PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

PACLITAXEL 30 VIATRIS (concentrate for dilution for infusion)

PACLITAXEL 100 VIATRIS (concentrate for dilution for infusion)

PACLITAXEL 300 VIATRIS (concentrate for dilution for infusion)

WARNING:

PACLITAXEL VIATRIS (paclitaxel) should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in patients receiving PACLITAXEL VIATRIS. Patients receiving PACLITAXEL VIATRIS should be pre-treated with corticosteroids, promethazine, and H_2 antagonists to prevent these reactions (see section 4.2). Patients who experience severe hypersensitivity reactions to PACLITAXEL VIATRIS should not be rechallenged with the medicine.

PACLITAXEL VIATRIS therapy should not be given to patients with baseline neutrophil counts of less than 1 500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving PACLITAXEL VIATRIS.

The polyoxyethylated castor oil in PACLITAXEL VIATRIS can result in phthalate leaching from polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted PACLITAXEL VIATRIS should be carried out by using non-plasticised PVC-containing equipment.

2 QUALITIVE AND QUANTITIVE COMPOSITION:

Each 5 ml of PACLITAXEL 30 VIATRIS contains 30 mg paclitaxel (6 mg/ml) and 39,5 % *v/v* of dehydrated alcohol. Sugar free

Each 16,7 ml of PACLITAXEL 100 VIATRIS contains 100 mg paclitaxel (6 mg/ml) and 39,5 % *v/v* of dehydrated alcohol. Sugar free

Each 50 ml of PACLITAXEL 300 VIATRIS contains 300 mg paclitaxel (6 mg/ml) and 39,5 % *v/v* of dehydrated alcohol. Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for dilution for infusion.

A clear, yellowish, viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PACLITAXEL VIATRIS is indicated for:

1. The palliative treatment of Stage 3 or 4 advanced local carcinoma of the ovary after surgical resection, in combination with cisplatin.
2. The palliative management of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.
3. The treatment of metastatic carcinoma of the breast after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
4. Palliative treatment of advanced non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

4.2 Posology and method of administration

Indication 1:

Primary treatment of ovarian carcinoma:

A combination regimen consisting of PACLITAXEL VIATRIS 175 mg/m2 administered intravenously over 3 hours, followed by cisplatin 75 mg/m2 given every 3 weeks.

Alternatively a combination regimen consisting of PACLITAXEL VIATRIS 135 mg/m² administered over 24 hours, followed by cisplatin 75 mg/m², every 3 weeks. PACLITAXEL VIATRIS should be administered before cisplatin.

Indications 2 and 3:

Secondary treatment of ovarian and breast cancer: PACLITAXEL VIATRIS at a dose of 175 mg/m² administered intravenously over 3 hours every 3 weeks has been shown to be effective in patients with metastatic carcinoma of the ovary or breast after the failure of first line or subsequent chemotherapy.

Indication 4:

Palliative treatment of advanced non-small cell lung carcinoma: the recommended dose of PACLITAXEL VIATRIS is 175 mg/m² administered over a period of 3 hours; followed by a platinum compound, with a 3 week interval between courses.

PACLITAXEL VIATRIS should not be re-administered until the neutrophil count is at least 1 500/mm³ and the platelet count is at least 100 000/mm³. Patients who experience severe neutropenia (neutrophil count < 500/mm³) or moderate to severe peripheral neuropathy should receive a dose reduction of 20 % for subsequent courses (see section 4.4). The incidence and severity of neurotoxicity and haematologic toxicity increases with dose.

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to PACLITAXEL VIATRIS administration, e.g. dexamethasone 20 mg orally approximately 12 and 6 hours before PACLITAXEL VIATRIS or 20 mg IV approximately 30 to 60 minutes prior to

PACLITAXEL VIATRIS, promethazine 25 mg IV 30 to 60 minutes prior to PACLITAXEL VIATRIS and cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before PACLITAXEL VIATRIS.

