

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

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)

WARNING:

Patients should receive **CIPLA-PACLITAXEL** (paclitaxel) under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic agents. Complications can be appropriately managed only when adequate diagnostic and treatment facilities are readily available.

Severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain, tachycardia, hypotension requiring treatment, angioedema, and generalised urticaria have been reported in patients treated with **CIPLA-PACLITAXEL**. Patients receiving **CIPLA-PACLITAXEL** should be given pretreatment with corticosteroids, promethazine, and H₂-antagonists to prevent these reactions (see "**DOSAGE AND DIRECTIONS FOR USE**"). Patients who develop severe hypersensitivity reactions to **CIPLA-PACLITAXEL** should not be rechallenged with this agent. **CIPLA-PACLITAXEL** should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³. In order to monitor the development of bone marrow suppression, primarily neutropenia (which may be severe and result in infection), it is advised that frequent peripheral blood cell counts are obtained in all patients receiving **CIPLA-PACLITAXEL**. The polyoxyethylated castor oil in **CIPLA-PACLITAXEL** can cause DEHP (di-2-ethylhexyl phthalate) to leach from polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Therefore, the preparation, storage and administration of diluted **CIPLA-PACLITAXEL** should be performed using non-plasticized PVC-containing equipment.

COMPOSITION:

CIPLA-PACLITAXEL 30 mg/5 ml:

Each 5 ml single-dose vial of **CIPLA-PACLITAXEL 30 mg/5 ml** 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.

All three formulations contain in addition to the above polyoxyethylated castor oil and anhydrous citric acid as excipients.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Paclitaxel, an antimicrotubule agent, promotes the assembly of microtubules from tubulin dimers. In addition, paclitaxel stabilises microtubules through the prevention of depolymerisation. This stability gives rise to inhibition of the normal dynamic reorganisation of the microtubule network that is fundamental to vital interphase and mitotic cellular functions. Furthermore, paclitaxel brings about abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Pharmacokinetics:

Subsequent to intravenous administration, paclitaxel demonstrates a biphasic decline in plasma concentration. The initial rapid decline signifies distribution to the peripheral compartment and elimination; the later phase is partially the result of a relatively slow efflux of paclitaxel from the peripheral compartment. In patients who receive doses of 135 and 175 mg/m² as 3- and 24-hour infusions, mean terminal half-life ranges from 3,0 to 52.7 hours. Mean total body clearance ranges from 11,6 to 24 l/h/m², while mean steady state volume of distribution ranges from 198 to 688 l/m²; these values are indicative of extensive extravascular distribution and/or tissue binding. Paclitaxel displays non-linear pharmacokinetics. Dose increases lead to disproportionately large increases in C_{max} and AUC, which are accompanied by apparent dose-related decreases in total body clearance. These findings are most readily seen in patients in whom high plasma levels of paclitaxel are achieved. It is possible that saturable processes in distribution and elimination/metabolism are responsible for these findings.

There is no evidence to suggest that paclitaxel accumulates with multiple treatment courses. *In vitro* studies examining human serum protein binding, using paclitaxel concentrations ranging from 0,1 to 50 µg/ml, show that, on average, 89 % of the compound is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not influence paclitaxel protein binding. Paclitaxel disposition has not been fully clarified in humans. Following intravenous administration, mean values of cumulative urinary recovery of unchanged compound ranged from 1,3 to 12,6 % of the dose. This indicates that extensive non-renal clearance occurs. Hepatic metabolism and biliary clearance may be the chief mechanisms for elimination of paclitaxel. Cytochrome P450 enzymes are primarily responsible for paclitaxel metabolism with the formation of principally hydroxylated metabolites. CYP2C8, 3A4 and both 2C8 and 3A4 catalyse the formation of 6α-hydroxypaclitaxel, 3'-p-hydroxypaclitaxel and 6α,3'-p-dihydroxypaclitaxel, respectively. The influence of renal or hepatic dysfunction on the pharmacokinetic properties of paclitaxel has not been investigated. While cimetidine pretreatment did not affect the clearance of paclitaxel, paclitaxel metabolism may be inhibited by ketoconazole. Concomitant administration of paclitaxel and doxorubicin may cause an increase in plasma levels of doxorubicin and doxorubicinol (see "**INTERACTIONS**").

