

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paclitaxel medac 6 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml 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 50 ml contains 300 mg paclitaxel.

Excipients:

Macrogolglycerol ricinoleate 527 mg/ml

Ethanol, anhydrous 395 mg/ml

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Paclitaxel medac is a clear, colourless to light yellowish viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian carcinoma: For first-line treatment of carcinoma of the ovary, paclitaxel is indicated in combination with cisplatin in patients with advanced disease or a residual tumour (> 1 cm) following laparotomy.

For second-line treatment of carcinoma of the ovary, paclitaxel is indicated for treatment of metastatic carcinoma of the ovary after failure of standard therapy with platinum-containing preparations.

Breast carcinoma: As adjuvant treatment paclitaxel is indicated in treatment of node-positive breast carcinoma after anthracycline and cyclophosphamide (AC) treatment. Adjuvant treatment with paclitaxel should be considered as an alternative to prolonged AC treatment.

Paclitaxel is indicated as initial treatment of locally advanced or metastatic breast carcinoma either in combination with anthracycline in patients in whom anthracycline treatment is suitable or in combination with trastuzumab, in patients who over-express HER-2 at a level of 3+ as determined by immunohistochemistry methods and to patients to whom anthracycline treatment is not suitable (see sections 4.4 and 5.1).

Paclitaxel is indicated as a single agent for treatment of metastatic breast carcinoma in patients in whom standard anthracycline therapy has failed or in whom anthracycline therapy is not suitable.

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

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

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

4.2 Posology and method of administration

All patients must be premedicated with corticosteroids, antihistamines, and H₂ antagonists prior to paclitaxel therapy, e.g.

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

* 8-20 mg for KS patients

** equivalent antihistamine (e.g. chlorpheniramine)

Paclitaxel should be administered through an in-line filter with a microporous membrane $\leq 0.22 \mu\text{m}$ (see section 6.6).

First-line treatment of ovarian carcinoma:

Although other dosage regimens are being investigated, a combination regimen of paclitaxel and cisplatin is recommended. Depending on the duration of the infusion, two doses of paclitaxel are recommended: paclitaxel 175 mg/m² administered intravenously over three hours, followed by cisplatin at a dose of 75 mg/m² in three week intervals, or paclitaxel 135 mg/m², as a 24-hour infusion, followed by cisplatin 75 mg/m², with a three-week interval between treatment cycles (see section 5.1).

Second-line treatment of ovarian carcinoma:

The recommended dose for paclitaxel is 175 mg/m² administered over a period of three hours, with a three-week interval between treatment cycles.

Adjuvant chemotherapy of breast carcinoma:

The recommended dose for paclitaxel is 175 mg/m² administered over a period of three hours, with a three-week interval during 4 treatment cycles, after AC treatment.

First-line treatment of breast carcinoma:

When paclitaxel is used in combination with doxorubicin (50 mg/m²), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose for paclitaxel is 220 mg/m² administered intravenously over a period of three hours, with a three-week interval between treatment cycles (see sections 4.5 and 5.1). In combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m² administered intravenously over a period of three hours, with a three-week interval between treatment cycles (see section 5.1). In combination with trastuzumab the paclitaxel infusion can begin on the day after the first trastuzumab dose or directly after a follow-up dose of trastuzumab if the preceding trastuzumab dose was well tolerated (see the Summary of Product Characteristics of trastuzumab for detailed information on dosing).

Second-line treatment of breast carcinoma:

The recommended dose for paclitaxel is 175 mg/m² administered over a period of three hours, with a three-week interval between treatment cycles.

Treatment of advanced NSCLC:

The recommended dose for paclitaxel is 175 mg/m² administered over a period of three hours, followed by cisplatin 80 mg/m², with a three-week interval between treatment cycles.