PACLITAXEL VIATRIS should be administered through an in-line filter with a microporous membrane not greater than 0,22 microns.

Special populations

Hepatic impairment:

See section 4.4**.** Dosage adjustment is recommended as shown below:

Transaminase levels	**Bilirubin levels (a)**	**Recommended PACLITAXEL VIATRIS dose (b)**
24 hour infusion		
< 2 x ULN and 2-< 10 x ULN and < 10 x ULN and ≥ 10 x ULN or	≤ 1,5 mg/dl ≤ 1,5 mg/dl 1,6 - 7,5 mg/dl > 7,5 mg/dl	135 mg/m^2 100 mg/m^2 50 mg/m^2 Not recommended
3 hour infusion		
< 10 x ULN and < 10 x ULN and < 10 x ULN and ≥ 10 x ULN or	≤ 1,25 x ULN 1,26 – 2,0 x ULN 2,01 – 5,0 x ULN > 5,0 ULN	175 mg/m^2 135 mg/m^2 90 mg/m^2 Not recommended
(a) Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design. (b) Dosage recommendations are for the first course of therapy: further dose reduction in subsequent courses should be based on individual tolerance.		

ULN = upper limit of normal.

Paediatric population:

The safety and efficacy of PACLITAXEL VIATRIS in children has not been established (see section 4.4).

Method of administration

For intravenous use.

For instructions on preparation, dilution, disposal and other handling, see section 6.6.

4.3 Contraindications

PACLITAXEL VIATRIS is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other medicines formulated with polyoxyethylated castor oil or to any of the excipients listed in section 6.1.

PACLITAXEL VIATRIS should not be used in patients with baseline neutrophils < 1 500/mm^3.

Pregnancy and lactation (see section 4.6).

The safety and effectiveness of PACLITAXEL VIATRIS in children have not been established.

4.4 Special warnings and precautions for use

PACLITAXEL VIATRIS should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines. Since severe hypersensitivity reactions may occur, appropriate supportive equipment should be available.

PACLITAXEL VIATRIS should be administered as a diluted infusion.

PACLITAXEL VIATRIS should be given before cisplatin when used in combination.

Patients should be pre-treated with corticosteroids, antihistamines and H_2 antagonists before receiving PACLITAXEL VIATRIS.

Hypersensitivity reactions:

Anaphylaxis and severe hypersensitivity reactions, probably histamine-mediated, characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema and generalised urticaria have occurred in patients receiving PACLITAXEL VIATRIS.

Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g. ciclosporine for injection concentrate and teniposide for injection concentrate) should not be treated with PACLITAXEL VIATRIS. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with PACLITAXEL VIATRIS should be premedicated with corticosteroids (such as dexamethasone), promethazine and H_2 antagonists (such as cimetidine or ranitidine).

Rare fatal reactions have occurred in patients despite pre-treatment. In cases of severe hypersensitivity reactions, PACLITAXEL VIATRIS infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be rechallenged with the medicine.

Minor hypersensitivity reactions such as flushing or rash do not require interruption of therapy.

Bone marrow suppression:

Bone marrow suppression (primary neutropenia) is the principal dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during PACLITAXEL VIATRIS treatment. Patients should not be retreated with subsequent cycles of PACLITAXEL VIATRIS until neutrophils recover to a level >1 500 cells/mm^3 and platelets recover to a level > 100 000 cells/mm^3. In the case of severe neutropenia (< 500 cells/mm^3 for seven days or more) during a course of PACLITAXEL VIATRIS therapy, a 20 % reduction in dose for subsequent courses of therapy is recommended. The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

Cardiovascular:

Severe cardiac conduction abnormalities have been reported. If patients develop significant conduction abnormalities during PACLITAXEL VIATRIS administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent

therapy with PACLITAXEL VIATRIS. Severe cardiovascular events were observed more frequently in patients with non-small cell lung carcinoma than breast or ovarian carcinoma.

