

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-VINORELBINE 10 (Intravenous injection)

CIPLA-VINORELBINE 50 (Intravenous injection)

COMPOSITION:

CIPLA-VINORELBINE 10: Each single dose vial contains 13.85 mg of vinorelbine tartrate which is equivalent to 10 mg of vinorelbine base per millilitre of solution.

CIPLA-VINORELBINE 50: Each single dose vial contains 69.25 mg of vinorelbine tartrate which is equivalent to 50 mg of vinorelbine base per 5 millilitre of solution.

PHARMACOLOGICAL CLASSIFICATION:

A 26. Cytostatic agents.

PHARMACOLOGICAL ACTION:

Vinca alkaloids are compounds which are structurally similar and consist of two multiringed units, vindoline and catharanthine. Vinorelbine is a vinca alkaloid in which the site of structural modification is the catharanthine unit. This structural change confers pharmacological properties which may result in clinical benefits in patients with a variety of malignancies. Vinorelbine tartrate interferes with microtubule assembly. The antitumour activity of vinorelbine is believed to be mainly due to inhibition of mitosis at metaphase (G2 + M phase) via its interaction with tubulin, where it inhibits tubulin polymerisation. It acts primarily on the mitotic microtubules and at high concentrations it interferes with the axonal microtubules. Vinorelbine may also interfere with the metabolism of amino acids, glutathione and cyclic AMP as well as; calmodulin-dependent Ca²⁺ transport ATPase activity; biosynthesis of nucleic acids and lipids; and cellular respiration.

Pharmacokinetics:

Following intravenous administration of vinorelbine, its plasma concentration decays in a triphasic manner. The initial rapid decline is due to distribution of the medicine in peripheral compartments and the metabolism of the medicine. The prolonged terminal phase half-life is 27.7 to 43.6 hours on average; the average plasma clearances range from 0.97 to 1.26 l/hr/kg; and the volume of distribution at steady state (V_{ss}) ranges from 25.4 to 40.1 l/kg.

Antitumour activity has been shown to be possessed by one metabolite of vinorelbine, deacetylvinorelbine. Deacetylvinorelbine has been detected but not quantified in human plasma. The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been evaluated. The pharmacokinetics of vinorelbine are not affected by the concurrent administration of cisplatin with vinorelbine.

INDICATIONS:

CIPLA-VINORELBINE is indicated in the following:

- Palliative treatment of patients with advanced inoperable non-small cell lung cancer (NSCLC) as a single agent or in combination. Combination therapy is more effective than monotherapy.
- Treatment of patients with metastatic breast cancer who have failed first-line monotherapy with anthracyclines for metastatic disease or who have relapsed within 6 months of anthracycline-based adjuvant therapy.

CONTRA-INDICATIONS:

CIPLA-VINORELBINE is contra-indicated in:

- Patients with known hypersensitivity to **CIPLA-VINORELBINE**.
- Patients who have severe drug-induced granulocytopenia or severe thrombocytopenia.
- Pregnant and lactating women (see "**PREGNANCY AND LACTATION**").
- Patients with severe hepatic insufficiency.

WARNINGS:

CIPLA-VINORELBINE is a cytotoxic medicine and should be used only by medical practitioners experienced with cancer chemotherapeutic medicines. Blood counts should be obtained prior to the next dose. Discontinue **CIPLA-VINORELBINE** or reduce the dosage upon evidence of abnormal depression of the bone marrow (see table).

CIPLA-VINORELBINE IS FOR INTRAVENOUS USE ONLY. CIPLA-VINORELBINE is a tissue irritant and can produce phlebitis or extravasation injury. After peripheral administration, inadequate flushing of the vein may increase the risk of phlebitis. It is extremely important that the needle is properly positioned in the vein before this product is injected. If leakage into surrounding tissue occurs during intravenous administration of **CIPLA-VINORELBINE**, it may result in severe irritation. The injection should be stopped immediately, and the remaining portion of the dose should then be introduced into another vein.

Mortality (1%) due to neutropenic sepsis has been reported (see "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**"). Bone marrow toxicity, specifically granulocytopenia, is a dose-limiting adverse effect. Full blood counts with differentials should be performed and the results reviewed prior to each dose of **CIPLA-VINORELBINE**. **CIPLA-VINORELBINE** should not be administered to patients with granulocytopenia < 1000 cells/mm³. Patients who develop severe granulocytopenia should be carefully monitored for evidence of infection and/or fever (see "**DOSAGE AND DIRECTIONS FOR USE**").