Treatment of AIDS-related KS:

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

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

Administration of paclitaxel should not be repeated until the neutrophil count is $\geq 1.5 \times 10^9/l$ ($\geq 1 \times 10^9/l$ for KS patients) and the platelet count is $\geq 100 \times 10^9/l$ ($\geq 75 \times 10^9/l$ for KS patients). If patients develop severe neutropenia (neutrophils $< 0.5 \times 10^9/l$ for seven days or more) or severe peripheral neuropathy, the dosage in subsequent treatment cycles should be reduced by 20 % (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.

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

4.3 Contraindications

Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipient, particularly macrogolglycerol ricinoleate (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 $< 1.5 \times 10^9/l$ ($< 1 \times 10^9/l$ 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 given under the supervision of a physician with experience in using cancer chemotherapeutic agents. Appropriate equipment for emergency treatment should be available, since severe hypersensitivity reactions may occur.

The patient should be premedicated with corticosteroids, antihistamines and H₂ antagonists before treatment with paclitaxel (see section 4.2).

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

Severe hypersensitivity reactions, characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in < 1 % of the patients treated with paclitaxel after adequate premedication. These reactions are probably histamine-mediated. At the first sign of severe hypersensitivity reactions, the paclitaxel infusion should be discontinued immediately. Symptomatic treatment should be initiated and the patient should not be treated with paclitaxel again.

Myelosuppression (primarily neutropenia) is the dose-limiting toxicity. The blood count should be monitored frequently during the paclitaxel treatment. The patient should not be treated until the neutrophil count is $\geq 1.5 \times 10^9/l$ ($\geq 1 \times 10^9/l$ for KS patients) and the platelets are $\geq 100 \times 10^9/l$ ($\geq 75 \times 10^9/l$ for KS patients). In the KS clinical study, most of patients received Granulocyte-Colony Stimulating Factor (G-CSF).

Severe cardiac conduction disorders have seldom been reported after treatment with paclitaxel as a single agent. If patients develop clear cardiac conduction disorders during treatment with paclitaxel, suitable treatment should be initiated and the cardiac function monitored continuously during subsequent treatment with paclitaxel. Hypotension, hypertension, and bradycardia have been seen during administration of paclitaxel; the patients are normally asymptomatic and in general they do not require any treatment. Frequent monitoring of vital signs is recommended, especially during the first hour of the paclitaxel infusion. Severe cardiovascular events were seen more often in patients with NSCLC than in patients 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 doxorubicin or trastuzumab for initial treatment of metastatic breast carcinoma, special attention to monitoring of the cardiac function should be given. Patients, who are candidates for treatment with paclitaxel in these combinations should undergo baseline cardiac examinations, including medical history, clinical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be monitored during the entire treatment period (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and the treating physician should carefully evaluate the cumulative dose (mg/m²) of anthracycline when making decisions regarding the frequency of examination of the ventricular function. If the examination indicates aggravation of the cardiac function, even if it is asymptomatic, the treating physician should carefully assess the clinical benefits of further treatment in relation to the potential to induce cardiac impairment, including potentially irreversible injury. If further treatment is administered, the cardiac function should be monitored more frequent (e.g every second treatment cycle). For further information see Summary of Products Characteristics for trastuzumab or doxorubicin.

Although **peripheral neuropathy** can often occur, the development of serious symptoms is rare. In severe cases, a dose reduction of 20 % (25 % for KS patients) is recommended for all subsequent treatment cycles with paclitaxel. Severe neurotoxicity occurred more often in patients with NSCLC and ovarian carcinoma having undergone first-line chemotherapy with paclitaxel given as a three-hour infusion in combination with cisplatin, than in patients who received either paclitaxel alone or 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 medac contains ethanol (395 mg/ml), possible CNS and other influences should be considered.

Cautions should be observed to avoid intra-arterial administration of paclitaxel, since severe tissue reactions have been seen after intra-arterial administration in animal local tolerance studies.

