Approved Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

PCH PACLITAXEL 30 (concentrate for infusion)

PCH PACLITAXEL 100 (concentrate for infusion)

PCH PACLITAXEL 300 (concentrate for infusion)

Sugar free.

WARNING:

PCH PACLITAXEL should only be administered by a medical practitioner skilled in the use of cancer chemotherapeutic medicines. In the case of complications, sufficient diagnostic and treatment facilities should be available to treat such complications.

Patients receiving **PCH PACLITAXEL** can suffer serious hypersensitivity reactions. These include dyspnoea, flushing, chest pain, tachycardia and hypotension requiring treatment, angioedema and generalised urticaria. Patients receiving **PCH PACLITAXEL** should be pre-treated with corticosteroids, promethazine, and H_2-antagonists to prevent these hypersensitivity reactions (see **section 4.2**). Treatment should not be repeated if patients have experienced severe hypersensitivity reactions to **PCH PACLITAXEL** therapy.

If the baseline neutrophil count of a patient decreases to below 1,5 x 10^9/l, therapy should not be initiated. Regular peripheral blood cell counts must be performed on patients receiving **PCH PACLITAXEL** in order to detect the occurrence of bone marrow suppression and primarily neutropenia. The bone marrow suppression could be serious and result in infection.

PCH PACLITAXEL contains polyoxyethylated castor oil that can, over time and in increased concentrations cause the leaching of phthalate from the polyvinyl chloride (PVC) containers.

Therefore, only equipment without PVC should be used when preparing, storing or administrating diluted **PCH PACLITAXEL**.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 1 ml contains paclitaxel 6 mg.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

PCH PACLITAXEL:

A clear, yellowish, slightly viscous solution, essentially free of particles.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

PCH PACLITAXEL is indicated for the following conditions:

1. The palliative treatment of stage 3 and 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. The palliative treatment of advanced non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.
5. First line therapy of advanced or metastatic breast cancer in combination with trastuzumab in patients who over-express HER-2 at a 2+ or 3+ level as determined by immunohistochemistry.

4.2. Posology and method of administration:

Posology:

Indication 1: Primary treatment of ovarian carcinoma:

A combination regimen consisting of **PCH PACLITAXEL** 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin, given every 3 weeks.

Alternatively, a combination regimen consisting of **PCH PACLITAXEL** 135 mg/m^2 administered over 24 hours, followed by cisplatin, every 3 weeks. **PCH PACLITAXEL** should be administered before cisplatin.

Indication 2 and 3: Secondary treatment of ovarian carcinoma:

PCH PACLITAXEL 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 failure of first line or subsequent chemotherapy.

Indication 4: Palliative treatment of advanced non-small-cell lung carcinoma:

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

Indication 5: Combination, first-line therapy of advanced or metastatic breast cancer:

In combination with trastuzumab, the recommended dose of **PCH PACLITAXEL** is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses. **PCH PACLITAXEL** infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent dose of trastuzumab if the preceding dose of trastuzumab was well tolerated.

PCH PACLITAXEL should not be re-administered until the neutrophil count reaches a level of at least 1,5 x 10^9/l and platelets count a level of at least 100 x 10^9/l. The dose should be reduced by

20 % for subsequent courses in patients that have previously suffered from severe neutropenia (neutrophil count < 0,5 x 10^9/l) or moderate to severe peripheral neuropathy (see **sections 4.8** and **4.4**).

The incidence and severity of neurotoxicity and haematological toxicity increases with dose.

All patients should be pre-medicated prior to **PCH PACLITAXEL** administration in order to prevent severe hypersensitivity reactions. Such pre-medication may consist of corticosteroids (such as dexamethasone) 20 mg orally administered approximately 12 and 6 hours before **PCH PACLITAXEL** administration or 20 mg IV dexamethasone approximately 30 to 60 minutes before **PCH PACLITAXEL**, antihistamines (such as promethazine) 25 mg intravenous administration 30 to 60 minutes before **PCH PACLITAXEL**, and H_2-antagonists (such as cimetidine 300 mg or ranitidine 50 mg) intravenous administration 30 to 60 minutes before **PCH PACLITAXEL**.