Hypotension, hypertension and bradycardia have been observed during administration of PACLITAXEL VIATRIS but generally do not require treatment. In severe cases, PACLITAXEL VIATRIS infusions may need to be interrupted or discontinued at the discretion of the treating medical practitioner.

Frequent vital sign monitoring, particularly during the first hour of PACLITAXEL VIATRIS infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

Cases of myocardial infarction have been reported. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Patients may experience severe cardiovascular events possibly related to PACLITAXEL VIATRIS administration and include: hypertension, venous thrombosis, ventricular tachycardia, and atrioventricular conduction block.

ECG alterations are experienced by some patients. The most frequently reported are non-specific repolarisation abnormalities, sinus tachycardia and premature beats. The relationship between PACLITAXEL VIATRIS administration and ECG alterations is not clear.

Neurologic:

Neurologic symptoms may occur following the first course and the frequency of symptoms may increase with increasing exposure to PACLITAXEL VIATRIS. Sensory symptoms have usually improved or resolved within several months of PACLITAXEL VIATRIS discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for PACLITAXEL VIATRIS therapy. Although the occurrence of peripheral neuropathy is frequent, the development of moderate to severe symptomatology is unusual and requires a dose reduction of 20 % for all subsequent courses of PACLITAXEL VIATRIS.

In non-small cell lung carcinoma patients, the administration of PACLITAXEL VIATRIS in combination with cisplatin resulted in greater incidence of neurotoxicity than usually seen in patients receiving single-agent PACLITAXEL VIATRIS.

Hepatic:

Patients with hepatic impairment may be at increased risk of toxicity particularly grade III-IV myelosuppression. Dose adjustment is recommended (see section 4.2).

There is no evidence that the toxicity of PACLITAXEL VIATRIS is increased when given as a 3-hour infusion in patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis.

When PACLITAXEL VIATRIS is given as a 24-hour infusion to patients with moderate to severe hepatic impairment, increased myelosuppression may be seen as compared to patients with mildly elevated liver function tests given 24-hour infusions. Patients should be monitored closely for the development of profound myelosuppression. Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Analysis restricted to patients with normal baseline liver function, shows instances of elevated bilirubin, elevated alkaline phosphate and elevated AST (SGOT).

Injection site reaction:

A specific treatment for extravasation reactions is unknown. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during administration.

Paediatric use:

The safety and effectiveness of PACLITAXEL VIATRIS in children have not been established (see section 4.3).

There have been reports of central nervous system toxicity (including death) in a clinical trial in paediatric patients in which PACLITAXEL VIATRIS was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the PACLITAXEL VIATRIS vehicle given over a short infusion time. The use

of concomitant antihistamines may intensify these effects. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dose) must be considered in assessing the safety of PACLITAXEL VIATRIS for use in this population.

Pseudomembranous colitis:

Pseudomembranous colitis has been reported, rarely, including cases in patients who have not received concurrent antibiotic treatment. This reaction should be considered in the differential diagnosis of severe or persistent cases of diarrhoea occurring during or shortly after treatment with PACLITAXEL VIATRIS.

A combination of pulmonary radiotherapy and PACLITAXEL VIATRIS treatment (irrespective of the order of the treatments) may promote the development of interstitial pneumonitis.

Fertility:

PACLITAXEL VIATRIS has been shown to be a teratogen, embryotoxic and a mutagen in several experimental systems. Therefore, female and male patients of reproductive age must take contraceptive measures for themselves and/or their sexual partners during and for at least 6 months after therapy (see section 4.6). Male patients are advised to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with PACLITAXEL VIATRIS.

Macular oedema:

There have been reports of reduced visual acuity due to cystoid macular oedema (CME) during treatment with PACLITAXEL VIATRIS. Patients with visual impairment during PACLITAXEL VIATRIS treatment should seek a prompt and complete ophthalmologic examination. Discontinue PACLITAXEL VIATRIS treatment if a CME diagnosis is confirmed.

