1.3.1.1 PROFESSIONAL INFORMATION FOR HUMAN USE

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Paclitaxel 30 mg/5 ml Fresenius, Concentrate for solution for infusion

Paclitaxel 100 mg/16,7 ml Fresenius, Concentrate for solution for infusion

Paclitaxel 300 mg/50 ml Fresenius, Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 6 mg paclitaxel.

Excipient with known effect: Macrogolglycerol ricinoleate (530 mg/ml) and ethanol, anhydrous (393 mg/ml)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, slightly yellowish solution practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paclitaxel Fresenius is indicated for:

- The palliative treatment of Stage 3 or 4 advanced local carcinoma of the ovary after surgical resection, in combination with cisplatin.
- The palliative management of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.

- 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.
- 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

Posology

All patients must be pre-medicated with corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel Fresenius administration, e.g. dexamethasone 20 mg orally approximately 12 and 6 hours before Paclitaxel Fresenius or 20 mg IV dexamethasone approximately 30 to 60 minutes before Paclitaxel Fresenius, promethazine 25 mg IV 30 to 60 minutes prior to Paclitaxel Fresenius and IV cimetidine 300 mg or ranitidine 50 mg 30 to 60 minutes before Paclitaxel Fresenius.

Paclitaxel Fresenius should be administered through an in-line filter with a microporous membrane not greater than 0,22 µm.

Paclitaxel Fresenius should be administered under the supervision of a qualified medical practitioner with experience with chemotherapeutic treatment.

Palliative treatment of Stage 3 or 4 advanced local carcinoma of the ovary after surgical resection, in combination with cisplatin:

A combination regimen consisting of Paclitaxel Fresenius 135 mg/m^2 administered over 24 hours, followed by cisplatin 75 mg/m^2, every 3 weeks. Paclitaxel Fresenius should be administered before cisplatin.

Alternatively, a combination consisting of Paclitaxel Fresenius 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin 75 mg/m^2, given every 3 weeks.

Palliative management of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy and treatment of metastatic carcinoma of the breast after failure of first combination chemotherapy or relapse within 6 months of adjuvant therapy:

Paclitaxel Fresenius at a dose of 175 mg/m^2 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.

Palliative treatment of advanced non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy:

The recommended dose of Paclitaxel Fresenius is 175 mg/m^2 administered over a period of 3 hours; followed by a platinum compound, with a 3-week interval between courses.

All indications:

Paclitaxel Fresenius should not be re-administered until the neutrophil count is at least 1 500/mm^3 and the platelet count is at least 100 000/mm^3. Patients who experience severe neutropenia (neutrophil count < 500/mm^3) 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.

Injection site reaction

A specific treatment for extravasation reactions is unknown at this time.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during Paclitaxel Fresenius administration.

Paediatric use

The safety and effectiveness of Paclitaxel Fresenius in children have not been established. There have been reports of central nervous system toxicity (associated with death) in a clinical trial in paediatric patients in which Paclitaxel Fresenius was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2.

Hepatic impairment:

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

Degree of hepatic impairment		
Transaminase levels	**Bilirubin Levels (a)**	**Recommended Paclitaxel Fresenius dose (b)**
24 HOUR INFUSION		
<2xULN and	25,65 µmol/ℓ	135 mg/m^2
2-<10xULN and	25,65 µmol/ℓ	100 mg/m^2
<10xULN and	27,36 – 128,25 µmol/ℓ	50 mg/m^2
≥10xULN or	128,25 µmol/ℓ	Not recommended
3 HOUR INFUSION		
<10xULN and	≤1,25xULN	175 mg/m^2
<10xULN and	1,26-2,0xULN	135 mg/m^2
<10xULN and	2,01-5,0xULN	90 mg/m^2
≥10xULN or	>5,0xULN	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.

Method of administration

For instructions on dilution of the Paclitaxel Fresenius before administration, see section 6.6.

4.3 Contraindications

- Paclitaxel Fresenius is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other medicines formulated with poly-oxy-ethylated castor oil or any other ingredients of Paclitaxel Fresenius.
- Paclitaxel Fresenius should not be used in patients with baseline neutrophils <1 500/mm^3.
- Pregnancy and lactation (see section 4.6).
- The safety and efficacy of Paclitaxel Fresenius in children have not been established.