INDICATIONS:

CIPLA-PACLITAXEL is indicated for:

- The palliative management of stage 3 or 4 advanced local carcinoma of the ovary following surgical resection. For this indication **CIPLA-PACLITAXEL** is given in combination with cisplatin.
- The palliative treatment of metastatic carcinoma of the ovary after the patient has failed to respond to first-line or subsequent chemotherapy.
- The management of metastatic breast carcinoma following failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. Unless clinically contra-indicated, an anthracycline should have formed part of the prior treatment regime.
- First-line treatment of advanced or metastatic carcinoma of the breast in combination with trastuzumab in patients who over-express HER-2 at a 2+ or 3+ level as demonstrated by immunohistochemistry.
- Palliative management of advanced non-small cell lung cancer in patients who do not qualify for potentially curative surgery and/or radiation therapy.

CONTRA-INDICATIONS:

CIPLA-PACLITAXEL is contra-indicated in patients who have previously demonstrated severe hypersensitivity reactions to **CIPLA-PACLITAXEL** or other medicines formulated with polyoxyethylated castor oil.

CIPLA-PACLITAXEL should not be administered to patients with baseline neutrophils < 1500/mm³. **CIPLA-PACLITAXEL** is contra-indicated in pregnancy and lactation (see "**PREGNANCY AND LACTATION**").

The safety and effectiveness of **CIPLA-PACLITAXEL** in children have not been established.

WARNINGS:

CIPLA-PACLITAXEL should be given under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic agents. Due to the possibility of severe hypersensitivity reactions, appropriate supportive equipment should be available.

CIPLA-PACLITAXEL should be given as a diluted infusion.

CIPLA-PACLITAXEL should be administered prior to cisplatin when used in combination. Patients should receive pretreatment with corticosteroids, antihistamines and H₂-antagonists prior to the administration of **CIPLA-PACLITAXEL**. 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 developed in patients receiving **CIPLA-PACLITAXEL**. In the event of a severe hypersensitivity reaction, **CIPLA-PACLITAXEL** infusion should be immediately discontinued, symptomatic treatment should be initiated and the patient should not be rechallenged with the compound.

Interruption of therapy is not required for minor hypersensitivity reactions, such as flushing and rash. Suppression of bone marrow function (primarily neutropenia) is the principal dose-limiting toxicity. Patients require frequent monitoring of blood cell counts during **CIPLA-PACLITAXEL** therapy. Patients should not receive retreatment until neutrophils recover to a level > 1500/mm³ and platelets recover to a level > 100 000/mm³ (see "**DOSAGE AND DIRECTIONS FOR USE**"). There have been reports of severe cardiac conduction abnormalities. If significant conduction abnormalities occur during **CIPLA-PACLITAXEL** administration, appropriate therapy should be administered and patients should receive continuous cardiac monitoring during subsequent treatment with **CIPLA-PACLITAXEL**. Severe cardiovascular events were noted more frequently in patients with non-small cell lung carcinoma than with cancers of the breast or ovary.

INTERACTIONS:

For the primary treatment of ovarian carcinoma the recommended regimen of **CIPLA-PACLITAXEL** administration is for **CIPLA-PACLITAXEL** to be administered before cisplatin. When administered before cisplatin, the safety profile of **CIPLA-PACLITAXEL** is consistent with that demonstrated for single agent use. When **CIPLA-PACLITAXEL** was administered subsequent to cisplatin, patients demonstrated more profound myelosuppression and an approximately 33 % decrease in paclitaxel clearance.

