Module 1.3.1.1: APPROVED PACKAGE INSERT FOR CIPLA BLEOMYCIN

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA BLEOMYCIN (Powder for solution for injection)

COMPOSITION:

Each vial contains bleomycin sulphate 7,5 mg equivalent to 15 units of bleomycin as a lyophilised solid powder or cake.

Other ingredients include sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Bleomycin is a water soluble glycopeptide antitumour antibiotic. Bleomycin has a strong affinity for squamous cell carcinomas. Bleomycin has not been shown to have an immunosuppressive effect *in vitro* and no significant inhibition of immune response has been observed in patients treated with bleomycin.

It is known that bleomycin inhibits the synthesis of DNA (deoxyribonucleic acid) in tumour cells.

Pharmacokinetic properties:

When given parenterally, bleomycin reaches high concentrations in the skin, lungs, kidneys, peritoneum, lymphatics and tumour tissue. Tissue concentrations are particularly high in the skin and lungs. Bleomycin is not readily metabolised or inactivated following parenteral administration.

The major route of excretion of bleomycin is the kidney with 60 to 70 percent of an administered dose recovered in the urine as active bleomycin. Renal dysfunction can significantly prolong excretion.

In patients, with creatinine clearance of < 35 mℓ per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases.

Decreased renal function is associated with enhanced bleomycin-related toxicities. Pharmacokinetic/pharmacodynamic relationships suggest that enhancement of toxicity is the consequence of reduced renal clearance of bleomycin resulting in prolonged elimination half-life and increased area under-the-plasma-concentration-vs.-time-curve compared to patients with normal renal function. Dosage reductions of 40 – 75 % have been recommended for patients with creatinine clearance values < 40 mℓ/min.

In the treatment of malignant pleural effusion, bleomycin acts as a sclerosing agent. Following intrapleural administration resultant bleomycin plasma concentrations

suggest a systemic absorption rate of approximately 45 %.

INDICATIONS:

CIPLA BLEOMYCIN is primarily indicated for the treatment of squamous cell carcinomas of the skin, head and neck, including the oesophagus. Additionally, **CIPLA BLEOMYCIN** has been used in a number of patients with squamous cell carcinoma of the penis, uterine cervix and in cases of choriocarcinoma and embryonal carcinoma of the testes.

CIPLA BLEOMYCIN has produced remissions in some cases of malignant lymphoma, Hodgkin's disease, and non-Hodgkin's lymphoma. **CIPLA BLEOMYCIN** is generally not effective against malignancies of the haematopoietic system.

Note:

Treatment of patients with **CIPLA BLEOMYCIN** after radiation therapy is less successful than treatment prior to radiation therapy (see **"INTERACTIONS"**).

CONTRAINDICATIONS:

CIPLA BLEOMYCIN is contraindicated in:

- Patients who have demonstrated a hypersensitive or idiosyncratic reaction to bleomycin or any of the ingredients of **CIPLA BLEOMYCIN**.
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).

WARNINGS:

CIPLA BLEOMYCIN should be administered under supervision of a qualified

medical practitioner experienced in the use of cancer chemotherapeutic agents. Patients receiving **CIPLA BLEOMYCIN** must be observed carefully and frequently during and after therapy. Adequate diagnostic and treatment facilities should be available to allow appropriate management of therapy and possible complications.

CIPLA BLEOMYCIN should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function. A repeat course of therapy is contraindicated in any patient who has shown signs of pneumonitis or decreased pulmonary function.

