**PACKAGE INSERT FOR**

**CIPLA-DOXORUBICIN 10 / 50**

**SCHEDULING STATUS:**

S4

**PROPRIETARY NAME** (AND DOSAGE FORM):

**CIPLA-DOXORUBICIN 10** (Powder for solution for injection)

**CIPLA-DOXORUBICIN 50** (Powder for solution for injection)

**COMPOSITION:**

**CIPLA-DOXORUBICIN 10:** Each vial contains doxorubicin hydrochloride 10 mg.

Inactive ingredients include lactose monohydrate and sodium hydroxide.

**CIPLA-DOXORUBICIN 50:** Each vial contains doxorubicin hydrochloride 50 mg.

Inactive ingredients include lactose monohydrate and sodium hydroxide.

**PHARMACOLOGICAL CLASSIFICATION:**

A26 Cytostatic agents.

**PHARMACOLOGICAL ACTION:**

**Pharmacodynamic properties:**

Doxorubicin is an antimitotic and cytostatic antibiotic, isolated from cultures of *Streptomyces peucetius var. caesius* with an antineoplastic action. Its exact mechanism of action of antineoplastic activity is unknown, but may involve binding to DNA by intercalatian between base pairs and inhibition of DNA and RNA synthesis by template disordering and obstruction. Other possible mechanisms of antineoplastic activity include binding to cell membrane lipids, thus altering a variety of cellular functions and interacting with topoisomerase II to form DNA-cleavable complexes.

**Pharmacokinetic properties:**

**Distribution:**

Doxorubicin is quickly and widely distributed into the extravascular compartments, as indicated by a rapid (5 to 10 min) distribution half-life and by a steady state distribution volume in excess of 20 to 30 litres/kg. However, doxorubicin does not cross the blood-brain barrier in detectable amounts but may cross the placenta and is distributed into breast milk. Binding of doxorubicin to plasma proteins is extensive.

**Metabolism:**

Doxorubicin is metabolised to a significant extent by the liver. The major active metabolite is 13-OH-doxorubicinol.

**Excretion:**

The elimination half-life of doxorubicin and 13-OH-doxorubicinol is 20 to 48 hours. Forty to fifty percent of the administered dose is recovered in the bile or in the faeces in seven days, about half of which is as unchanged compound. Renal excretion is modest, accounting for only 5 – 10 percent of the administered dose in 5 days.

## INDICATIONS:

**CIPLA-DOXORUBICIN** is indicated for the treatment of:

- Acute leukaemias (acute lymphoblastic leukaemia [ALL] and acute myelogenous leukaemia [AML]), lymphomas and a number of solid tumours.
- Metastatic adenocarcinoma of the breast, carcinoma of the bladder, bronchogenic carcinoma and neuroblastoma.
- Metastatic thyroid carcinoma, carcinoma of the endometrium, testes, prostate, cervix, head and neck, and plasma cell myeloma.
- Carcinoma of the ovary against which it is active when administered with cisplatin and cyclophosphamide.
- Carcinoma of the breast and small (oat) cell carcinoma of the lung when administered concurrently with other cytotoxic medicines.
- A wide range of sarcomas including osteogenic, Ewing's and soft tissue sarcoma.
- Hodgkin's disease where it is effective in the ABVD (doxorubicin/bleomycin/vinblastin/dacarbazine) combination.
- Non-Hodgkin's lymphomas if administered concurrently in the BACOP combination.

## CONTRA-INDICATIONS:

- Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones.
- Persistent myelosuppression.
- Hepatic impairment.
- Myocardial insufficiency.

- Recent myocardial infarction.
- Severe dysrhythmias.
- Previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones (see **"WARNINGS"**).
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION**).

**WARNINGS:**

**CIPLA-DOXORUBICIN** should be administered only under the supervision of a doctor experienced in cancer chemotherapy.

Patients should be advised not to conceive and the use of reliable contraceptives is advised (see **"CONTRA-INDICATIONS"** and **"PREGNANCY AND LACTATION"**).

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia and generalised infections) before beginning treatment with **CIPLA-DOXORUBICIN**.

**CIPLA-DOXORUBICIN** is incompatible with heparin and should also not be mixed with other medicines.

**CIPLA-DOXORUBICIN** should be given with great care, in reduced doses, to elderly patients and to those with hepatic impairment.