Medicines co-administered with **CIPLA-PACLITAXEL** (e.g., corticosteroids, antihistamines, and H₂-antagonists) did not appear to interact negatively; however, possible interactions of **CIPLA-PACLITAXEL** with co-administered medicines have not been formally investigated.

Ketoconazole may inhibit the metabolism of paclitaxel. This conclusion is based on data generated with *in vitro* tests. As a result, caution is required when treating patients with **CIPLA-PACLITAXEL** when they are concurrently receiving ketoconazole therapy.

Plasma levels of doxorubicin and doxorubicinol may be increased when **CIPLA-PACLITAXEL** and doxorubicin are administered in combination. Cytochrome P450 isoenzymes CYP2C8 and CYP3A4 catalyse the metabolism of paclitaxel. Caution is therefore required when **CIPLA-PACLITAXEL** is given concomitantly with known substrates or inhibitors of these isoenzymes.

The undiluted concentrate must not come into contact with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion. In order to reduce patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, to a minimum, diluted **CIPLA-PACLITAXEL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and infused through polyethylene-lined administration sets.** **CIPLA-PACLITAXEL** should be infused through an in-line filter with a microporous membrane not greater than 0,22 microns. Utilisation of filter devices, such as IVEX-2 filters which feature short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

Cimetidine pretreatment does not affect the clearance of **CIPLA-PACLITAXEL**.

PREGNANCY AND LACTATION:

Animal studies have shown that **CIPLA-PACLITAXEL** is embryo- and foetotoxic and that it decreases fertility.

CIPLA-PACLITAXEL should not be used during pregnancy. Women of childbearing potential should be advised to avoid pregnancy while they are receiving therapy with **CIPLA-PACLITAXEL**, and to inform the treating doctor immediately should they fall pregnant (see "**CONTRA-INDICATIONS**").

It is unknown whether **CIPLA-PACLITAXEL** is excreted in human milk. Breast feeding should be interrupted for the duration of **CIPLA-PACLITAXEL** treatment.

DOSAGE AND DIRECTIONS FOR USE:

Indication 1:

Primary treatment of ovarian carcinoma: a combination regimen consisting of **CIPLA-PACLITAXEL** 135 mg/m² administered as a 24-hour infusion, followed by cisplatin 75 mg/m², every 3 weeks. **CIPLA-PACLITAXEL** should be infused before cisplatin. Alternatively, a combination regimen consisting of **CIPLA-PACLITAXEL** 175 mg/m² infused over 3 hours, followed by cisplatin 75 mg/m², administered every 3 weeks.

Indication 2 and 3:

Secondary treatment of ovarian carcinoma: **CIPLA-PACLITAXEL** at a dose of 175 mg/m² given intravenously over 3 hours every 3 weeks has been demonstrated to be effective in patients with metastatic ovarian or breast carcinoma after 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 **CIPLA-PACLITAXEL** dose is 175 mg/m² infused over a period of 3 hours, with a 3-week interval between treatments. **CIPLA-PACLITAXEL** infusion may be initiated the day following the first dose of trastuzumab or immediately following the subsequent dose of trastuzumab if the patient tolerated the preceding dose of trastuzumab well.

Indication 5:

Palliative treatment of advanced non-small cell lung carcinoma: the recommended **CIPLA-PACLITAXEL** dose is 175 mg/m² infused over a 3-hour period; followed by a platinum compound, with a 3-week interval between treatments.

Patients should not receive **CIPLA-PACLITAXEL** until the neutrophil count is at least 1500/mm³ and the platelet count is at least 100 000/mm³. A dose reduction of 20 % for subsequent cycles should be effected for patients who develop severe neutropenia (neutrophil count < 500/mm³) or moderate to severe peripheral neuropathy (see "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**"). The incidence and severity of neuro- and bone marrow toxicity increase with dose.