The most serious delayed effect is pulmonary toxicities. In some treated patients interstitial pneumonitis induced by **CIPLA BLEOMYCIN** progressed to irreversible pulmonary fibrosis and death. Interstitial pneumonitis and fibrosis occurs in 10 % of patients and is associated with an overall mortality rate of 10 % of patients treated with **CIPLA BLEOMYCIN**. Pulmonary toxicity is more frequent in patients over 70 years of age and in those receiving total doses greater than 400 units. Although pulmonary toxicity is age- and dose-related, the toxicity is unpredictable. Renal impairment is a risk factor for the development of pulmonary toxicity. Frequent monitoring is essential to identify and treat interstitial pneumonitis immediately (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

INTERACTIONS:

There may be an increased risk of pulmonary toxicity in patients given **CIPLA BLEOMYCIN** who receive oxygen, for example as part of a general anaesthetic procedure; a reduction in inspired oxygen concentration has been recommended

(see **"Special Precautions"**).

Vascular toxicities coincident with the use of **CIPLA BLEOMYCIN** in combination with other antineoplastic agents have been reported. These events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, haemolytic-uraemic syndrome or cerebrovascular arteritis. There are also reports of Raynaud's phenomenon occurring in patients treated with bleomycin, as contained in **CIPLA BLEOMYCIN**, in combination with vinblastine with or without cisplatin or, in few cases, with **CIPLA BLEOMYCIN** as single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, **CIPLA BLEOMYCIN**, vinblastine, hypomagnesaemia, or a combination of any of these factors (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

Cisplatin-induced renal impairment may result in delayed clearance of **CIPLA BLEOMYCIN**, leading to increased bleomycin toxicity. It seems reasonable to assume that similar interactions might occur if **CIPLA BLEOMYCIN** were given with other nephrotoxic agents. It has been suggested that apart from a decrease in **CIPLA BLEOMYCIN** dosage if nephrotoxicity occur with such a combination, giving **CIPLA BLEOMYCIN** by constant infusion rather than intermittent bolus might be less toxic.

An increased incidence of pulmonary toxicity has been reported in patients receiving **CIPLA BLEOMYCIN** as part of the ABVD regimen (with doxorubicin, vinblastine, and dacarbazine) who were given granulocyte colony-stimulating factor to alleviate

neutropenia. A case of rapidly developing and fatal pneumonitis in a patient given BEP (bleomycin, etoposide, and cisplatin) with granulocyte colony-stimulating factor has been reported.

Analysis of data failed to show increased pulmonary toxicity when granulocyte colony-stimulating factor was added to bleomycin-containing regimens in patients with germ cell tumours or non-Hodgkin's lymphoma. In a retrospective review of patients with Hodgkin's lymphoma, however, use of bleomycin, as contained in **CIPLA BLEOMYCIN**, with granulocyte colony-stimulating factor was associated with a statistically significant increase in pulmonary toxicity.

Ulceration of the mucous membranes may be exacerbated if **CIPLA BLEOMYCIN** is combined with radiation therapy, or combined with other medicines that are toxic to the mucous membranes.

Concurrent radiation therapy may result in increased **CIPLA BLEOMYCIN** toxicity, including bone marrow depression (which is less frequently caused by bleomycin alone) and in pulmonary toxicity. Dosage adjustment may be necessary.

Cytotoxic medicines, such as **CIPLA BLEOMYCIN**, may reduce the absorption of phenytoin. When combined with bleomycin, the phenytoin plasma concentration may be decreased resulting in loss of seizure control.

PREGNANCY AND LACTATION:

Pregnancy:

The use of **CIPLA BLEOMYCIN** is contraindicated during pregnancy (see

"CONTRAINDICATIONS").

The use of a contraceptive is recommended for women of childbearing potential.

Lactation:

It is not known whether **CIPLA BLEOMYCIN** is excreted into breast milk; however breastfeeding is contraindicated for the duration of **CIPLA BLEOMYCIN** therapy.

DOSAGE AND DIRECTIONS FOR USE:

Because of the possibility of an anaphylactoid reaction, patients with lymphoma should be treated with 2 units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedules are recommended:

Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma:

0,25 to 0,5 units/kg (10 to 20 units/m^2) given intramuscularly, subcutaneously or intravenously, weekly or twice weekly.