Hepatic impairment**:** See **section 4.4.**

Dosage adjustment is recommended as shown below:

Degree of hepatic impairment		
Transaminase levels	**Bilirubin Levels [(a)]**	**Recommended PCH PACLITAXEL dose [(b)]**
24 HOUR INFUSION		
< 2 x ULN and	≤ 0,026 mmol/l	135 mg/m^2
2- < 10 x ULN and	≤ 0,026 mmol/l	100 mg/m^2
< 10 x ULN and	0,027 – 0,128 mmol/l	50 mg/m^2
≥ 10 x ULN or	> 0,128 mmol/l	Not recommended
3 HOUR INFUSION		
< 10 x ULN and	≤ 1,25 x ULN	175 mg/m^2

< 10 x ULN and	1,26 - 2,0 x ULN	135 mg/m^2
< 10 x ULN and	2,01 - 5,0 x ULN	90 mg/m^2
≥ 10 x ULN or	> 5,0 x ULN	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.

4.3. Contraindications:

PCH PACLITAXEL should not be administered to patients with a known history of severe hypersensitivity reactions to **PCH PACLITAXEL** or any of the excipients, especially for polyoxyethylated castor oil.

PCH PACLITAXEL is contraindicated in patients who, at the start of the therapy, have a neutrophilic granulocytes count of < 1,5 x 10^9/l.

4.4. Special warnings and precautions for use:

Patients should be administered with **PCH PACLITAXEL** only by a medical practitioner skilled in the use of cancer chemotherapeutic medicines. Adequate supporting equipment should be available, as serious hypersensitivity reactions may occur.

PCH PACLITAXEL should be diluted before administration.

If **PCH PACLITAXEL** is administered concomitantly with cisplatin, **PCH PACLITAXEL** should be administered before cisplatin.

The safety and efficacy of concomitant ketoconazole use as a **PCH PACLITAXEL** sparing medicine has not been demonstrated and it is not recommended (see **section 4.5**).

Hypersensitivity effects:

Since **PCH PACLITAXEL** injection concentrates contain polyoxyethylated castor oil, patients sensitive to this ingredient should not be treated with **PCH PACLITAXEL**. Patients should be pre-treated before each treatment cycle with corticosteroids, antihistamines and H_2-antagonists to avoid severe hypersensitivity reactions. **Even after adequate pre-medication, patients can suffer severe hypersensitivity reactions during the first or second course of treatment, such as dyspnoea, hypotension and tachycardia that requires treatment, angioedema and generalised urticaria.** Immediate symptomatic therapy and immediate discontinuation of **PCH PACLITAXEL** are required to treat severe reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema or generalised urticaria. Further treatment with **PCH PACLITAXEL** should be avoided in patients that have suffered from severe hypersensitivity reactions. These reactions are likely to be related to histamine release.

Haematological effects:

Generally patients do not need a platelet transfusion, although bleeding episodes do occur in some patients. The baseline haemoglobin indicates the incidence and severity of anaemia. Some patients do need red cell transfusions.

Do not administer **PCH PACLITAXEL** to patients with baseline neutrophil counts of less than 1,5 x 10^9/l. Peripheral blood cell counts should be frequently performed on all patients receiving **PCH PACLITAXEL**, to determine the possibility of myelotoxicity. New cycles of **PCH PACLITAXEL** should not be started in patients until the neutrophil levels have increased to > 1,5 x 10^9/l and platelets to > 100 x 10^9/l. The dose should be reduced by 20 % for subsequent courses in patients that have previously suffered from serious neutropenia (neutrophil count < 0,5 x 10^9/l for seven

days or more). Neutropenia occurs less often when **PCH PACLITAXEL** is administered as a 3-hour infusion rather than a 24-hour infusion. Neutropenia can usually be reversed quickly, although serious neutropenia has been noted in some patients, especially those who have previously received radiotherapy. Neither the duration of treatment, nor the cumulative exposure seems to influence neutropenia.

The appearance of bone marrow suppression (primary neutropenia) should signal toxicity and a decrease in dose. Blood counts should frequently be monitored during **PCH PACLITAXEL** treatment.

Cardiovascular effects:

Usually no treatment is required for the hypotension and bradycardia that have been noted after administration of **PCH PACLITAXEL**.

