PROFESSIONAL INFORMATION FOR

CIPLA PACLITAXEL 30 / 100 / 300

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPLA-PACLITAXEL 30 mg/5 ml, Concentrate for dilution for infusion

CIPLA-PACLITAXEL 100 mg/16.7 ml, Concentrate for dilution for infusion

CIPLA-PACLITAXEL 300 mg/50 ml, Concentrate for dilution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPLA-PACLITAXEL 30 mg/5 ml:	Each 5 ml single-dose vial of CIPLA-PACLITAXEL 30 contains 30 mg paclitaxel and 49,7 % v/v dehydrated alcohol per vial.
CIPLA-PACLITAXEL 100 mg/16.7 ml:	Each single-dose vial of CIPLA-PACLITAXEL 100 mg/16.7 ml contains 100 mg paclitaxel and 49,7 % v/v dehydrated alcohol per vial.
CIPLA-PACLITAXEL 300 mg/50 ml:	Each 50 ml single-dose vial of CIPLA-PACLITAXEL 300 mg/50 ml contains 300 mg paclitaxel and 49,7 % v/v dehydrated alcohol per vial.

Sugar free. (3.2.P.1)

Inactive ingredients: dehydrated alcohol and purified polyoxyethylated castor oil.

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

3. PHARMACEUTICAL FORM

Concentrate for dilution for Infusion.

CIPLA-PACLITAXEL 30 mg/5 ml: A clear, colourless, viscous solution, free from visible particles

CIPLA-PACLITAXEL 100 mg/16.7 ml: A clear, colourless, viscous solution, free from visible particles

CIPLA-PACLITAXEL 300 mg/50 ml: A clear, colourless, viscous solution, free from visible particles

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPLA-PACLITAXEL 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 contra-indicated.
4. 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.
5. 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

Indication 1:

Primary treatment of ovarian carcinoma: A combination regimen consisting of CIPLA PACLITAXEL 175 mg/m2 administered intravenously over 3 hours, followed by cisplatin, given every 3 weeks.

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

Indication 2 and 3:

Secondary treatment of ovarian carcinoma: CIPLA PACLITAXEL 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**:**

Combination, first-line therapy of advanced or metastatic breast cancer: In combination with trastuzumab, the recommended dose of CIPLA PACLITAXEL is 175 mg/m2 administered intravenously over a period of 3 hours, with a 3-week interval between courses. CIPLA 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.

Indication 5:

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

CIPLA PACLITAXEL should not be re-administered until the neutrophil count is at least 1 500/mm3 and the platelet count is at least 100 000/mm^3. 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 4.8**). The incidence and severity of neurotoxicity and haematologic toxicity increases with dose.

All patients must be premedicated prior to CIPLA PACLITAXEL administration to reduce the risk of severe hypersensitivity reactions.

Such premedications may be corticosteroids, antihistamines, and H2 antagonists prior to CIPLA PACLITAXEL administration, e.g., dexamethasone 20 mg orally approximately 12 and 6 hours before CIPLA PACLITAXEL or 20 mg IV approximately 30 to 60 minutes before CIPLA PACLITAXEL, promethazine 25 mg IV 30 to 60 minutes prior to CIPLA PACLITAXEL, and cimetidine 300 mg or ranitidine 50 mg, IV 30 to 60 minutes before CIPLA PACLITAXEL.

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

Special populations

Hepatic Impairment: See **section 4.4.**

Dosage adjustment is recommended as shown below:

Degree of Hepatic Impairment

Transaminase levels	Bilirubin Levels (a)	Recommended CIPLA 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	≤ 0,026 mmol/ℓ
< 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

Paediatric population

The safety and efficacy of CIPLA PACLITAXEL in children not yet been established.

- No data are available.

Method of administration

CIPLA PACLITAXEL must be diluted prior to infusion. CIPLA PACLITAXEL 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 25ºC) 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 CIPLA PACLITAXEL since they can cause the stopper to collapse resulting in loss of sterile integrity of the CIPLA PACLITAXEL solution.

