PROPOSED PACKAGE INSERT FOR

CIPLA-VINORELBINE 10 AND CIPLA-VINORELBINE 50

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 vinorelbine tartrate equivalent to 10 mg vinorelbine base per millilitre of solution.

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

PHARMACOLOGICAL CLASSIFICATION:

A 26. Cytostatic agents.

PHARMACOLOGICAL ACTION:

Vinca alkaloids are structurally similar compounds comprising two multiringed units, vindoline and catharanthine. Vinorelbine is a vinca alkaloid in which the catharanthine unit

is the site of structural modification. This structural change imparts pharmacological properties which may translate into clinical benefits for patients with various malignancies. Vinorelbine tartrate is a vinca alkaloid which interferes with microtubule assembly. The antitumour activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase (G2 + M phase) through its interaction with tubulin, where it inhibits the polymerisation of tubulin. It acts mainly on the mitotic microtubules and interferes with the axonal microtubules at high concentrations. Vinorelbine may also interfere with amino acid, cyclic AMP, and glutathione metabolism; calmodulin-dependent Ca^{2+} transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis.

Pharmacokinetics:

Following intravenous administration of vinorelbine, its concentration in plasma decays in a triphasic manner. The initial rapid decline represents distribution of the medicine in peripheral compartments and metabolism of the medicine. The prolonged terminal phase half-life averages 27.7 to 43.6 hours; the mean plasma clearances range from 0.97 to 1.26 l/hr/kg; and steady state volume of distribution (Vss) values range from 25.4 to 40.1 l/kg.

One metabolite of vinorelbine, deacetylvinorelbine, has been shown to possess antitumour activity. This metabolite has been detected but not quantified in human plasma. The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed. The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin with vinorelbine.

INDICATIONS:

CIPLA-VINORELBINE is indicated in the following:

- Palliative treatment of advanced inoperable non-small cell lung cancer (NSCLC) as a single agent or in combination. Combination therapy proves to be more effective than monotherapy.
- Treatment of patients with metastatic breast cancer who have failed anthracycline first-line monotherapy 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 drug-induced severe 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 taken prior to the next dose. Discontinue 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. Inadequate flushing of the vein after peripheral administration may increase the risk of phlebitis. It is extremely

important that the needle be properly positioned in the vein before this product is injected. If leakage into surrounding tissue would occur during intravenous administration of **CIPLA-VINORELBINE**, it may cause severe irritation. The injection should be discontinued immediately, and any 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 dose-limiting. Complete blood counts with differentials should be performed and results reviewed prior to each dose of **CIPLA-VINORELBINE**. **CIPLA-VINORELBINE** should not be administrated to patients with granulocytopenia < 1000 cells/mm^3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Granulocytes (cells/mm^3) on days of treatment	**Dose of CIPLA-VINORELBINE (mg/m^2)**
+ 1500	30
1000 to 1499	15
< 1000	Do not administer. Repeat granulocyte count in 1 week. If granulocyte count is < 1000 cells/mm^3 for 3 weeks, discontinue **CIPLA-VINORELBINE**.

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:

In single-agent therapy, the usual dose is 25 to 30 mg/m^2 administered weekly. The dosage schedule for metastatic disease is 30 mg/m^2 per week.

In polychemotherapy, the dose and the frequency depend on the protocol.

Administration precautions:

CIPLA-VINORELBINE must be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any **CIPLA-VINORELBINE** is injected. Leakage into surrounding tissue during intravenous administration of **CIPLA-VINORELBINE** may cause considerable irritation, local tissue necrosis and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then 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 medicine and minimise discomfort associated with the extravasation of other vinca alkaloids.

Caution should be exercised in handling and preparing the solution of **CIPLA-VINORELBINE**. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of **CIPLA-VINORELBINE** contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with other vinca alkaloids, including **CIPLA-VINORELBINE**. If this happens with **CIPLA-VINORELBINE** the eye should be washed with water immediately and thoroughly.

Preparation for the intravenous administration:

CIPLA-VINORELBINE injection must be diluted in either a syringe or I.V. bag using one of the recommended solutions. The diluted **CIPLA-VINORELBINE** should be administered over 6 to 10 minutes into the side port of a free-flowing I.V. line 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 between 1.5 and 3.0 mg/ml.

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

Parenteral products: Syringe:

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

The following solutions may be used for dilution:

0.9 % Sodium chloride injection, preferably.

5 % Dextrose injection.

Parenteral products: I.V. bags:

CIPLA-VINORELBINE diluted to a concentration of 0.5 to 2.0 mg/ml may be stored for a period of up to 24 hours after preparation if stored in polyvinyl chloride bags between 5°C

and 30°C.

The following solutions may be used for dilution:

0.9 % Sodium chloride solution, preferably.

5 % Dextrose solution.

As with all the parenteral medicine products, intravenous mixtures should be inspected visually for clarity, particulate matter, discolouration and leakage prior to administration, whenever solution and container permit. Any 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 case of overdose, the patient must be closely monitored for the appearance of severe granulocytopenia with an increased risk of serious secondary infections. Treatment to be followed must be supportive as no known antidote is available for **CIPLA-VINORELBINE** overdose.

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:

42/26/**00**83

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

CIPLA MEDPRO (PTY) LTD

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

09 October 2009

REFERENCES FOR THE PACKAGE INSERT:

REFERENCES	MRF1 PAGES
1. Central Clinical Committee Recommendation dated 15/6 March 2009	
2. MCC-approved package insert for NAVELBINE (originator) (Tema Medical); MIMS Desk Reference 2009; p 1621-1624	
3. USP DI. Drug Information for the Healthcare Professional. 25th Ed. Volume 1. pg 2947-2951.	1C-027