4.4 Special warnings and precautions for use

WARNINGS

Paclitaxel Fresenius (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 Fresenius. Patients receiving Paclitaxel Fresenius 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 Fresenius should not be re-challenged with Paclitaxel Fresenius.

Paclitaxel Fresenius 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 Fresenius.

Paclitaxel Fresenius 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 Fresenius should be administered as a diluted infusion.

Paclitaxel Fresenius should be given before cisplatin if given in combination.

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 Fresenius. Fatal reactions have occurred in patients despite pre-treatment. In cases of severe hypersensitivity reactions, Paclitaxel Fresenius infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be re-challenged with the Paclitaxel Fresenius.

Minor hypersensitivity reactions such as flushing, 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 Fresenius treatment. Patients should not be retreated until neutrophils recover to a level > 1 500/mm^3 and platelets recover to a level > 100 000/mm^3. In cases of severe neutropenia (< 500 cells/mm^3) during a course of Paclitaxel Fresenius, a 20 % reduction in dose for subsequent courses of therapy is recommended. The incidence of neurotoxicity and severity of neutropenia increase with increased doses within a regimen.

Cardiovascular events

Hypotension, hypertension and bradycardia have been observed during administration of Paclitaxel Fresenius. In severe cases Paclitaxel Fresenius 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 Fresenius infusion, is recommended.

Severe cardiac conduction abnormalities have been reported. If patients develop significant conduction abnormalities during Paclitaxel Fresenius administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Paclitaxel Fresenius. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

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

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

Fertility

Paclitaxel Fresenius may have an antifertility effect, which could be irreversible. Male patients are therefore advised not to father a child during, and up to 6 months after, treatment and to seek advice on conservation of sperm prior to treatment.

Neurotoxicity

Cross-study comparison of neurotoxicity suggests that when Paclitaxel Fresenius is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a Paclitaxel Fresenius 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 %).

The occurrence of peripheral neuropathy is frequent, and the development of moderate to severe symptomatology requires a dose reduction of 20 % for all subsequent courses of Paclitaxel Fresenius.

Hepatic impairment

Patients with hepatic impairment may be at increased risk of toxicity particularly grade III-IV myelosuppression. Dose adjustment is recommended (see section 4.2). Patients should be monitored closely for the development of profound myelosuppression.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Elevations in alkaline phosphatase and AST (SGOT) have been reported.

Information on the excipients

Paclitaxel Fresenius contains 49,7 % *v/v* anhydrous ethanol (393 mg/mℓ). 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 Fresenius also contains poly-oxy-ethylated castor oil, which may cause serious allergic reaction in hypersensitive patients (see section 4.3 - “Hypersensitivity reactions”).

4.5 Interactions with other medicines and other forms of interaction

The recommended regimen of Paclitaxel Fresenius administration for the primary treatment of ovarian carcinoma is for Paclitaxel Fresenius to be given before cisplatin. When Paclitaxel Fresenius is given before cisplatin; the safety profile of Paclitaxel Fresenius is consistent with that reported for single product use. When Paclitaxel Fresenius given after cisplatin, patients showed a more profound myelosuppression and an approximately 33 % decrease in paclitaxel clearance.

Medicines concomitantly administered with Paclitaxel Fresenius (e.g. corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely; however, possible interactions of Paclitaxel Fresenius with concomitantly administered medicines have not been formally investigated.

Based on *in vitro* data, there is the possibility of an inhibition of Paclitaxel Fresenius metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with Paclitaxel Fresenius when they are receiving ketoconazole as concomitant therapy.

Plasma levels of doxorubicin and doxorubicinol may be increased when Paclitaxel Fresenius and doxorubicin are used in combination. Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use when Paclitaxel Fresenius is administered before doxorubicin and using longer than recommended infusion times. Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, Paclitaxel Fresenius for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see 5.2).

The metabolism of Paclitaxel Fresenius is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering Paclitaxel Fresenius concomitantly with known substrates, 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 Fresenius may be increased due to higher paclitaxel exposure. Administering Paclitaxel Fresenius concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

Contact of the undiluted concentrate with plasticised polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended.

4.6 Fertility, pregnancy and lactation

Paclitaxel Fresenius is contraindicated in pregnancy and lactation.

Pregnancy

Paclitaxel Fresenius has been shown to be embryotoxic, fetotoxic and to decrease fertility in animal studies. Paclitaxel Fresenius may cause foetal harm when administered to pregnant women.