Parenteral medicine products 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. CIPLA PACLITAXEL should be administered through an in-line 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.

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

4.3 Contraindications

CIPLA PACLITAXEL is contraindicated in:

- Patients with known hypersensitivity to Paclitaxel or to any of the excipients CIPLA PACLITAXEL (see **section 6.1**).
- CIPLA PACLITAXEL should not be used in patients with baseline neutrophils < 1 500/mm^3. (see **section 6.1**).

4.4 Special warnings and precautions for use

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

CIPLA PACLITAXEL should be administered as a diluted infusion.

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

Patients should be pretreated with corticosteroids, antihistamines and H2 antagonists before receiving CIPLA PACLITAXEL. Anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema and generalised urticaria have occurred in patients receiving CIPLA PACLITAXEL. These reactions are probably histamine-mediated. Fatal reactions have occurred in patients despite pre-treatment. In cases of severe hypersensitivity reactions, CIPLA PACLITAXEL infusion

should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be rechallenged with paclitaxel.
Minor hypersensitivity reactions such as flushing, skin reactions, not requiring treatment do not require interruption of therapy.

Bone marrow suppression (primary neutropenia) is the principal dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during CIPLA PACLITAXEL 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 CIPLA PACLITAXEL, 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 CIPLA PACLITAXEL administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with CIPLA PACLITAXEL. 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 CIPLA PACLITAXEL, but generally do not require treatment. In severe cases CIPLA PACLITAXEL 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 CIPLA PACLITAXEL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

When CIPLA PACLITAXEL is used in combination with trastuzumab for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Neurologic:

Cross-study comparison of neurotoxicity suggests that when CIPLA PACLITAXEL is given in combination with cisplatin, the incidence of severe neurotoxicity is more common at a CIPLA PACLITAXEL 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 %).

CIPLA PACLITAXEL contains dehydrated alcohol, 396 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.

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 CIPLA PACLITAXEL.

Hepatic:

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

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 population

The safety and effectiveness of CIPLA PACLITAXEL in children have not been established. There have been reports of central nervous system toxicity (including death) in a clinical trial in paediatric patients in which CIPLA PACLITAXEL 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 CIPLA 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 CIPLA PACLITAXEL for use in this population.

Sugar/excipient name

CIPLA PACLITAXEL contains dehydrated alcohol and purified polyoxyethylated castor oil.

4.5 Interaction with other medicines and other forms of interaction

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

Medications concomitantly administered with CIPLA PACLITAXEL (e.g., corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely; however, possible

interactions of CIPLA PACLITAXEL with concomitantly administered medications have not been formally investigated.

Based on in vitro data, there is the possibility of an inhibition of CIPLA PACLITAXEL metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with CIPLA PACLITAXEL when they are receiving ketoconazole as concomitant therapy. Plasma levels of doxorubicin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination. Sequence effects characterised by more profound neutropenic and stomatitis episodes, have been observed with combination use of CIPLA PACLITAXEL and doxorubicin when CIPLA PACLITAXEL was administered BEFORE doxorubicin and using longer than recommended infusion times.

The metabolism of paclitaxel is catalysed by cytochrome P_{450} isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical interaction studies, caution should be exercised when administering CIPLA PACLITAXEL concomitantly with known substrates, inducers or inhibitors of these isoenzymes.

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 CIPLA PACLITAXEL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

CIPLA PACLITAXEL should be administered through an in-line filter with a microporous membrane not greater that 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

Male patients on treatment with a genotoxic or aneugenic compound should use effective contraceptive measures (such as a condom plus an additional contraceptive method) whilst on treatment until five times the terminal half-life of the compound plus 90 days, after systemic exposure to the compound.

Female patients on treatment with a genotoxic or aneugenic compound shall be on contraception during the treatment and for five half-lives of the compound at the end of treatment, plus 6 months.

