- if you have heart problems

If you experience any of these conditions your doctor may wish to stop treatment or reduce the dose.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, because they could interact with Abraxane.

Using Abraxane with food and drink
Abraxane is unaffected by food and drink.

Pregnancy and breast-feeding
Paclitaxel may cause serious birth defects and should therefore not be used if you are pregnant.

Women of childbearing age should use effective contraception during and up to 1 month after receiving treatment with Abraxane. Male patients are advised to not father a child during and up to six months after treatment and should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Abraxane.

It is not known if paclitaxel passes into breast milk. Because of the possibility of harm to the infant, breast-feeding must be discontinued for the duration of treatment.

Ask your doctor for advice before taking this medicine.

Driving and using machines
Abraxane may cause side effects such as tiredness (very common) and dizziness (common) that may affect your ability to drive and use machinery. If you experience these symptoms, do not drive or operate machinery until they have fully resolved.

If you are given other medicines as part of your treatment, you should ask your doctor for advice on driving and using machines.

Important information about some of the ingredients of Abraxane
This medicinal product contains approximately 425 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE ABRAXANE

Abraxane will be given to you by a doctor or nurse into a vein from an intravenous drip. The dose you receive is based on your body surface area and blood test results. The usual dose is 260 mg/m^2 of body surface area.

How often will you receive Abraxane?
Abraxane is usually given every three weeks.

How long will it take to give you your intravenous drip?
Abraxane is given over a 30 minute period.

If you have any further questions on the use of this product ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Abraxane can cause side-effects, although not everyone gets them.

The very common side-effects (reported in at least 1 out of 10 patients) are:
- Loss of hair
- Abnormal decrease in the number of neutrophils in the blood
- Decrease in the number of white blood cells in the blood
- Deficiency of red blood cells
- Reduction in the number of lymphocytes in the blood
- Effect of peripheral nerves (pain, and numbness)
- Pain in a joint or joints
- Pain in the muscles
- Nausea, diarrhoea
- Vomiting
- Weakness and tiredness

The common side-effects (reported in at least 1 in 100 patients) are:
- Skin rash, itching, dry skin, nail disorder
- Infection, fever, flushing

- Throat or abdominal pain
- Indigestion, abdominal discomfort, or constipation
- Difficulty in breathing
- Loss of appetite, weight loss
- Bone pain, muscle pain
- Dizziness, diminished muscular coordination or difficulty in reading
- Changes in heart rate or rhythm
- Swelling of mucosal and soft tissues, soreness of the mouth or tongue, oral thrush
- Sleep problems

The uncommon side-effects (reported in at least 1 in 1000 patients) are:

- Increased blood pressure, increased weight, increased lactate in the blood, decreased kidney function, increased blood sugar, increased phosphorus in the blood, decreased potassium in the blood
- Nerve disorder, decreased or lack of reflexes, involuntary movements, pain along a nerve, loss of feeling, fainting, dizziness when standing up, painful numbness or tingling, shaking
- Irritated eyes, painful eyes, red eyes, itchy eyes, blurred or double vision, reduced vision, or seeing flashing lights
- Ear pain, ringing in your ears
- Coughing with phlegm, shortness of breath when walking or climbing stairs, stuffy nose, runny nose, or dry nose, decreased breath sounds, water on the lung, loss of voice, difficulty breathing
- Difficulty swallowing, gas, dry mouth, loose stools, heartburn, stomach cramps, painful or sore mouth and gums, rectal bleeding
- Painful urination, frequent urination, blood in the urine, inability to hold your urine
- Fingernail pain; fingernail discomfort, loss of fingernails, hives, skin pain, red skin from sunlight, skin discoloration, red rash, itchy rash, increased sweating, night sweats, white areas on the skin, less hair, overall itching, sores, swollen face
- Chest pain, neck pain, groin pain, muscle cramps, pain or weakness, back pain, pain in the arm or leg
- Decreased phosphorus in the blood, fluid retention, low albumin in the blood, increased thirst, decreased calcium in the blood, decreased sugar in the blood, decreased sodium in the blood
- Thrush, pain and swelling in the nose and throat, skin infections, infection in the lungs, infection due to catheter line, infection, redness or swelling at the site where the needle entered the body
- Bruising
- Pain at site of tumour, death of the tumour
- Decreased blood pressure, decreased blood pressure when standing up, coldness in your hands and feet
- Chest pain or heaviness, difficulty walking, swelling
- Allergic reaction
- Decreased liver function, increased size of liver
- Pain in the breast
- Restlessness