Excipients:

PACLITAXEL VIATRIS contains dehydrated alcohol, 39,5 % *v/v*. Consideration should be given to possible central nervous system and other effects of alcohol for all patients. Children may be more sensitive than adults to the effects of alcohol.
PACLITAXEL VIATRIS contains polyoxyethylated castor oil which may cause severe allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Cisplatin: The recommended regimen of PACLITAXEL VIATRIS administration for the primary treatment of ovarian carcinoma is for PACLITAXEL VIATRIS to be given before cisplatin. When PACLITAXEL VIATRIS is given before cisplatin, the safety profile of PACLITAXEL VIATRIS is consistent with that reported for single-agent use. When PACLITAXEL VIATRIS was given after cisplatin, patients showed a more profound myelosuppression and an approximately 33 % decrease in paclitaxel clearance.
Patients treated with PACLITAXEL VIATRIS and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

Ketoconazole: Medicines concomitantly administered with PACLITAXEL VIATRIS (e.g. corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely, however, possible interactions of PACLITAXEL VIATRIS with concomitantly administered medicines have not been formally investigated. Based on *in vitro* data, there is the possibility of an inhibition of PACLITAXEL VIATRIS metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with PACLITAXEL VIATRIS when they are receiving ketoconazole as concomitant therapy.

Doxorubicin: Plasma levels of doxorubicin and doxorubicinol may be increased when PACLITAXEL VIATRIS and doxorubicin are used in combination.
Sequence effects characterised by more profound neutropenic and stomatitis episodes, have been observed with combination use of PACLITAXEL VIATRIS and doxorubicin, when PACLITAXEL VIATRIS was administered before doxorubicin and using longer than recommended infusion times.

Active substances metabolised in the liver: The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering PACLITAXEL VIATRIS concomitantly with known substrates or inducers or inhibitors of these isoenzymes, (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of PACLITAXEL VIATRIS may be increased due to higher paclitaxel exposure. Administering PACLITAXEL VIATRIS concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

PVC equipment: Contact of the undiluted concentrate with plasticised polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted PACLITAXEL VIATRIS solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.
PACLITAXEL VIATRIS should be administered through an in-line filter with a microporous membrane not greater than 0,22 microns. Use of filter devices such as IVEX-2 filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant during therapy with PACLITAXEL VIATRIS and to inform the treating medical practitioner immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraception for at least 6 months after treatment with PACLITAXEL VIATRIS.

Pregnancy

PACLITAXEL VIATRIS should not be used during pregnancy.

There is no information on the use of PACLITAXEL VIATRIS in pregnant women. PACLITAXEL VIATRIS may cause foetal harm when administered to pregnant women.

Breastfeeding

It is not known whether PACLITAXEL VIATRIS is excreted in human milk. Breastfeeding should be discontinued for the duration of PACLITAXEL VIATRIS therapy.

Fertility

PACLITAXEL VIATRIS has been shown to be embryotoxic, foetotoxic and to decrease fertility in animal studies.

Male patients should seek advice regarding cryo-conservation of sperm prior to treatment with PACLITAXEL VIATRIS because of the possibility of infertility.

4.7 Effects on ability to drive and use machines

PACLITAXEL VIATRIS contains alcohol which may impair the ability to drive or operate machines. Consideration should be given to possible CNS and other effects of alcohol.