Pregnancy

There is no information on the use of CIPLA PACLITAXEL in pregnant women. CIPLA PACLITAXEL may cause foetal harm when administered to pregnant women. CIPLA PACLITAXEL should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with CIPLA PACLITAXEL, and to inform the treating medical practitioner immediately should this occur.

Breastfeeding

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

Fertility

CIPLA PACLITAXEL has been shown to be embryotoxic, fetotoxic and to decrease fertility in animal studies.

4.7 Effects on ability to drive and use machines

No data available

4.8 Undesirable effects

Summary of the safety profile

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

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent CIPLA 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.

Haematologic toxicities: Bone marrow suppression was the major dose-limiting toxicity of CIPLA 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 CIPLA PACLITAXEL dose and schedule.

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

Rare 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 CIPLA PACLITAXEL therapy. The frequency and severity of HSR were not affected by the dose or schedule of CIPLA PACLITAXEL administration. The most frequent symptoms observed during these severe reactions were dyspnoea, flushing, chest pain and tachycardia.

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 CIPLA 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 CIPLA PACLITAXEL therapy. If patients develop significant conduction abnormalities during CIPLA PACLITAXEL administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with CIPLA PACLITAXEL.

Gastrointestinal (GI) Toxicity: Mild to moderate nausea/vomiting, diarrhoea and mucositis (also reported as pharyngitis or chelitis) 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 CIPLA PACLITAXEL alone and in combination with other chemotherapeutic agents.

Unless otherwise noted, Table 1 below lists undesirable effects regardless of severity associated with the administration of single agent CIPLA PACLITAXEL (812 patients treated in clinical studies) and Table 2 lists additional undesirable effects reported in the postmarketing surveillance of CIPLA PACLITAXEL.

The frequency of undesirable effects listed in Table 1 is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000).

Tabulated list of adverse reactions

Table 1: Undesirable effects associated with the administration of CIPLA PACLITAXEL in clinical studies.

MedDRA system organ class	Frequency	Side effects
Infections and infestations	Frequent	Infection
	Frequency unknown	Septic shock
Blood and the lymphatic system disorders:	Frequent	Myelosuppression, Neutropenia, Anaemia, Thrombocytopenia, Leukopenia, Fever, Bleeding
	Less frequent	Febrile neutropenia
Immune system disorders	Frequent	Minor hypersensitivity reactions (mainly flushing and rash)
	Frequency unknown	Significant hypersensitivity reactions requiring therapy (e.g., hypotension, Angioneurotic oedema, Respiratory distress, Generalised urticaria, Oedema, back pain, chills)
Nervous system disorders:	Frequent	Neurotoxicity (mainly peripheral neuropathy)
Cardiac disorders	Frequent	Abnormal ECG
	Frequent	Bradycardia
	Frequency unknown	Cardiomyopathy, Asymptomatic ventricular tachycardia, Tachycardia with bigeminy, AV block and syncope, Myocardial infarction
Vascular disorders	Frequent	Hypotension

	Less frequent	Hypertension, Thrombosis, Thrombophlebitis
Gastrointestinal disorders	Frequent	Nausea, Vomiting, Diarrhoea, Mucosal inflammation
Skin and subcutaneous tissue disorders	Frequent	Alopecia
	Frequent	Transient and mild nail and skin changes
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, Myalgia
General disorders and administration site conditions	Frequent	Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis)
Investigations	Frequent	Severe elevation in AST (SGOT), severe elevation in alkaline phosphatase
	Frequency unknown	Severe elevation in bilirubin

Table 2: Additional undesirable effects reported during post marketing surveillance

Infections and infestations:	Pneumonia, sepsis
Blood and the lymphatic system disorders:	Acute myeloid leukemia, myelodysplastic syndrome
Immune system disorders:	Anaphylactic reactions (with fatal outcome), anaphylactic shock