Pseudomembranous colitis has been rarely reported. Pseudomembranous colitis has been seen even in patients who were not given concomitant antibiotic treatment. 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 may in combination with radiotherapy of the lung and irrespective of the chronological order contribute to the development of interstitial pneumonitis.

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

This medicinal product contains macrogolglycerol ricinoleate, which may cause severe allergic reactions.

4.5 Interactions with other medicinal products and other forms of interaction

Paclitaxel clearance is not influenced by premedication with cimetidine.

It is recommended to administer paclitaxel *before* cisplatin in first-line paclitaxel treatment of ovarian carcinoma. If paclitaxel is given *before* cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel is given *after* cisplatin, patients showed a more profound myelosuppression and an approximately 20 % decrease in paclitaxel clearance. Patient who are treated with paclitaxel and cisplatin may have increased risk of renal impairment as seen in treatment with cisplatin alone in gynecological carcinoma.

The elimination of doxorubicin and its active metabolites may be reduced when paclitaxel and doxorubicin are administered too close in time and therefore paclitaxel as initial treatment of metastatic breast carcinoma should be administered 24 hours after doxorubicin (see section 5.2).

Metabolism of paclitaxel is partly catalysed by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see section 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel to 6 α -hydroxypaclitaxel is the major metabolic pathway in humans. Based on current knowledge no clinically relevant interactions between paclitaxel and other CYP2C8 substances are to be expected. Concomitant administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; subsequently the two medicinal products can be administered concomitantly without dosage adjustment. Further data concerning potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Caution is therefore required when concurrently administering paclitaxel with medicinal products known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

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

Pregnancy:

Paclitaxel has been shown to be embryotoxic and foetotoxic in rabbits, and to reduce the fertility in rats.

There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm in treatment of pregnant women. Paclitaxel is contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during treatment with paclitaxel, and to inform the treating physician immediately if pregnancy occurs.

Lactation:

It is not known whether paclitaxel is excreted into human breast milk. Paclitaxel is contraindicated in lactating women. Breast-feeding should be interrupted during paclitaxel treatment.

4.7 Effects on ability to drive and use machines

It has not been shown that paclitaxel affect this ability. However, paclitaxel contains alcohol (see sections 4.4 and 6.1). The ability to drive or to use machines may be decreased due to the alcohol content of the medicinal product.

4.8 Undesirable effects

Unless otherwise mentioned, the following description refers to the collected database of 812 patients with solid tumours treated with monotherapy of 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,

Unless otherwise mentioned, the incidence and severity of the reported adverse events was generally similar in patients receiving paclitaxel for treatment of ovarian or breast carcinoma, or NSCLC. None of the observed toxicities were clearly affected by age.

The most frequent adverse reaction was **myelosuppression**. Severe neutropenia ($< 0.5 \times 10^9/l$) was observed in 28 % of the patients, but had no association to episodes of fever. Only 1 % of the patients had severe neutropenia for ≥ 7 days. Thrombocytopenia was observed in 11 % of the patients. 3 % of the patients had a platelet count nadir of $< 50 \times 10^9/l$ at least once during the study. Anaemia was seen in 64 % of the patients, but was only severe (Hb < 5 mmol/l) in 6 % of the patients. The incidence and severity of the anaemia is related to the baseline haemoglobin values.

Neurotoxicity, primarily peripheral neuropathy, appeared to be more frequent and more severe from a 3-hour infusion of 175 mg/m² (85 % neurotoxicity, 15 % severe) than from 24-hour infusion of 135 mg/m² (25 % peripheral neuropathy, 3 % severe) when paclitaxel was combined with cisplatin. There is an apparent increase in the incidence of severe neurotoxicity in patients with NSCLC and ovarian carcinoma given a 3-hour infusion of paclitaxel followed by cisplatin. Peripheral neuropathy may occur during the first treatment cycle and can deteriorate with increasing exposure to paclitaxel. Peripheral neuropathy caused discontinuation of paclitaxel in a few cases. Sensory symptoms improved or abated within a few months after the discontinuation of paclitaxel. Pre-existing neuropathy resulting from prior treatment is not a contraindication for treatment with paclitaxel.