4.8 Undesirable effects

a. Summary of the safety profile

The frequency and severity of adverse events are generally similar between patients receiving PACLITAXEL VIATRIS for the treatment of ovarian, breast or lung carcinoma. None of the observed toxicities were clearly influenced by age.

b. Tabulated list of adverse reactions

System organ class	**Frequency**	**Adverse reaction**
Infections and	Frequent	Infection (mainly urinary tract infections and

infestations		infections in the upper respiratory tract), with reported cases of fatal outcome
	Less frequent	Septic shock, pneumonia, peritonitis, sepsis
Blood and lymphatic system disorders	Frequent	Myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding
	Less frequent	Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome
	Frequency unknown	Disseminated intravascular coagulation (DIC)
Immune system disorders	Frequent	Mild hypersensitivity reactions (mainly flushing and rash)
	Less frequent	Significant hypersensitivity reactions requiring treatment (e.g. hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension), anaphylactic reactions, anaphylactic shock
	Frequency unknown	Bronchospasm
Metabolism and nutrition disorders	Less frequent	Anorexia, dehydration
	Frequency unknown	Tumour lysis syndrome
Psychiatric disorders	Less frequent	Confusional state
Nervous system disorders	Frequent	Neurotoxicity (mainly peripheral neuropathy; can persist beyond 6 months of PACLITAXEL VIATRIS discontinuation)
	Less frequent	Motor neuropathy (with resultant minor distal

		weakness), autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders	Less frequent	Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended
	Frequency unknown	Macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders	Less frequent	Ototoxicity, loss of hearing, tinnitus, vertigo
Cardiac disorders	Frequent	Abnormal ECG, bradycardia
	Less frequent	Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV-block and syncope, myocardial infarction, cardiac failure, atrial fibrillation, supraventricular tachycardia
Vascular disorders	Frequent	Hypotension
	Less frequent	Hypertension, thrombosis, thrombophlebitis, shock
	Frequency unknown	Phlebitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure, cough
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, mucositis
	Less frequent	Bowel obstruction, bowel perforation, ischaemic

		colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis
Hepatobiliary disorders	Less frequent	Hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)
Skin and subcutaneous tissue disorders	Frequent	Alopecia, transient and mild nail and skin changes
	Less frequent	Pruritus, rash, erythema, Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
	Frequency unknown	Palmar-plantar erythrodysesthesia syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, myalgia
	Frequency unknown	Systemic lupus erythematosus, scleroderma
General disorders and administration site conditions	Frequent	Injection site reactions (including localised oedema, pain, erythema, induration, extravasation with phlebitis or cellulitis, skin fibrosis and skin necrosis)
	Less Frequent	Asthenia, pyrexia, oedema, malaise
Investigations	Frequent	Severe elevation of AST (SGOT), severe elevation of alkaline phosphatise
	Less frequent	Severe elevation in bilirubin, increase in blood creatinine

c. Description of selected adverse reactions

Unless otherwise noted, the following discussion refers to published information on the overall safety database of 812 patients with solid tumours treated with single-agent paclitaxel in clinical

studies administered as one of two doses (135 or 175 mg/m^2) and one of the two schedules (3 or 24 hours) in the metastatic setting.

Haematological toxicities: Bone marrow suppression was the major dose-limiting toxicity of PACLITAXEL VIATRIS. Neutropenia, the most important haematological toxicity, was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (< 500 cells/ mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy. Infectious episodes occurred very commonly and were fatal in 1 % of all patients, and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

Twenty percent of the patients experienced a drop in their platelet count below 100 000 cells/ mm^3 at least once while on treatment; 7 % had a platelet count < 50 000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4 % of all courses and by 14 % of all patients but most of the haemorrhagic episodes were localised and the frequency of these events was unrelated to the PACLITAXEL VIATRIS dose and schedule.

Neurologic: In general, the frequency and severity of neurologic manifestations were dose dependent in patients receiving single-agent PACLITAXEL VIATRIS. The frequency of peripheral neuropathy increased with cumulative dose. Paraesthesia commonly occurs in the form of hyperaesthesia. Peripheral neuropathy was the cause of PACLITAXEL VIATRIS discontinuation in 1 % of all patients. Sensory symptoms have usually improved or resolved within several months of PACLITAXEL VIATRIS discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for PACLITAXEL VIATRIS therapy.