The systemic clearance of doxorubicin is reduced in obese patients (i.e. > 130 % ideal

body weight) (see **"DOSAGE AND DIRECTIONS FOR USE"**).

**CIPLA-DOXORUBICIN** contains lactose monohydrate. Patients with hereditary galactose intolerance or the rare Lapp lactose deficiency should therefore not receive **CIPLA-DOXORUBICIN**.

**Cardiac function:**

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

**Early events:** This consists mainly of sinus tachycardia and/or ECG abnormalities, such as non-specific ST-T wave changes. Tachydysrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia as well as atrioventricular and bundle-branch block have also been reported. These events do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for discontinuation of **CIPLA-DOXORUBICIN** treatment.

**Late events:** Delayed cardiotoxicity usually develops late in the course of therapy with **CIPLA-DOXORUBICIN** or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF), such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects, such as

pericarditis/myocarditis, have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicine.

Cardiac function should be assessed before patients undergo treatment with **CIPLA-DOXORUBICIN** and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of **CIPLA-DOXORUBICIN** at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluations of LVEF) includes multi-gated radionuclide angiography or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a multi-gated radionuclide angiography scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated multi-gated radionuclide angiography or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses.

To reduce the effects of cardiotoxicity the total cumulative dose of doxorubicin should not exceed 500 mg/m$^2$ body surface area.

**Haematological toxicity:**

**CIPLA-DOXORUBICIN** may produce myelosuppression. Haematological profiles should be assessed before and during each cycle of therapy with **CIPLA-DOXORUBICIN**, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukaemia and/or granulocytopenia (neutropenia) is the

predominant manifestation of **CIPLA-DOXORUBICIN** haematological toxicity and is the most common acute dose-limiting toxicity of this medicine. Leukopenia and neutropenia generally reach the nadir between days 10 – 14 after medicine administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

**Secondary leukaemia:**

See **"Special Precautions"**.

**Fertility impairment:**

In women, **CIPLA-DOXORUBICIN** may cause infertility during the time of medicine administration. **CIPLA-DOXORUBICIN** may cause amenorrhoea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

**CIPLA-DOXORUBICIN** is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent. Men undergoing **CIPLA-DOXORUBICIN** treatment should use effective contraceptive methods.

**Gastrointestinal:**

**CIPLA-DOXORUBICIN** is emetogenic. Mucositis/stomatitis generally appears early after medicine administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

**Liver function:**

The major route of elimination of **CIPLA-DOXORUBICIN** is the hepatobiliary system. Serum total bilirubin should be monitored before and during treatment with **CIPLA-DOXORUBICIN**. Patients with elevated bilirubin may experience slower clearance of the medicine with an increase in overall toxicity. Lower doses are recommended in these patients (see **"DOSAGE AND DIRECTIONS FOR USE"**). Patients with severe hepatic impairment should not receive **CIPLA-DOXORUBICIN** (see **"CONTRA-INDICATIONS"**).

**Effects at site of injection:**

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (see **"DOSAGE AND DIRECTIONS FOR USE"**).

**Extravasation:**

Extravasation of **CIPLA-DOXORUBICIN** during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of **CIPLA-DOXORUBICIN**, the medicine infusion should be stopped immediately.

**INTERACTIONS:**

**CIPLA-DOXORUBICIN** is mainly used in combination with other cytotoxic medicines. Additive toxicity may occur especially with regard to bone marrow/haematological and

gastrointestinal effects (see **"WARNINGS"**). The use of **CIPLA-DOXORUBICIN** in combination chemotherapy with other potentially cardiotoxic medicines, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment. Changes in hepatic function induced by concomitant therapies may affect **CIPLA-DOXORUBICIN** metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

**PREGNANCY AND LACTATION:**

The use of **CIPLA-DOXORUBICIN** is contra-indicated during pregnancy and lactation as safety and efficacy have not been established (see **"CONTRA-INDICATIONS"** and **"WARNINGS"**).

**DOSAGE AND DIRECTIONS FOR USE:**

**CIPLA-DOXORUBICIN** should not be given orally and should not be injected intramuscularly or subcutaneously. It is administered by intravenous injection.