Arthralgia or myalgia were seen in 60 % of the patients and was severe in 13 % of the patients.

Serious hypersensitivity reactions with possibly fatal outcome (defined as hypotension requiring treatment, angioedema, respiratory distress requiring bronchodilator treatment, or generalised urticaria) were seen in 2 patients (< 1 % of the patients). 34 % of the patients (17 % of all treatment cycles) experienced mild hypersensitivity reactions. These mild reactions, mainly flush and rash, did not require any treatment or discontinuation of paclitaxel.

Injection site reactions during intravenous administration may lead to local oedema, pain, erythema, and induration. Extravasations may result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. There are single reports about skin reactions so called "recall", at sites of previous extravasations following administration of paclitaxel at a different site. A specific treatment of extravasation reactions is unknown at this time.

The table below shows undesirable effects independent of their intensity associated with single treatment with paclitaxel given as 3-hour infusion in metastatic disease (812 patients treated in clinical trials) and undesirable effects reported in post-marketing surveillance* of paclitaxel.

The occurrence of undesirable effects is described below and defined according to the following rules: Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare ($< 1/10,000$).

Infections and infestations	<i>Very common:</i> infection (mainly urinary tract infections and infections in the upper respiratory tract) with reported cases of fatal outcome. <i>Uncommon:</i> septic shock <i>Rare*:</i> pneumonia, peritonitis, sepsis
Blood and lymphatic system disorders	<i>Very common:</i> myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, bleeding <i>Rare*:</i> febrile neutropenia <i>Very rare*:</i> acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders	<i>Very common:</i> mild hypersensitivity reactions (mainly flush and rash) <i>Uncommon:</i> significant hypersensitivity reactions requiring treatment (e.g. hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in the limbs, diaphoresis and hypertension) <i>Rare*:</i> anaphylactic reactions <i>Very rare*:</i> anaphylactic shock
Metabolism and nutrition disorders	<i>Very rare*:</i> anorexia
Psychiatric disorders	<i>Very rare*:</i> confusional state
Nervous system disorders	<i>Very common:</i> neurotoxicity (mainly peripheral neuropathy) <i>Rare*:</i> motor neuropathy (with resultant minor distal weakness) <i>Very rare*:</i> autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders	<i>Very rare*:</i> optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended
Ear and labyrinth disorders	<i>Very rare*:</i> ototoxicity, loss of hearing, tinnitus, vertigo
Cardiac disorders	<i>Common:</i> bradycardia <i>Uncommon:</i> cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with extrasystole, AV-block and syncope, myocardial infarction <i>Very rare*:</i> atrial fibrillation, supraventricular tachycardia
Vascular disorders	<i>Very common:</i> hypotension <i>Uncommon:</i> hypertension, thrombosis, thrombophlebitis <i>Very rare*:</i> shock
Respiratory, thoracic and mediastinal disorders	<i>Rare*:</i> dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure <i>Very rare*:</i> cough
Gastrointestinal disorders	<i>Very common:</i> nausea, vomiting, diarrhoea, mucositis <i>Uncommon*:</i> bowel obstruction, bowel perforation, ischemic colitis, pancreatitis <i>Very rare*:</i> mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis
Hepatobiliary disorders	<i>Very rare*:</i> hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders	<i>Very common:</i> alopecia <i>Common:</i> transient, mild nail and skin changes <i>Rare*:</i> pruritus, rash, erythema <i>Very rare*:</i> Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should use sun protection on hands and feet)
Musculoskeletal and	<i>Very common:</i> arthralgia, myalgia

connective tissue disorders	
General disorders and administration site conditions	<i>Common:</i> injection site reactions (including localised oedema, pain, erythema, induration, occasionally extravasation can result in cellulites, skin fibrosis and skin necrosis) <i>Rare*:</i> asthenia, pyrexia, dehydration, oedema, malaise
Investigations	<i>Common:</i> severe elevation of AST (SGOT), severe elevation of alkaline phosphatase <i>Uncommon:</i> severe elevation of bilirubin <i>Rare*:</i> increase in blood creatinine