All patients must receive premedication with corticosteroids, antihistamines, and H₂-antagonists prior to **CIPLA-PACLITAXEL** infusion. An example of such a premedication regimen is dexamethasone 20 mg orally approximately 12 and 6 hours prior to **CIPLA-PACLITAXEL**, promethazine 25 mg intravenously 30 to 60 minutes before **CIPLA-PACLITAXEL**, and cimetidine 300 mg or ranitidine 50 mg, intravenously 30 to 60 minutes prior to **CIPLA-PACLITAXEL**.

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

Hepatic impairment:

See "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**".

The following dosage adjustments are recommended:

Degree of hepatic impairment		
Transaminase levels	Bilirubin levels (a)	Recommended CIPLA-PACLITAXEL dose (b)
24 HOUR INFUSION		
< 2 x ULN and	≤1,5 mg/dl	135 mg/m ²
2 - < 10 x ULN and	≤1,5 mg/dl	100 mg/m ²
< 10 x ULN and	1,6 – 7,5 mg/dl	50 mg/m ²
≥10 x ULN or	> 7,5 mg/dl	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 concentrations between the 3- and 24-hour infusions are due to differences in clinical study design.

b) Dosage recommendations are for the first cycle of treatment; further dose reduction in subsequent cycles should be based on individual tolerance. ULN = Upper limit of normal.

Directions for use/Handling:

Handling:

Caution is required when handling **CIPLA-PACLITAXEL**. Dilution should be performed by trained staff in a designated area. It is necessary to wear adequate protective gloves. Precautions to avoid contact with the skin and mucous membranes should be adhered to. Following topical exposure, tingling, burning and redness may occur. If **CIPLA-PACLITAXEL** should come into contact with the skin, the area should be washed with soap and water. If contact with mucous membranes should occur, these should be flushed thoroughly with water. Following inhalation, dyspnoea, chest pain, burning eyes, sore throat and nausea have occurred.

Due to the possibility of extravasation, close monitoring of the injection site for possible infiltration during **CIPLA-PACLITAXEL** infusion is advised.

Preparation for IV administration:

CIPLA-PACLITAXEL requires dilution prior to infusion. Suitable dilution solutions include 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. Using one of these solutions, **CIPLA-PACLITAXEL** should be diluted to a final concentration of 0.3 to 1.2 mg/ml. Following dilution, the prepared solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. However, from a microbiological perspective, the prepared solution must be used immediately. Medicines for parenteral administration should be inspected visually for particulate matter and discolouration prior to and regularly during infusion whenever solution and container permit. Administration should be discontinued if a precipitate is present.

Upon preparation, solutions may appear hazy and this is attributed to the formulation vehicle. **CIPLA-PACLITAXEL** should be infused through an in-line filter with a microporous membrane not greater than 0,22 µm. No significant losses in potency have been observed following delivery of the solution through intravenous tubing featuring an in-line filter.

There have been some reports of precipitation during paclitaxel administration, with precipitation usually occurring towards the end of a 24-hour infusion period. To reduce the risk of precipitation, **CIPLA-PACLITAXEL** should be administered as soon as possible following dilution and undue shaking and agitation should be avoided.

In order to keep patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from plasticized PVC infusion bags or sets, to a minimum, **diluted CIPLA-PACLITAXEL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and infused through polyethylene-lined administration sets.** Use of filter devices, which feature short inlet and/or outlet plasticized PVC tubing, does not produce significant leaching of DEHP.

Disposal:

All items utilised during reconstitution and administration of or otherwise coming into contact with **CIPLA-PACLITAXEL** should be disposed of according to local guidelines for the handling of cytotoxic agents.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The frequency and severity of adverse reactions are generally similar following the administration **CIPLA-PACLITAXEL** for the treatment of ovarian, breast or lung carcinoma. Age does not clearly influence any of the observed toxicities. Safety of the paclitaxel (as in **CIPLA-PACLITAXEL**)/platinum combination has been evaluated in a randomised trial in patients with ovarian cancer and 2 phase III trials in patients with non-small cell lung carcinoma. Unless otherwise indicated, the combination of **CIPLA-PACLITAXEL** with platinum compounds does not give rise to clinically relevant changes to the safety profile of single agent **CIPLA-PACLITAXEL**.