The rare side-effects (reported in at least 1 in 10,000 patients) are:

- Lung infection
- Skin reaction to another agent following radiation
- Blood clot

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

5. HOW TO STORE ABRAXANE

Keep out of the reach and sight of children.

Do not use Abraxane after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

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

After first reconstitution the suspension should be used immediately. If not used immediately, the suspension may be stored in a refrigerator (2°C – 8°C) for up to 8 hours in the vial when kept in the outer carton in order to protect it from light.

The reconstituted suspension in the intravenous drip may be stored for up to 8 hours at a temperature not above 25ºC.

6. FURTHER INFORMATION

What Abraxane contains

- The active substance is paclitaxel. Each vial contains 100 mg of paclitaxel.
- After reconstitution, each ml of suspension contains 5 mg of paclitaxel.
- The other ingredient is human albumin (containing sodium, sodium caprylate and N-acetyl DL tryptophanate).

What Abraxane looks like and contents of the pack

Abraxane is a white to yellow powder for suspension for infusion available in glass vials containing 100 mg paclitaxel.

Marketing Authorisation Holder
Abraxis BioScience Limited
West Forest Gate
Wellington Road
Wokingham
Berkshire
RG40 2AQ
United Kingdom

Manufacturer
Catalent UK Packaging Ltd
Lancaster Way
Wingates Industrial Park
Westhoughton
BL5 3XX
United Kingdom

This leaflet was last approved in {MM/YYYY}

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

Instructions for use, handling and disposal

Preparation and administration precautions

Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Abraxane. Gloves, goggles and protective clothing should be used. If Abraxane suspension contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If Abraxane contacts mucous membranes, the membranes should be flushed thoroughly with water. Abraxane should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Abraxane.

Reconstitution of the product and administration

Abraxane should be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents.

Abraxane is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of suspension contains 5 mg of paclitaxel.

Using a sterile syringe, 20 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should be injected into a vial of Abraxane over a minimum of 1 minute. The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming.

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete resuspension of any powder occurs. The generation of foam should be avoided. If foaming or clumping occurs, the suspension should stand for at least 15 minutes until foam subsides.

The reconstituted suspension should be milky and homogenous without visible precipitates. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Some settling of the reconstituted suspension may occur. Complete resuspension should be ensured by mild agitation of the vial before use.

If precipitates are observed, the reconstituted suspension should be discarded.

The exact total dosing volume of 5 mg/ml suspension required for the patient should be calculated and the appropriate amount of reconstituted Abraxane should be injected into an empty, sterile, polyvinyl chloride (PVC) type IV bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Abraxane infusions. In-line filters should not be used.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Any unused product or waste material should be disposed of in accordance with local requirements.

Stability
Unopened vials of Abraxane are stable until the date indicated on the package when the vial is kept in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of the reconstituted suspension in the vial
After first reconstitution, the suspension should be filled into an infusion bag immediately. However, chemical and physical in use stability has been demonstrated for 8 hours at 2°C - 8°C in the original carton, and protected from bright light.

Stability of the reconstituted suspension in the infusion bag
After reconstitution, the reconstituted suspension in the infusion bag should be used immediately. However chemical and physical in use stability has been demonstrated for 8 hours not above 25°C.