**Intravenous administration:**

Intravenous administration of **CIPLA-DOXORUBICIN** should be performed with caution. It is recommended that **CIPLA-DOXORUBICIN** be administered into the tubing of a freely flowing intravenous infusion (isotonic sodium chloride or 5 % glucose solution) over a period of 3 to 5 minutes. This technique is intended to minimise the risk of thrombosis or perivenous extravasation.

Any unused portion must be discarded as this preparation is intended for single dose administration.

**Treatment of solid tumours:**

When **CIPLA-DOXORUBICIN** is administered as a single agent, the recommended dose per cycle is 60 – 90 mg/m$^2$ of body surface area every 3 – 4 weeks.

Administration of **CIPLA-DOXORUBICIN** in a weekly regimen of 10 – 20 mg/m$^2$ has also been shown to be effective. The medicine is generally given as a single dose per cycle; however, it is possible to give the dosage per cycle in divided administrations:

- 0,6 mg/kg/day for 3 days (25 mg/m$^2$/day for 3 days), or
- 0,8 mg/kg/day for 2 days (30 mg/m$^2$/day for 2 days), or
- 1,6 mg/kg/day for 1 day (60 mg/m$^2$/day for 1 day).

If **CIPLA-DOXORUBICIN** is used in combination with other antitumour agents, the recommended dose per cycle is in the 30 – 60 mg/m$^2$ range, repeated every 21 days. As **CIPLA-DOXORUBICIN** is a myelosuppressive agent, the interval between cycles may need to be increased, or the dosage reduced, in patients whose WBC counts (particularly neutrophils) are below the range of normal values before any treatment cycle. Dosage may also need to be reduced in children, in the elderly, obese patients and in pretreated patients in whom the marrow reserve may be low.

**Hepatic dysfunction:**

In the presence of impaired hepatic function, it is suggested that **CIPLA-DOXORUBICIN** dosage be reduced as follows:

| Serum Bilirubin | Dose Reduction |
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| 1,2 – 3,0 mg / 100 ml | 50 % (i.e. 50 % of normal dose to be |

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| | given) |
| > 3 mg / 100 ml | 75 % (i.e. 25 % of normal dose to be given) |

**CIPLA-DOXORUBICIN** should not be administered to patients with severe hepatic impairment (see **"CONTRA-INDICATIONS"**).

**Treatment of acute leukaemias:**

In acute leukaemia the dosage schedule is based on the patient's response.

0,4 – 0,5 mg/kg/day for 3 days is the recommended starting dose. According to the antileukaemia and myelosuppressive effect obtained, this course can be repeated a second or even a third time with an interval between courses of not less than 7 – 10 days.

**Incompatibilities:**

**CIPLA-DOXORUBICIN** should not be mixed with other medicines. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. **CIPLA-DOXORUBICIN** should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

**Instructions for use/handling:**

**Preparation of the freeze-dried powder for intravenous administration:**

Dissolve powder in 0,9 % sodium chloride or water for injection to give a final concentration of 2 mg/ml (10 mg/5 ml or 50 mg/25 ml). The vial contents are under negative pressure. To minimise aerosol formation during reconstitution, particular care

should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

**Intravenous administration:**

**CIPLA-DOXORUBICIN** should be administered into the tubing of a freely flowing intravenous infusion (0,9 % sodium chloride or 5 % glucose solution) for not less than 3 – 10 minutes to minimise the risk of thrombosis or perivenous extravasation.

A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see **"WARNINGS"**).

**Protective measures:**

The following protective recommendations are given due to the toxic nature of the substance:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with **CIPLA-DOXORUBICIN**.
- Personnel handling **CIPLA-DOXORUBICIN** should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1 %

available chlorine) solution, preferably by soaking, and then water.

- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a medical practitioner.
- Always wash hands after removing gloves.

## SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

### Side-Effects:

The following adverse events have been reported in association with **CIPLA-DOXORUBICIN** therapy:

**Infections and infestations:**

*Frequent:* Infection, sepsis/septicaemia.

**Blood and lymphatic system disorders:**

*Frequent:* Leukopenia (see **"WARNINGS"**), anaemia, thrombocytopenia, haemorrhage, and neutropenia.

*Less frequent:* Acute lymphocytic leukaemia, acute myelogenous leukaemia (see **"Special Precautions"**).

**Immune system disorders:**

*Less frequent:* Anaphylaxis, allergic reaction.