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Paclitaxel Fresenius, and to inform the treating medical practitioner immediately should this occur.

Breastfeeding

It is not known whether Paclitaxel Fresenius is excreted in human milk. Women should not breastfeed their babies when treated with Paclitaxel Fresenius.

Fertility

Paclitaxel Fresenius may have an antifertility effect, which could be irreversible. Male patients are therefore advised not to father a child during, and up to 6 months after, treatment and to seek advice on conservation of sperm prior to treatment.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery may be impaired due to the alcohol content of Paclitaxel Fresenius and some of its side effects (dizziness, vertigo and confusion - see section 4.8). Patients should not be allowed to go home unaccompanied if these effects are observed.

4.8 Undesirable effects

Summary of the safety profile

The frequency and severity of adverse events are generally similar between patients receiving Paclitaxel Fresenius for the treatment of ovarian, breast or lung carcinoma.

Unless otherwise noted, the following discussion refers to published information on the overall safety database of 812 patients with solid tumours treated with paclitaxel (monotherapy) 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.

Hypersensitivity reactions (HSR): All patients in clinical trials received premedication prior to paclitaxel therapy. The frequency and severity of HSR were not affected by the dose or schedule of paclitaxel 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.

Haematologic toxicities: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important haematologic 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 dose and schedule.

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

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

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 therapy.

Injection site reactions: During intravenous administration, injection site reactions were usually mild and consisted of localised oedema, pain, erythema, tenderness, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. 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 therapy. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with paclitaxel.

Gastrointestinal (GI) toxicity: Mild to moderate nausea/vomiting, diarrhoea and mucositis (also reported as pharyngitis or cheilitis) were reported very commonly by all patients. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

Rare reports of neutropenic enterocolitis (typhlitis), despite the co-administration of G-CSF, were observed in patients treated with paclitaxel as monotherapy and in combination with other chemotherapeutic medicines.

Tabulated list of adverse reactions:

System organ class	Frequency/ Adverse events
Infections and infestations:	*Frequent:* Infection *Less frequent:* Septic shock
Blood and lymphatic disorders:	*Frequent:* Anaemia, thrombocytopenia, leukopenia or neutropenia with or without infection, myelosuppression, fever, bleeding. *Less frequent:* Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	*Frequent*: Hypersensitivity reactions (mainly flushing and rash) *Less frequent:* Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioedema, respiratory distress, generalised urticaria, oedema, back pain, chills), anaphylactic reactions with fatal outcome, anaphylactic shock
Metabolism and nutrition disorders:	*Less frequent*: Anorexia
Psychiatric disorders:	*Less frequent:* Confusional state
Nervous system disorders:	*Frequent*: Peripheral neuropathy including paraesthesia occurs and is dose dependent. *Less frequent:* Seizures, optic nerve disturbances and neuroencephalopathy, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, dizziness, headache, ataxia

Eye disorders:	*Less frequent:* Reversible visual disturbance (scintillating scotomata), particularly in patients who have received higher doses than recommended, photopsia, visual floaters
Ear and labyrinth disorders:	*Less frequent:* Hearing loss, tinnitus, vertigo, ototoxicity
Cardiac disorders:	*Frequent*: Abnormal ECG, bradycardia *Less frequent*: Congestive heart failure and abnormal electrocardiogram, atrial fibrillation, supraventricular tachycardia, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction
Vascular disorders:	*Frequent:* Hypotension *Less frequent:* Hypertension, thrombosis, thrombophlebitis, shock
Respiratory, thoracic and mediastinal disorders:	*Less frequent:* Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough
Gastro-intestinal disorders:	*Frequent*: Diarrhoea, nausea, vomiting and mucositis. *Less frequent*: Bowel obstructions/perforations and ischaemic colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, esophagitis, constipation, ascites
Hepato-biliary disorders:	*Less frequent:* Elevated serum hepatic enzymes, hepatic necrosis and hepatic encephalopathy