Patients with breast carcinoma, who received paclitaxel as an adjuvant treatment after AC, experienced neurotoxicity, allergic reactions, arthralgia/myalgia, anemia, infection, fever, nausea/vomiting and diarrhoea more often compared to patients, who received AC alone. The frequency of these adverse reactions was consistent with the use of paclitaxel alone, as reported above.

Combination treatment

The following description refers to two large studies of first-line chemotherapy in ovarian carcinoma (paclitaxel + cisplatin: more than 1050 patients), two phase III studies in first-line treatment of metastatic breast carcinoma, one which investigated the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients), and another which investigated the combination with trastuzumab (planned subgroup analysis paclitaxel + trastuzumab: 188 patients) and two phase III studies in treatment of advanced NSCLC (paclitaxel + cisplatin: more than 360 patients) (see section 5.1).

Neurotoxicity, arthralgia/myalgia and hypersensitivity were reported more often and were more severe in patients given paclitaxel as a 3-hour infusion followed by cisplatin for first-line chemotherapy of ovarian carcinoma than in those treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared less often and to a lesser degree with 3-hour paclitaxel infusion followed by cisplatin compared to cyclophosphamide followed by cisplatin.

In first-line chemotherapy in metastatic breast carcinoma, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever and diarrhoea were more severe and frequently reported when paclitaxel (220 mg/m²) was administered as 3-hour infusion 24 hours after doxorubicin (50 mg/m²) compared to standard FAC treatment (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting seemed to occur more seldom and were less severe with paclitaxel (220 mg/m²) / doxorubicin (50 mg/m²) regimen compared to standard FAC regimen. The use of corticosteroids may have contributed to lower occurrence and less severity of the nausea and vomiting in the paclitaxel/doxorubicin group.

When paclitaxel was administered with trastuzumab as a 3-hour infusion for first-line treatment of patients with metastatic breast carcinoma, the following events were reported more often than with paclitaxel given as monotherapy (regardless of a relationship to paclitaxel or trastuzumab): 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 %), hypertension (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 reactions (7 % vs 1 %). Some of these frequency differences can be attributed to a greater number and duration of treatment cycles with the paclitaxel / trastuzumab combination compared to paclitaxel as monotherapy. Severe adverse events were reported at a similar rate for paclitaxel / trastuzumab and paclitaxel monotherapy.

When doxorubicin was administered in combination with paclitaxel in metastatic breast carcinoma, **abnormal heart contraction** (≥ 20 % reduction of the left ventricular output fraction) were observed in 15 % of the patients compared with 10 % treated with standard FAC regimen. **Congestive heart failure** was observed in < 1 % in both paclitaxel/doxorubicin and standard FAC treatment. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines showed an increase of the number and severity of **cardiac dysfunction** as compared

with paclitaxel monotherapy (NYHA class I/II: 10 % vs 0 %; NYHA class III/IV: 2 % vs 1 %) and is seldom associated with death (see Summary of Product Characteristics for trastuzumab). Aside from these rare cases, all patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients concurrently receiving 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 lymphatic system disorders:

Myelosuppression was the major dose limiting toxicity. Neutropenia is the most important haematological toxicity. During the initial treatment severe neutropenia occurred ($< 0.5 \times 10^9/l$) in 20 % of the patients. Through the entire treatment period severe neutropenia was observed in 39 % of the patients. Neutropenia was seen for > 7 days in 41 % of the patients and for 30-35 days in 8 % of the patients. Within 35 days the neutropenia had disappeared in all patients who were examined. The occurrence of grade 4 neutropenia, which lasted ≥ 7 days was 22 %.