Granulocytes (cells/mm ³) on treatment days	Dose of CIPLA-VINORELBINE (mg/m ²)
+ 1500	30
1000 to 1499	15
< 1000	Do not administer. The granulocyte count must be repeated in 1 week. CIPLA-VINORELBINE must be discontinued if the granulocyte count is < 1000 cells/mm ³ for 3 weeks.

INTERACTIONS:

Mitomycin:

Acute pulmonary reactions have been reported with **CIPLA-VINORELBINE** used in conjunction with mitomycin. **CIPLA-VINORELBINE** should be administered with caution in combination with mitomycin.

Paclitaxel:

Concomitant or sequential use may result in neuropathy, thus routine monitoring for symptoms of neuropathy is recommended.

Cisplatin:

Although the pharmacokinetics of **CIPLA-VINORELBINE** are not influenced by the concurrent administration of cisplatin, the incidence of toxicities, specifically granulocytopenia, with the combination of **CIPLA-VINORELBINE** and cisplatin is significantly higher than with single-agent **CIPLA-VINORELBINE**.

Radiation therapy:

Concurrent use of radiation therapy and **CIPLA-VINORELBINE** may increase the bone marrow depressant effect of radiation therapy.

Vaccines, killed virus:

Because normal defence mechanisms may be suppressed by **CIPLA-VINORELBINE** therapy, the patient's antibody response to the vaccine may be decreased. The interval between discontinuation of medicines that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medicine used, the underlying disease, and other factors; estimates vary from 3 months to 1 year.

Vaccines, live virus:

Because normal defence mechanisms may be suppressed by **CIPLA-VINORELBINE** therapy, concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the side-/adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine; immunisation of these patients should be undertaken only with extreme caution after careful review of the patient's haematological status and only with the knowledge and consent of the physician managing **CIPLA-VINORELBINE** therapy. The interval between discontinuation of medicines that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medicine used, the underlying disease, and other factors; estimates vary from 3 months to 1 year. Patients with leukaemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy. Immunisation with oral poliovirus vaccine should also be postponed in persons in close contact with the patient, especially family members.

PREGNANCY AND LACTATION:

The use of **CIPLA-VINORELBINE** during pregnancy and lactation is not recommended as safety and efficacy has not been established (see "**CONTRA-INDICATIONS**").

Adequate contraception to avoid pregnancy is essential.

Lactation should be discontinued before treatment with **CIPLA-VINORELBINE**.

DOSAGE AND DIRECTIONS FOR USE:

Dosage:

When used as single-agent therapy, the usual dose is 25 to 30 mg/m² administered weekly. For metastatic disease, the dosage schedule is 30 mg/m² per week.

When **CIPLA-VINORELBINE** is used as a component of polychemotherapy, the dose and the frequency depend on the protocol.

Administration precautions:

CIPLA-VINORELBINE must be administered intravenously. It is extremely important to ensure that the intravenous needle or catheter is properly positioned before **CIPLA-VINORELBINE** is injected. Leakage of **CIPLA-VINORELBINE** into surrounding tissue during intravenous administration may cause considerable irritation, local tissue necrosis and/or thrombophlebitis. If extravasation occurs, the injection should be stopped immediately, and the remaining portion of the dose should be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage have been reported to help disperse the medicine and reduce discomfort associated with the extravasation of other vinca alkaloids.

The handling and preparation of the solution of **CIPLA-VINORELBINE** should be undertaken with caution. Cutaneous reactions may occur with accidental exposure, and therefore the use of gloves is recommended. If the solution of **CIPLA-VINORELBINE** comes into contact with the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. There have been reports of severe irritation of the eye

with accidental contamination of the eye with other vinca alkaloids, including **CIPLA-VINORELBINE**. In the event of contamination of the eye with **CIPLA-VINORELBINE**, the eye should be washed with water immediately and thoroughly.

Preparation for intravenous administration:

CIPLA-VINORELBINE injection must either be diluted in a syringe or I.V. bag and one of the recommended solutions must be used. The diluted **CIPLA-VINORELBINE** should be administered over 6 to 10 minutes into the side port of a free-flowing I.V. line. This should be followed by flushing with at least 75 to 125 ml of one of the solutions. For diluents that may be used, see "**Parenteral products**".

Parenteral products: Syringe: The calculated dose of **CIPLA-VINORELBINE** should be diluted to a concentration of 1.5 to 3.0 mg/ml.