**Metabolism and nutrition disorders:**

*Less frequent:* Hyperuricaemia or uric acid nephropathy. This occurs most commonly during initial treatment of patients with leukaemia or lymphoma as a result of rapid cell breakdown that leads to elevated serum uric acid concentrations.

**Eye disorders:**

*Less frequent:* Conjunctivitis/keratitis, lacrimation.

**Cardiac disorders:**

*Frequent:* ECG abnormalities, sinus tachycardia, tachydysrhythmias, atrioventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction, and congestive heart failure (see **"WARNINGS"**).

**Vascular:**

*Less frequent:* Phlebitis, thrombophlebitis, thromboembolism.

Hot flushes.

**Gastrointestinal:**

*Frequent:* Oesophagitis, stomatitis, nausea and vomiting (may be severe), diarrhoea, mucositis, abdominal pain, anorexia,

| | |
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| | and dehydration. |
| *Less frequent:* | Gastric erosions, gastrointestinal bleeding, hyperpigmentation of the oral mucosa, colitis, and gastrointestinal ulceration. |

**Hepatobiliary disorders:**

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| *Less frequent:* | Changes in transaminase levels. |

**Skin and subcutaneous tissue disorders:**

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| *Frequent:* | Alopecia, rash/itch, skin changes. |
| *Less frequent:* | Skin and nail hyperpigmentation, hypersensitivity reactions in irradiated skin (radiation recall reactions), photosensitivity urticaria, and acral erythema. |

**Renal and urinary disorders:**

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| *Frequent:* | Red colouration of urine for 1 to 2 days after administration. |

**Reproductive system and breast disorders:**

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| *Frequent:* | Amenorrhoea, oligospermia, azoospermia. |

**General disorders and administrative site conditions:**

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| *Frequent:* | Malaise/asthenia, fever, chills, shock.<br>Local toxicity. |
| *Less frequent:* | Extravasation, cellulitis or tissue necrosis at injection site, phlebosclerosis. |

**Special Precautions:**

Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function. Blood counts and measurement of haemoglobin concentration should be carried out routinely.

The occurrence of secondary acute myeloid leukaemia with or without a preleukaemic phase has been reported rarely in patients concurrently treated with doxorubicin, as in **CIPLA-DOXORUBICIN**, in association with DNA-damaging antineoplastic agents. Such cases could have a short (1 – 3 years) latency period.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Acute overdosage would be likely to cause the symptoms listed above, i.e. gastrointestinal symptoms, buccal ulceration and bone marrow depression. Should these symptoms occur, therapy should be stopped. A cumulative dosage above 500 mg/$m^2$ may cause irreversible cardiac failure. Treatment is supportive and symptomatic.

**IDENTIFICATION:**

**Freeze-dried powder:**

**CIPLA-DOXORUBICIN 10:** Orange/red-coloured powder or cake.

**CIPLA-DOXORUBICIN 50:** Orange/red-coloured powder or cake.

**Reconstituted solution:**

**CIPLA-DOXORUBICIN 10:** A clear red-coloured solution free from visible particles.

**CIPLA-DOXORUBICIN 50:** A clear red-coloured solution free from visible particles.

**PRESENTATION:**

**CIPLA-DOXORUBICIN 10:** Carton containing a 15 ml clear, transparent glass vial closed by a grey slotted rubber stopper and 20 mm blue flip-off-tear-off seal.

**CIPLA-DOXORUBICIN 50:** Carton containing a 50 ml clear, transparent glass vial closed by a grey slotted rubber stopper and 20 mm red flip-off-tear-off seal.

**STORAGE INSTRUCTIONS:**

**Freeze-dried powder:**

Store at or below 25 ºC. Protect from light.

Vials should not be frozen. Keep vial in the outer carton until required for use.

**KEEP OUT OF REACH OF CHILDREN.**

**Reconstituted solution:**

The reconstituted solution is stable for 24 hours at room temperature below 25 ºC or for 48 hours in a refrigerator between 2 – 8 ºC. Protect from light.

**KEEP OUT OF REACH OF CHILDREN.**

**REGISTRATION NUMBERS:**

**CIPLA DOXORUBICIN 10:** 41/26/0034

**CIPLA DOXORUBICIN 50:** 41/26/0035

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:**

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