Bone marrow suppression and peripheral neuropathy are the principal dose-related adverse events associated with the administration of **CIPLA-PACLITAXEL**. Myelosuppression is less frequent and less severe with a 3-hour infusion compared with a 24-hour infusion schedule. The recommended **CIPLA-PACLITAXEL**/cisplatin regimen for the primary treatment of carcinoma of the ovary causes more severe myelosuppression than single dose **CIPLA-PACLITAXEL** using the recommended schedule of 175 mg/m² infused over 3 hours. There is no increase in clinical sequelae, however.

Neutropenia is the most important haematological toxicity. It is dependent on the dose and schedule of **CIPLA-PACLITAXEL** and is generally rapidly reversible. Severe neutropenia (< 500 cells/mm³) occurs more frequently with a 24-hour versus 3-hour infusion. Infusion duration impacts more severely on myelosuppression than dose. Cumulative exposure does not appear to increase neutropenia. It does not seem as if neutropenia occurs more frequently or that it is more severe in patients who previously received radiation therapy.

Infectious complications, including sepsis, pneumonia, and peritonitis, may be fatal. Infections of the urinary and upper respiratory tract are the most common infectious complications. Supportive therapy, including G-CSF, is recommended for all patients who develop severe neutropenia.

The frequency and severity of neurological complications are dose dependent with **CIPLA-PACLITAXEL** monotherapy. The frequency of peripheral neuropathy increases with cumulative dose and may lead to treatment discontinuation. Patients commonly experience paraesthesia in the form of hyperesthesia. Sensory symptoms usually improve or resolve within several months of cessation of **CIPLA-PACLITAXEL** therapy. Pre-existing neuropathy due to prior treatment is not a contra-indication to **CIPLA-PACLITAXEL** therapy.

There have been rare reports of abnormal visual evoked potentials suggestive of persistent optic nerve damage.

The frequency and severity of hypersensitivity reactions are neither influenced by the dose nor schedule of **CIPLA-PACLITAXEL** administration. The most frequent syptoms reported during hypersensitivity reactions include dyspnoea, chest pain, flushing, and tachycardia. Abdominal pain, diaphoresis, pain in the extremities, and hypertension were also observed. Minor hypersensitivity reactions, manifesting mainly as flushing or rash, do not require therapeutic intervention and are not contra-indications to continuation of treatment with **CIPLA-PACLITAXEL**.

Injection site reactions following intravenous administration are usually mild and consist of localised oedema, pain, erythema, tenderness and induration. Occasionally extravasation can lead to cellulitis. Sloughing and/or peeling of the skin has been observed; sometimes in relation to extravasation. Patients may develop discolouration of the skin. Such reactions were noted more frequently with 24-hour versus 3-hour infusions. In some instances the injection site reaction developed during a prolonged infusion, but the onset can also be delayed by a week or 10 days.

Hypotension may occur during the first 3 hours of infusion, as may bradycardia. ECG changes in the form of repolarisation abnormalities, such as sinus tachycardia, sinus bradycardia, and premature beats, have been reported during clinical trials. Severe cardiac conduction abnormalities have been observed in < 1 % of patients who received **CIPLA-PACLITAXEL**. If patients experience significant conduction abnormalities during **CIPLA-PACLITAXEL** infusion, appropriate therapy should be provided and continuous electrocardiographic monitoring should be performed during subsequent treatment with **CIPLA-PACLITAXEL**.

All patients commonly experience mild to moderate nausea/vomiting, diarrhoea, and mucositis (reported as pharyngitis or cheilitis). Mucositis depends on the schedule and occurs more frequently with the 24-hour versus the 3-hour infusion.