Neutropenic fever related to paclitaxel was reported in 14 % of the patients and in 1.3 % of the treatment cycles. There were 3 fatal septic episodes (2.8 %) during the paclitaxel administration, which were related to the medicinal product.

Thrombocytopenia was observed in 50 % of the patients, and was severe ($< 50 \times 10^9/l$) in 9 % of the cases. Only 14 % experienced fall in the number of platelets $< 75 \times 10^9/l$, at least once during the treatment. Bleeding episodes related to paclitaxel was reported in < 3 % of the patients, but the bleedings were found.

Anaemia (Hb < 11 g/dL) was observed in 61 % of the patients and was severe (Hb < 8 g/dL) in 10 % of the cases. Red cell transfusions were needed in 21 % of the patients.

Hepatobiliary disorders: In the patients (> 50 % used protease inhibitor) with normal baseline liver function, 28 % had enhanced bilirubin, 43 % enhanced alkaline phosphatase and 44 % enhanced AST (SGOT). For each of these parameters the increase was severe in 1 % of the cases.

4.9 Overdose

No antidote is known for paclitaxel overdose. The commonly expected complications of over-dose will be myelosuppression, peripheral neuropathy 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 antimicrotubuler agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic re-organisation 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/m²/cisplatin 75 mg/m²)

trials. In the Intergroup trial (B-MS CA 139-209), over 650 patients with stage II_{b-c}, III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m² over 3 hours) followed by cisplatin (75 mg/m²) or control. The second major trial (GOG-111/B-MS CA 139-022) evaluated a maximum of 6 courses of either paclitaxel (135 mg/m² over 24 hours) followed by cisplatin (75 mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residual disease after staging laparotomy, or with distant metastases. 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 three-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 4 courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18 % in the risk of disease recurrence 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 randomised to receive or not 4 courses of paclitaxel at a higher dose of 225 mg/m² following 4 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 the 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 favoured the paclitaxel arm. In this study patients with hormone receptor positive tumours 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 tumours 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 8 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 paclitaxel and trastuzumab was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of trastuzumab in combination with paclitaxel in patients who did not received 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 over-expressing HER-2 (2+ or 3+ 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/m² followed by cisplatin 80 mg/m² has been evaluated in two phase III trials (367 patients on paclitaxel containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100 mg/m², the other used teniposide 100 mg/m² teniposide followed by cisplatin 80 mg/m² 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 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 mg/m² and 175 mg/m². 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/hour/m²; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m², indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For a 30 % increase in dose from 135 mg/m² to 175 mg/m² the C_{max} and AUC_{0-∞} 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 C_{max} was 1,530 ng/ml (range 761-2,860 ng/mL) and the mean AUC 5,619 ng hr/mL (range 2,609-9,428 ng hr/mL). Clearance was 20.6 l/h/m² (range 11-38 l/h/m²) and the volume of distribution was 291 l/m² (range 121-638 l/m²). The terminal elimination half-time averaged 23.7 hours (range 12-33 hours).

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

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

The metabolic 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 mechanisms for disposition of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome P450 enzymes. Following administration of a radiolabelled paclitaxel, an average of 26 %, 2 % and 6 % of the radioactivity was excreted in the faeces as 6 α -hydroxypaclitaxel, 3'-p-hydroxy-paclitaxel, and 6 α -3'-p-dihydroxy-paclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, -3A4 and both -2C8 and -3A4 respectively. The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who receive a 3-hour infusion of paclitaxel 135 mg/m² were within the range of those defined in non-dialysis patients.

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

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

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel may be carcinogenic and genotoxic due to its 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

Macrogolglycerol ricinoleate
Ethanol, anhydrous
Citric acid, anhydrous

6.2 Incompatibilities

Polyethoxylated castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from polyvinyl chloride (PVC) containers at levels which increases with time and concentration. Consequently the preparation, storage and administration of diluted Paclitaxel medac should be carried out using equipment not containing PVC.