Parenteral products: I.V. bag: The calculated dose of **CIPLA-VINORELBINE** should be diluted to a concentration of 0.5 to 2.0 mg/ml.

Parenteral products: Syringe:

CIPLA-VINORELBINE diluted to a concentration of 1.5 to 3.0 mg/ml may be used for up to 24 hours when it is stored in polypropylene syringes at 5 to 30°C.

The following solutions may be used to dilute CIPLA-VINORELBINE:

0.9 % Sodium chloride injection is preferred.

5 % Dextrose injection.

Parenteral products: I.V. bag:

When **CIPLA-VINORELBINE** is diluted to a concentration of 0.5 to 2.0 mg/ml, it may be stored for up to 24 hours after preparation if it is stored in polyvinyl chloride bags between 5°C and 30°C.

The following solutions may be used to dilute CIPLA-VINORELBINE:

0.9 % Sodium chloride solution is preferred.

5 % Dextrose solution.

As with all parenteral medicine products, intravenous mixtures should be visually inspected for clarity, particulate matter, discolouration and leakage prior to administration, if the solution and container permit. The unused portion should be discarded.

Special populations:

Hepatic impairment:

Dosage adjustment for hepatic insufficiency is:

- Total bilirubin 2 mg/dl or less: give 30 mg (base) per square meter of body surface area.
- Total bilirubin 2.1 to 3 mg/dl: give 15 mg (base) per square meter of body surface area.
- Total bilirubin 3 mg/dl or more: give 7.5 mg (base) per square meter of body surface area.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

The following adverse effects may occur with **CIPLA-VINORELBINE**:

Blood and lymphatic system disorders:

Frequent: Granulocytopenia, anaemia, leukopenia.

Less frequent: Thrombocytopenia.

Neuropsychiatric system disorders:

Frequent: Asthenia.

Less frequent: Mild to moderate peripheral neuropathy, including paraesthesia and hypoaesthesia, and weakness after prolonged treatment.

Cardiovascular system disorders:

Less frequent: Chest pain.

Respiratory system disorders:

Less frequent: Bronchospasm and dyspnoeic states, occurring within minutes or only some hours later.

Gastrointestinal system disorders:

Frequent: Constipation, nausea, vomiting, and anorexia.

Less frequent: Paralytic ileus, stomatitis, pancreatitis, and diarrhoea.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia.

Less frequent: Rash.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Joint or muscle pain.

Renal and urinary system disorders:

Less frequent: Haemorrhagic cystitis.

General disorders and administrative site conditions:

Frequent: Injection site reactions.

Less frequent: Jaw pain.

Investigations:

The following side-effects have been reported and frequencies

are unknown: Increases in alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and serum bilirubin values. Transient increases in alanine aminotransferase and aspartate aminotransferase values were reported in approximately 50 % of patients, but patients with elevated liver enzyme values were typically asymptomatic and did not require discontinuation of therapy. A somewhat greater effect was observed on total bilirubin concentrations, with 5 % of patients developing concentrations of grade 3 or 4 severity. Although **CIPLA-VINORELBINE** treatment may have contributed to these increases in bilirubin concentrations, these abnormalities also may be related to disease progression in the liver.

Special Precautions:

CIPLA-VINORELBINE should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinaemia during treatment with **CIPLA-VINORELBINE**, the dose should be adjusted (see "**DOSAGE AND DIRECTIONS FOR USE**").

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT:

In the event of overdose, the patient must be closely monitored for the appearance of severe granulocytopenia which is associated with an increased risk of serious secondary infections. Treatment of overdose is supportive as no known antidote is available for **CIPLA-VINORELBINE**.

IDENTIFICATION:

CIPLA-VINORELBINE 10: A clear solution filled in a 2 ml transparent flint glass vial.

CIPLA-VINORELBINE 50: A clear solution filled in a 5 ml transparent flint glass vial.

PRESENTATION:

CIPLA-VINORELBINE 10: A carton containing one 2 ml transparent flint glass vial with a rubber stopper and red coloured aluminium flip-off seal.

CIPLA-VINORELBINE 50: A carton containing one 5 ml transparent flint glass vial with a rubber stopper and red coloured aluminium flip-off seal.

STORAGE INSTRUCTIONS:

Store between 2 – 8°C. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

CIPLA-VINORELBINE 10: 42/26/0083

CIPLA-VINORELBINE 50: 42/26/0084

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

Rosen Heights, Pasita Street

Rosen Park, Bellville, 7530 RSA

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