In some patients severe cardiac conduction abnormalities were experienced. If patients develop serious conduction defects during **PCH PACLITAXEL** therapy, the appropriate treatment should be established with continuous cardiac monitoring during the follow-up treatment with **PCH PACLITAXEL**. For all other patients a frequent check-up of the vital functions, especially during the first hour of the **PCH PACLITAXEL** infusion, is recommended.

Patients with non-small-cell lung carcinoma presented more frequently with severe cardiovascular events than in patients with breast or ovarian carcinoma.

Nervous system effects:

During the first course of **PCH PACLITAXEL**, neurological symptoms may occur and the occurrence could increase with continued use of **PCH PACLITAXEL**.

A few months after the use of **PCH PACLITAXEL** has been discontinued, sensory symptoms will improve or disappear. **PCH PACLITAXEL** is not contraindicated in patients with pre-existing neuropathies. A dose reduction of 20 % for all future courses is required when peripheral

neuropathy is noted, although the symptoms are usually not severe. When **PCH PACLITAXEL** is administered in combination with cisplatin in patients with non-small-cell lung carcinoma, a greater incidence of neurotoxicity was observed than when receiving **PCH PACLITAXEL** alone.

Hepatic effects:

Patients with moderate to severe hepatic impairment receiving **PCH PACLITAXEL** as a 24-hour infusion showed more myelosuppression than patients with mildly elevated liver function tests given 24-hour infusions.

When analysing patients with a normal baseline liver function, some showed elevated bilirubin, alkaline phosphate and aspartate transaminase.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported. Elevations in alkaline phosphatase and AST (SGOT) have been reported.

Pseudomembranous colitis:

Pseudomembranous colitis has been reported rarely including cases in patients who have not been treated concomitantly with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.

Paclitaxel in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of interstitial pneumonitis.

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 medicine administration.

Paediatric Use:

The safety and effectiveness of **PCH PACLITAXEL** in children have not been established. There have been reports of central nervous system toxicity (including death) in a clinical trial report. The toxicity is most likely attributable to the high dose of the ethanol component of the **PCH PACLITAXEL** vehicle given over a short infusion time. The use of concomitant anti-histamines may intensify this effect. 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 **PCH PACLITAXEL** for use in this population.

PCH PACLITAXEL contains dehydrated alcohol, 396 mg/ml. Consideration should be given to possible central nervous system and other effects of alcohol for all patients.

4.5. Interaction with other medicines and other forms of interaction:

Although concomitantly administered medicines with **PCH PACLITAXEL** and possible interactions have not been investigated officially, interactions were not reported when **PCH PACLITAXEL** was used with corticosteroids, antihistamines, and H_2-antagonists.

Ketoconazole may inhibit the metabolism of **PCH PACLITAXEL**, as reported in *in vitro* studies. Therefore, careful concomitant use of ketoconazole and **PCH PACLITAXEL** is advised. The safety and efficacy of concomitant ketoconazole use as a **PCH PACLITAXEL** sparing medicine has not been demonstrated and it is not recommended (see **section 4.4**).
The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine,

gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel 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.

Undiluted concentrate should not come into contact with plasticised polyvinyl chloride (PVC) equipment or devices that are used to prepare solutions for infusions. Diluted **PCH PACLITAXEL** should be stored in glass bottles, polypropylene or plastic bags (polypropylene, polyolefin) and administered with polyethylene-lined administration sets, to avoid patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which can be leached from PVC infusion bags or sets. Use an in-line filter with a microporous membrane not greater than 0,22 microns, to administer **PCH PACLITAXEL**. To minimise the leaching of DEHP, use filters such as IVEX-2 that has PVC-coated short inlet and outlet tubing.

Antineoplastics:

Pre-treatment with cisplatin may reduce the clearance of **PCH PACLITAXEL**, resulting in increased toxicity, and when both medicines are given, **PCH PACLITAXEL** should be given first.

Plasma levels of doxorubicin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination. Sequence effects characterized by more profound neutropenic and stomatitis episodes, have been observed with combination use of **PCH PACLITAXEL** and doxorubicin when **PCH PACLITAXEL** was administered BEFORE doxorubicin and using longer than recommended infusion times.

Changes in the pharmacokinetics of **PCH PACLITAXEL** were reported when given concomitantly with gemcitabine.