Skin and subcutaneous tissue disorders:	*Frequently*: Alopecia. *Less frequent:* Transient and mild nail and skin changes and abnormalities (noted as pigmentation or discolouration), pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis, radiation recall, Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
Musculoskeletal, connective tissue and bone disorders:	*Frequent:* Myalgia or arthralgia, usually consisting of pain in the large joints of the arms and legs
General disorders and administration site conditions:	*Less frequent:* Extravasation, with phlebitis or cellulitis. Extravasation during intravenous administration may lead to oedema, pain, erythema and induration and ulceration. Extravasation can result in cellulitis. Recurrence of skin reactions at a site of previous extravasation following administration of Paclitaxel Fresenius at a different site i.e. "recall reaction" has been reported
Investigations:	*Frequent*: Severe elevation in AST (SGOT), severe elevation in alkaline phosphatase. *Less frequent:* Severe elevation in bilirubin, increase in blood creatinine

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. Healthcare 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 Fresenius overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Paclitaxel is an antimicrotubule substance 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

<u>Absorption</u>

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

<u>Distribution</u>

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/m^2 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/m^2. Mean steady state volume of distribution has ranged from 198 to 688 l/m^2, indicating extensive extravascular distribution and/or tissue binding.

The pharmacokinetics of paclitaxel are 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 course. *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 paclitaxel 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.

Biotransformation

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 is 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.

Elimination

After intravenous administration of paclitaxel, mean values of cumulative urinary recovery of unchanged paclitaxel ranged from 1,3 to 12,6 % of the dose, indicating extensive non-renal clearance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

49,7 % *v/v* Ethanol anhydrous, macrogolglycerol ricinoleate (poly-oxy-ethylated castor oil), citric acid anhydrous, nitrogen

6.2 Incompatibilities

The poly-oxy-ethylated castor oil in Paclitaxel Fresenius 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 Fresenius should be carried out by using non-plasticised PVC-containing equipment.

6.3 Shelf-life

24 months if stored at or below 25 degrees Celsius.

In-use shelf-life of 28 days for the undiluted but opened product stored at 2-8 degrees Celsius.

6.4 Special precautions for storage

Store at or below 25 °C.

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

After opening before dilution, the product may be stored for 28 days at 2-8 °C.

After dilution in 5 % glucose solution, 0,9 % sodium chloride solution, 5 % glucose solution in Ringer solution, and 5 % glucose solution / 0,9 % sodium chloride solution the product may be stored for 24 hours at 25 °C protected from light. Discard any unused portion.

6.5 Nature and contents of the container

Paclitaxel 30 mg/5 ml Fresenius with concentration 6 mg/ml, is packed in a 5 ml transparent glass vial with a green flip-off cap, with a fill volume of 5 ml. Pack sizes are 1 or 5 vials per outer cardboard carton.

Paclitaxel 100 mg/16,7 ml Fresenius with concentration 6 mg/ml, is packed in a 50 ml transparent glass vial with a blue flip-off cap, with a fill volume of 16,7 ml. Pack sizes are 1 or 5 vials per outer cardboard carton.

Paclitaxel 300 mg/50 ml Fresenius with concentration 6 mg/ml, is packed in a 50 ml transparent glass vial with a purple flip-off cap, with a fill volume of 50 ml. Pack sizes are 1 or 5 vials per outer cardboard carton.

6.6 Special precautions for disposal and other handling

Handling:

Caution should be exercised when handling Paclitaxel Fresenius. 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 extravasation, it is advisable to closely monitor the injection site for possible infiltration during Paclitaxel Fresenius administration.

Preparation for IV administration:

Paclitaxel Fresenius must be diluted prior to infusion.

Paclitaxel Fresenius should be diluted 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. The prepared solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25 °C) and room lighting conditions: infusions should be completed within this timeframe.

There have been reports of precipitation with longer than the recommended 3-hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use. Devices with spikes should not be used with vials of Paclitaxel Fresenius since they can cause the stopper to collapse resulting in loss of sterile integrity of the Paclitaxel Fresenius solution.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. Paclitaxel Fresenius should be administered through an in-liner filter with a microporous membrane not greater than 0,22 µm. No significant losses in potency have been noted following delivery of the solution through IV tubing containing an in-line filter. After dilution the solution is for single use only.

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 Fresenius 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 Fresenius should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Park,

162 Tonetti Street,

Halfway House, 1685,

South Africa

8. REGISTRATION NUMBERS

Paclitaxel 30 mg/5 ml Fresenius, 43/26/0237

Paclitaxel 100 mg/16,7 ml Fresenius, 43/26/0244

Paclitaxel 300 mg/50 ml Fresenius, 43/26/0239

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2013

10. DATE OF REVISION OF THE TEXT

Date of revision: 19 May 2022