There have been rare reports of neutropenic enterocolitis (typhlitis), despite concomitant administration of G-CSF, in patients who received **CIPLA-PACLITAXEL** alone or in combination with other chemotherapeutic agents.

Infections and infestations:

Frequent: Infection.

Less frequent: Septic shock, pneumonia, sepsis.

Blood and lymphatic system disorders:

Frequent: Myelosuppression, anaemia (red cell transfusions are required in some patients), thrombocytopenia (observed only during the first two courses), leucopenia, fever, bleeding, or neutropenia (compared to 24-hour infusion schedules, neutropenia is less common when **CIPLA-PACLITAXEL** is given as a 3-hour infusion). See also "**Special Precautions**". *Less frequent:* Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome.

Immune system disorders:

Frequent: Minor hypersensitivity reactions (mainly flushing and rash) or significant hypersensitivity reactions requiring therapeutic intervention and/or early discontinuation of **CIPLA-PACLITAXEL** infusion despite premedication (see "**WARNINGS**" and "**Special Precautions**"). *Less frequent:* Anaphylactic reactions (with fatal outcome), anaphylactic shock.

Metabolism and nutrition disorders:

Less frequent: Anorexia.

Neuropsychiatric disorders:

Frequent: Peripheral neuropathy, including mild paraesthesia (see "**Special Precautions**"). *Less frequent:* Confusional state, motor neuropathy (with resultant minor distal weakness), autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, and ataxia.

The following side-effects have been reported and frequencies are unknown: Other rare neurological manifestations are syncope and neuroencephalopathy.

Eye disorders:

Less frequent: Optic nerve and/or visual disturbances (scintillating scotomata) have been reported, particularly in patients who have received higher doses than recommended. These effects generally have been reversible.

Ear and labyrinth disorders:

Less frequent: Hearing loss, tinnitus, vertigo, and ototoxicity.

Cardiovascular disorders:

Frequent: Bradycardia, hypotension and ECG abnormalities (see "**WARNINGS**" and "**Special Precautions**").

Less frequent: Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular conduction block and syncope (see "**Special Precautions**"), myocardial infarction, atrial fibrillation, supraventricular tachycardia, hypertension, thrombosis, thrombophlebitis, and shock.

The following side-effects have been reported and frequencies are unknown:

Congestive heart failure (typically in patients who received other chemotherapy, notably anthracyclines).

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, and cough.

The following side-effects have been reported and frequencies are unknown:

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, and mucosal inflammation.

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

The following side-effects have been reported and frequencies are unknown: Neutropenic enterocolitis (typhlitis).

Hepatobiliary disorders:

Frequent: Elevated serum hepatic enzymes (see "**Special Precautions**"), hepatic necrosis (which may be fatal) and hepatic encephalopathy (which may be fatal).

Skin and subcutaneous tissue disorders:

Frequent: Alopecia, transient and mild nail and skin changes.

Less frequent: Pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis radiation recall, Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients receiving treatment should wear sun protection on hands and feet).

Musculoskeletal, connective tissue and bone disorders:

Frequent: Arthralgia/myalgia usually consisting of pain in the large joints of the arms and legs (usually mild) – these symptoms are usually transient occurring two or three days after **CIPLA-PACLITAXEL** administration and resolving within a few days.

General disorders and administrative site conditions:

Frequent: Injection site reactions (including localised oedema, pain, erythema, and induration). *Less frequent:* Extravasation during intravenous administration may lead to oedema, pain, erythema and induration and ulceration. Extravasation can also result in cellulitis. Skin discolouration may occur. Recurrence of skin reactions at a site of previous extravasation following administration of **CIPLA-PACLITAXEL** at a different site, i.e. "recall reactions", has been reported. A specific treatment for extravasation reactions is unknown at this time. *Less frequent:* Asthenia, malaise, pyrexia, dehydration, oedema. *The following side-effects have been reported and frequencies are unknown:* Fibrotic phlebitis.