Pretreatment with fluorouracil has been reported to inhibit **PCH PACLITAXEL** cytotoxic action, possibly by preventing tumor cells from entering the G2-M phases of the cell cycle. The effect also occurred when the two medicines were given simultaneously, suggesting that combination therapy might not be appropriate.

Anti-viral medicines (HIV-protease inhibitors):

PCH PACLITAXEL should be given with caution to patients receiving HIV-protease inhibitors. HIV-protease inhibitors are metabolised by the cytochrome P450 isoenzyme CYP3A4, but are also reported to inhibit CYP3A activity. This may lead to leukopenia when given with **PCH PACLITAXEL**.

4.6. Fertility, pregnancy and lactation:

Pregnancy:.

Women of childbearing potential:

Women of childbearing potential should be advised to avoid becoming pregnant during treatment, and should immediately inform their doctor should this occur.

Male and female patients of fertile age, and/or their partners, should use contraceptives during treatment and for at least 6 months after receiving treatment with **PCH PACLITAXEL**.

Lactation:

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

Fertility:

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with **PCH PACLITAXEL,** because of the possibility of irreversible infertility.

4.7. Effects on ability to drive and use machines:

PCH PACLITAXEL has not been demonstrated to interfere with the ability to drive and use machines. However, it should be noted that **PCH PACLITAXEL** contains alcohol.

The ability to drive or to use machines may be decreased due to the alcohol content of **PCH PACLITAXEL**.

4.8. Undesirable effects:

Infections and infestations:

Frequent: Infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome

Less frequent: Septic shock, sepsis, peritonitis, pneumonia

Blood and lymphatic system disorders:

Frequent: Myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, bleeding

Less frequent: Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome

Frequency unknown: Disseminated intravascular coagulation

Immune system disorders:

Frequent: Minor hypersensitivity reactions (mainly flushing and rash)

Less frequent: Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain,

tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension), anaphylactic reactions, anaphylactic shock

Metabolism and nutrition disorders:

Less frequent: Anorexia

Frequency unknown: Tumour lysis syndrome

Psychiatric disorders:

Less frequent: Confusional stage

Nervous system disorders:

Frequent: Neurotoxicity (mainly: peripheral neuropathy, which can persist beyond 6 months of paclitaxel discontinuation)

Less frequent: Motor neuropathy (with resultant minor distal weakness), grand mal seizures, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, convulsions, dizziness, ataxia, headache

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: Hearing loss, ototoxicity, tinnitus, vertigo

Cardiac disorders:

Frequent: Bradycardia

Less frequent: Myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, cardiac failure, atrial fibrillation, supraventricular tachycardia

Vascular disorders:

Frequent: Hypotension

Less frequent: Thrombosis, hypertension, thrombophlebitis, shock

Frequency unknown: Phlebitis

Respiratory, thoracic and mediastinal disorders:

Less Frequent: Respiratory failure, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion, cough

Gastrointestinal disorders:

Frequent: Diarrhoea, vomiting, nausea, mucosal inflammation

Less frequent: Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, ascites, oesophagitis, constipation

Hepatobiliary disorders:

Less frequent: Hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)

Skin and subcutaneous tissue disorders:

Frequent: Alopecia

Less frequent: Transient and mild nail and skin changes, 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: Scleroderma, palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia, myalgia

Frequency unknown: Systemic lupus erythematosus

General disorders and administration site conditions:

Frequent: Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)

Less frequent: Pyrexia, dehydration, asthenia, oedema, malaise

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9. Overdose:

See **section 4.8**. No antidote is known in case of overdosage with **PCH PACLITAXEL**. The

complications primarily to be expected due to overdosage are bone marrow suppression, peripheral neurotoxicity and mucositis. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

A 26 Cytostatic agents.

ATC code: L01CD01

PHARMACOLOGICAL ACTION:

Paclitaxel has the ability to promote microtubule formation at cold temperatures and in the absence of guanosine triphosphate. Paclitaxel binds specifically to the β-tubulin subunit of microtubules. It stimulates the production of microtubuli from tubulin dimers and which stabilises the microtubuli by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubuli network. Moreover, paclitaxel induces the production of abnormal series of microtubuli bundles during the entire cell cycle and the production of multiple asters of microtubules during mitosis. Cell killing is dependent on both medicine concentrations and duration of cell exposure.