Metabolism and nutrition disorders:	Anorexia
Psychiatric disorders:	Confusional state
Nervous system disorders	Motor neuropathy (with resultant distal weakness), autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders:	Reversible optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended, photopsia, visual floaters.
Ear and labyrinth disorders	Hearing loss, tinnitus, vertigo, ototoxicity
Cardiac disorders:	Atrial fibrillation, supraventricular tachycardia
Vascular disorders	Shock
Respiratory, thoracic and mediastinal disorders:	Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough
Gastrointestinal disorders	Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites
Hepato-biliary disorders	Hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)
Skin and subcutaneous tissue disorders:	Pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis, radiation recall, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis

	(patients on therapy should wear sun protection on hands and feet), scleroderma
General disorders and administration site conditions:	Asthenia, malaise, pyrexia, dehydration, oedema
Investigations	Increase in blood creatinine

Description of selected adverse reactions

CIPLA PACLITAXEL and cisplatin:

Cross-study comparison of neurotoxicity suggests that when CIPLA PACLITAXEL is given in combinations with cisplatin, the incidence of severe neurotoxicity is more common at a CIPLA PACLITAXEL 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 %).

CIPLA PACLITAXEL and Radiotherapy:

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

CIPLA PACLITAXEL and trastuzumab:

When administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to CIPLA PACLITAXEL or trastuzumab) were reported more frequently than with single agent CIPLA PACLITAXEL: heart failure, infection, chills, fever, cough, rash, arthralgia, tachycardia, diarrhoea, hypertonia, epistaxis, acne, herpes simplex, accidental injury, insomnia, rhinitis, sinusitis and injection site reaction. Some of these frequency differences may be due to the increased number and duration of treatments with CIPLA PACLITAXEL/trastuzumab combination vs. single agent CIPLA PACLITAXEL.

Administration of trastuzumab in combination with CIPLA PACLITAXEL in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with CIPLA PACLITAXEL single agent and rarely has been associated with death. In most cases, patients responded to appropriate medical treatment.

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 "Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

There is no antidote for CIPLA PACLITAXEL 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**.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic Agents

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, taxanes

ATC code: L01CD01

Mechanism of action

No data available

Pharmacodynamic effects

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

Clinical efficacy and safety

Not Applicable

5.2 Pharmacokinetic properties

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. 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/m^2. 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 are non-linear. There is a disproportionately large increase in Cmax 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.

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.

Elimination

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 pretreatment. Ketoconazole may inhibit the metabolism of paclitaxel. Plasma levels of doxorubicin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination.

Linearity/non-linearity

Not applicable

5.3 Preclinical safety data

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients: Dehydrated alcohol and purified polyoxyethylated castor oil.

6.2 Incompatibilities

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

- Store at or below 25 °C.
- To be kept in outer container until required. Protect from light.
- KEEP OUT OF REACH OF CHILDREN.

After first use any unused concentrate may be stored at or below 25 °C. for up to 28 days. Solutions for infusion prepared as recommended in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets, are stable at ambient temperature (approximately 25 °C.) and lighting conditions for up to 27 hours.

6.5 Nature and contents of container

CIPLA PACLITAXEL 30 mg/5 ml is packed in multidose vial individually in a carton.

CIPLA PACLITAXEL 100 mg/5 ml is packed in multidose vial individually in a carton.

CIPLA PACLITAXEL 300 mg multidose vial individually packed in a carton.

Pack sizes: 5 ml glass vial, 20 ml glass vial and 100 ml glass vial

6.6 Special precautions for disposal and other handling

Handling: Caution should be exercised when handling CIPLA PACLITAXEL. 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 extravasation, it is advisable to closely monitor the injection site for possible infiltration during medicine administration.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

CIPLA-PACLITAXEL 30 mg/5 ml: 41/26/0423

CIPLA-PACLITAXEL 100 mg/16.7 ml: 41/26/0424

CIPLA-PACLITAXEL 300 mg/50 ml: 41/26/0425

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 04 March 2011

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

February 2024