6.3 Shelf-life

Unopened vial: 3 years

After opening:

From a microbiological, chemical and physical point of view the product may be stored for maximum 28 days at 25 °C. Other storage periods and storage conditions are the responsibility of the user.

After dilution:

Diluted solution for infusion has been shown to be chemically and physically stable for up to 72 hours at 25 °C.

Diluted solutions should not be stored in a refrigerator (see section 6.6).

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

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Type I glass vials (with a PTFE coated bromobutyl rubber closure) containing 30 mg, 100 mg, or 300 mg paclitaxel in 5 ml, 16.7 ml or 50 ml solution respectively.

Each vial is packed separately in a box. Multi-pack with 10 boxes is also available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The current national guidelines for handling of chemotherapeutic agents should be followed.

Handling: As with all chemotherapeutic agents, caution should be exercised when handling paclitaxel. The dilution should be done by trained personnel in specially designated areas under aseptic conditions. Adequate protective gloves should be used. Precautions should be taken in order to avoid contact with the skin and mucous membrane. In case of contact with the skin the area must be rinsed with soap and water. After topic exposure tingling and burning sensation and redness have been observed. In the event of contact with mucous membranes, they should be rinsed immediately with water. Dyspnoea, chest pain, burning throat and nausea have been reported after inhalation.

Refrigerated storage of unopened vials can lead to precipitates, which re-dissolve with little or no agitation when the preparation has reached room temperature. The quality of the product is not affected. The vial should be discarded if the solution remains cloudy or if an insoluble precipitate is found.

Following multiple needle entries and product withdrawals, the vial maintain microbial, chemical and physical stability for up to 28 days at 25 °C. Other storage times and conditions are the responsibility of the user.

Use of the Chemo-Dispensing Pin or Spike is not recommended since it can damage the stopper, resulting in loss of sterility.

Preparation of the solution for infusion: Prior to infusion the paclitaxel should be diluted under aseptic conditions. Paclitaxel is diluted with 0.9% NaCl solution or 5% glucose solution or 5% glucose/0.9% NaCl solution or Ringer's solution plus 5% glucose to a concentration of 0.3 – 1.2 mg/ml.

Chemical and physical stability of diluted infusion at 25 °C is 72 hours.

From a microbiological point of view, the product should be used immediately. If the product is not used immediately the storage time and condition are the responsibility of the user.

After dilution the solution may be cloudy. This is attributed to the formulation vehicle and is not removed by filtration. Paclitaxel should be infused through an in-line filter with a microporous

membrane with a pore diameter not larger than 0.22 µm. Testing of an infusion system using an in-line filter revealed no significant losses in potency.

There have been rare reports of precipitates during the infusion of paclitaxel, usually at the end of a 24-hour infusion. Even though the cause of the precipitation is not known it may be due to possible supersaturating of the solution. In order to reduce the risk of precipitation paclitaxel should be used as quickly as possible after dilution and excessive vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. The appearance of the solution should be checked frequently during the infusion, and the infusion stopped if precipitates appear.

In order to minimise the exposure of the patients to DEHP (di-(2-ethylhexyl)phthalate), which may leach from PVC infusion bags, sets, and other medical equipments, diluted paclitaxel solution for infusion should be stored in non-PVC bottles (glass, polypropylene) or plastic containers (polypropylene, polyolefin) and administered through polyethylene-lined infusion sets. Filters (e.g. Ivex-2[®]) with short PVC inlets and outlets have not resulted in significant leaching of DEHP.

Disposal: All items used in the preparation, administration or otherwise coming into contact with paclitaxel must be disposed in accordance with local guidelines for disposal of chemotherapeutic agents.

7. MARKETING AUTHORISATION HOLDER

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Fehlandtstraße 3
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Germany

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