After intravenous administration, the plasma concentration of paclitaxel decreases biphasically.

5.2. Pharmacokinetic properties:

Intravenous paclitaxel exhibits a biphasic decline in plasma concentrations, with a mean terminal half-life of anywhere between about 3 and 52,7 hours.

The steady-state volume of distribution is reported to range from 198 to 688 litres/m^2, indicating extensive extravascular distribution, tissue binding, or both. Paclitaxel is on average 89 % bound to plasma protein *in vitro*.

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 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 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. 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.

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 6α-hydroxypaclitaxel, 3'-*p* -hydroxypaclitaxel and 6α, 3'-*p* dihydroxypaclitaxel is catalysed by CYP2C8, 3A4 and both 2C8 and 3A4 respectively. Metabolites are excreted in the faeces via the bile, the primary metabolite being 6α-hydroxypaclitaxel.

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:

The other ingredients in **PCH PACLITAXEL** are:

anhydrous citric acid, anhydrous ethanol, magrogolglycerol ricinoleate

6.2. Incompatibilities:

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

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

6.3. Shelf life:

Vial before opening:

24 months

PCH PACLITAXEL can be used as a multi-dose preparation. Once opened, the undiluted solution in the vial may be stored at or below 25 °C for 28 days. Discard any solution remaining after 28 days from initial use.

Diluted solution: When diluted as recommended, the infusion solutions are physically and chemically stable for up to 27 hours at room temperature (at or below 25 °C) and room lighting conditions. Discard any unused portion.

6.4. Special precautions for storage:

Unopened vials should be stored at or below 25 ºC, protected from light in the original carton (outer container), until required for use.

For storage conditions after first opening or dilution of **PCH PACLITAXEL**, see **section 6.3**

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container:

5 ml, 16,7 ml or 50 ml clear colourless glass vials of Type I with a grey bromobutyl rubber stopper with Teflon facing, 20 mm in diameter, with an aluminium seal and plastic snapcap packed into a cardboard box. Each vial is covered in an outer, transparent PVC sleeve.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

Handling:

Handle **PCH PACLITAXEL** with caution. Always wear protective gloves. Take care that **PCH PACLITAXEL** does not come into contact with skin and mucous membranes. Trained personnel should aseptically perform any dilution in a special facility for this purpose. If contact with the skin has occurred, the skin should be cleaned with water and soap. In case of contact with mucous membranes, flush with plenty of water. Dyspnoea, chest pain, burning eyes, sore throat and nausea have been reported upon inhalation.

Preparation for IV administration:

Dilute **PCH PACLITAXEL** aseptically before administration. 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 can be used to dilute **PCH PACLITAXEL** to the final concentration of 0,3 to 1,2 mg/ml.

The prepared solutions are physically and chemically stable at room temperature (approximately 25 ºC) and artificial light for a period of 27 hours (including preparation and administration).

After dilution the reconstituted solution must be inspected to identify particulate matter and discolouration. If precipitation is present, it will re-dissolve with little or no agitation upon reaching room temperature. However, if the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

After dilution the solutions may show haziness, but this is due to the formulation.

PCH PACLITAXEL should be administered through an in-line filter with a microporous membrane not greater than 0,22 microns. After simulated infusion through an IV catheter with in-line filter, no significant loss of effectiveness was observed. Diluted **PCH PACLITAXEL** should be stored in glass bottles, polypropylene or plastic bags (polypropylene, polyolefin) and administered with polyethylene-lined administration sets, to avoid patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which can be leached from PVC infusion bags or sets. To minimise the leaching of DEHP, use filters such as IVEX-2 that has PVC-coated short inlet and outlet tubing.

Disposal:

The local guidelines for the disposal of any item used in the reconstitution, administration or for any other purpose, of **PCH PACLITAXEL** and other cytotoxic medicines, should be followed.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West, Waterfall City

Midrand, Gauteng,

South Africa

8. REGISTRATION NUMBER:

PCH PACLITAXEL 30: A40/26/0609

PCH PACLITAXEL 100: A40/26/0610

PCH PACLITAXEL 300: A40/26/0611

9. DATE OF FIRST AUTHORISATION:

19 August 2009

10. DATE OF REVISION OF TEXT:

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