Infrequent reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

Hypersensitivity reactions (HSR): All patients in clinical trials received premedication prior to PACLITAXEL VIATRIS therapy. The frequency and severity of HSR were not affected by the dose or schedule of PACLITAXEL VIATRIS administration. The most frequent symptoms observed during these severe reactions were dyspnoea, flushing, chest pain and tachycardia.
A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1 %) patients. Thirty-four percent of patients (17 % of all courses) experienced minor hypersensitivity reactions.
Abdominal pain, pain in the extremities, diaphoresis and hypertension are also noted. Minor hypersensitivity reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of PACLITAXEL VIATRIS therapy.

Injection site reactions: During intravenous administration, injection site reactions were usually mild and consisted of localised oedema, pain, erythema, tenderness and indurations; on occasion, extravasations can result in cellulitis. Skin sloughing and/or peeling has been reported sometimes related to extravasations. Skin discolouration may also occur. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12 % of all patients and 3 % of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3 % of all patients and 1 % of all courses. ECG alterations in the form of re-polarisation abnormalities like sinus tachycardia, sinus bradycardia, and premature beats have been observed in clinical studies. Severe cardiac conduction abnormalities have been reported in < 1 % of patients during PACLITAXEL VIATRIS therapy. If patients develop significant conduction abnormalities during PACLITAXEL VIATRIS administration, appropriate therapy should be administered and

continuous electrocardiographic monitoring should be performed during subsequent therapy with PACLITAXEL VIATRIS.

Gastrointestinal (GI) toxicity: Mild to moderate nausea, vomiting, diarrhoea and mucositis (also reported as pharyngitis or cheilitis) were reported frequently by all patients. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion. Less frequent reports of neutropenic enterocolitis (typhilitis), despite the co-administration of G-CSF, were observed in patients treated with PACLITAXEL VIATRIS alone and in combination with other chemotherapeutic medicines.

PACLITAXEL VIATRIS and cisplatin: Cross-study comparison of neurotoxicity suggests that when PACLITAXEL VIATRIS is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a PACLITAXEL VIATRIS dose of 175 mg/m^2 given by 3-hour infusion (21 %) than at a dose of 135 mg/m^2 given by 24-hour infusion (3 %).

PACLITAXEL VIATRIS and radiotherapy: radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no antidote for PACLITAXEL VIATRIS overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

Overdoses in paediatric patients may be associated with acute ethanol toxicity. In case of overdose, the patient should be closely monitored.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic Agents

Pharmacotherapeutic group: antineoplastic agents (taxanes), ATC code: L01C D01.

Paclitaxel is an anti-microtubule 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.

5.2 Pharmacokinetic properties

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentration. The initial rapid decline represents distribution to the peripheral compartment and elimination; the later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m² given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3,0 to 52,7 hours. Mean values for total body clearance ranged from 11,6 to 24 L/h/m². Mean steady state volume of distribution has ranged from 198 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding.

The pharmacokinetics of paclitaxel is non-linear. There is a disproportionately large increase in C_{max} and AUC with increasing dose, accompanied by an apparent dose-related decrease in total body clearance. These findings are most readily observed in patients in whom high plasma

concentrations of paclitaxel are achieved. Saturable processes in distribution and elimination/metabolism may account for these findings.

There was no evidence of accumulation of paclitaxel with multiple treatment courses.
In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0,1 to 50 µg/ml, indicate that, on average, 89 % of the medicine is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.

The disposition of paclitaxel has not been fully elucidated in humans. After intravenous administration of paclitaxel, mean values of cumulative urinary recovery of unchanged drug ranged from 1,3 to 12,6 % of the dose, indicating extensive non-renal clearance.

Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel is metabolised primarily by cytochrome P450 enzymes. Hydroxylated metabolites have been demonstrated to be the principal metabolites. The formation of 6α-hydroxypaclitaxel,3'-p-hydroxypaclitaxel and 6α,3'-p-dihydroxypaclitaxel is catalysed by CYP2C8, 3A4 and both 2C8 and 3A4 respectively. The effect of the renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

The clearance of paclitaxel was not affected by cimetidine pre-treatment.
Ketoconazole may inhibit the metabolism of paclitaxel.
Plasma levels of doxorubicin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyoxyethylated castor oil (Cremophor EL)

Citric acid

Dehydrated alcohol

6.2 Incompatibilities

Polyoxyethylated castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels which increase with time and concentration.

Consequently, the preparation, storage and administration of diluted PACLITAXEL VIATRIS should be carried out using non-PVC-containing equipment.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:

36 months

After opening before dilution: Once opened, the product may be stored for a maximum of 28 days at 25 ºC.

After dilution: Diluted infusion solutions are chemically and physically stable for 72 hours at 25 ºC. The diluted solutions should not be stored refrigerated. From a microbiological viewpoint the solution should be used immediately.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

To be kept in outer container until required. For single use only. Discard any unused portion in accordance with local requirements.

Do not refrigerate or freeze.

For storage conditions of the diluted medicine, see section 6.3.

6.5 Nature and contents of container

PACLITAXEL 30 VIATRIS: 8 ml multi-dose type 1 clear glass injection vial closed with a bromobutyl rubber closure and a flip-off aluminium seal individually packaged in a carton.

PACLITAXEL 100 VIATRIS: 20 ml multi-dose type 1 clear glass injection vial closed with a bromobutyl rubber closure and a flip-off aluminium seal individually packaged in a carton.
PACLITAXEL 300 VIATRIS: 50 ml multi-dose type 1 clear glass injection vial closed with a bromobutyl rubber closure and a flip-off aluminium seal individually packaged in a carton.

6.6 Special precautions for disposal and other handling

Directions for Use/Handling:

Handling: Caution should be exercised when handling PACLITAXEL VIATRIS. This includes all handling activity in clinical settings, pharmacies, storerooms and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. Dilution should be carried out by trained personnel in a designated area. Adequate protective gloves should be worn. Precautions should be taken to avoid contact with the skin, and mucous membranes. Following topical exposure, tingling, burning and redness have been observed. In the event of contact with the skin, the area should be washed with soap and water. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning eyes, sore throat and nausea have been reported. Given the possibility of extravasations, it is advisable to closely monitor the injection site for possible infiltration during medicines administration.

Preparation for IV Administration:

PACLITAXEL VIATRIS must be diluted prior to infusion. PACLITAXEL VIATRIS must be diluted using aseptic techniques in 0,9 % sodium chloride injection, or 5 % dextrose injection, or 5 % dextrose and 0,9 % sodium chloride injection, or 5 % dextrose in Ringer's injection, to a final concentration of 0,3 to 1,2 mg/ml.
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5 ^{o}C and at 25 ^{o}C for 72 hours. The diluted solutions must not be stored refrigerated. From a microbiological point of view, the product should be used immediately.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. PACLITAXEL VIATRIS should be administered through an in-line filter with a microporous membrane ≤ 0,22 µm. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.

There have been rare reports of precipitation during PACLITAXEL VIATRIS infusions, usually towards the end of a 24-hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, PACLITAXEL VIATRIS should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.
In order to minimise patient exposure to the plasticiser DEHP [di-(2-ethylexyl) phthalate], which may be leached from plasticised PVC infusion bags or sets, diluted PACLITAXEL VIATRIS solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Use of filter devices which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Disposal: All items used for reconstitution, administration or otherwise coming into contact with PACLITAXEL VIATRIS should undergo disposal according to local guidelines for the handling of cytotoxic compounds.
The product must be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando, Johannesburg,

1609

8 REGISTRATION NUMBER(S)

PACLITAXEL 30 VIATRIS: 42/26/0657

PACLITAXEL 100 VIATRIS: 42/26/0658

PACLITAXEL 300 VIATRIS: 42/26/0659

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 July 2011

10 DATE OF REVISION OF TEXT

27 April 2024