Hodgkin's disease:

0,25 to 0,5 units/kg (10 to 20 units/m^2) given intramuscularly, subcutaneously or intravenously weekly or twice weekly.

After a 50 percent response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

NOTE:

PULMONARY TOXICITY FROM **CIPLA BLEOMYCIN** APPEARS TO BE DOSE-

RELATED WITH A STRIKING INCREASE WHEN THE TOTAL DOSE IS OVER 400 UNITS. TOTAL DOSES OVER 400 UNITS SHOULD BE GIVEN WITH GREAT CAUTION. FREQUENT CHEST X-RAYS AND CLOSE MONITORING OF PULMONARY FUNCTION DURING THERAPY ARE ADVISABLE. WHEN **CIPLA BLEOMYCIN** IS USED IN COMBINATION WITH OTHER ANTINEOPLASTIC AGENTS, PULMONARY TOXICITIES MAY OCCUR AT LOWER DOSES (SEE **"INTERACTIONS"**).

Administration:

CIPLA BLEOMYCIN may be given by intramuscular, subcutaneous or intravenous routes.

Note: CIPLA BLEOMYCIN should not be reconstituted with dextrose-containing solutions.

Any unused portion must be discarded as prescribed for antineoplastic medicines.

Intramuscular:

CIPLA BLEOMYCIN vial should be reconstituted with 1 to 5 mℓ of sterile water for injection or sodium chloride injection 0,9 % *m/v*.

Subcutaneous:

Prepare as for intramuscular injection.

Intravenous:

Dissolve the contents of the vial in 5 mℓ sodium chloride injection 0,9 % and

administer slowly over a period of 10 minutes.

CIPLA BLEOMYCIN may be administered in the commonly employed intravenous solution, i.e. water for injection or sodium chloride 0,9 % and is stable in solution at room temperature.

Handling and disposal:

Procedures for proper handling and disposal of anticancer medicines should be followed.

Personnel involved in preparation and administration of parenteral antineoplastics may be at some risk because of the potential mutagenicity, teratogenicity and/or carcinogenicity of these agents. Cautious handling both in preparation and disposal of antineoplastic agents is recommended. Precautions that have been suggested include:

- Use of a biological contamment cabinet during reconstitution and dilution of parenteral medicines and wearing of disposable surgical gloves and masks.
- Use of proper technique to prevent contamination of the medicine, work area and operator during transfer between containers (including proper training of personnel in this technique).
- Caution and proper disposal of needles, syringes, vials, ampoules and unused medicine.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

CIPLA BLEOMYCIN may cause bone marrow depression.

Immune system disorders:

Less frequent: Acute reactions (pulmonary oedema, shock syndromes, urticaria, rash) have been observed. In approximately 1 % of patients with lymphoma who were treated with **CIPLA BLEOMYCIN**, an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills and wheezing. Treatment is symptomatic including intravascular volume expansion, pressor agents, antihistamines and corticosteroids.

Metabolism and nutrition disorders:

Frequent: Anorexia and weight loss may persist long after termination of treatment with **CIPLA BLEOMYCIN**.

Cardiac disorders:

Frequent: Cardiorespiratory collapse in patients with lymphoma.

Vascular disorders:

Less frequent: Hypotension requiring symptomatic treatment.

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

Myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, haemolytic-uraemic syndrome or cerebrovascular arteritis, Raynaud's phenomenon (see **"INTERACTIONS"**).

Respiratory, thoracic and mediastinal disorders:

Frequent: Pulmonary toxicity is potentially the most serious side-effect of **CIPLA BLEOMYCIN** (see **"WARNINGS"**). Interstitial pneumonitis, can rapidly progress to pulmonary fibrosis and even death.

Less frequent: Bleomycin, as contained in **CIPLA BLEOMYCIN**, has been associated with local pain following intrapleural administration. Death has been reported in association with bleomycin pleurodesis.

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

Sudden onset of an acute chest pain syndrome, suggestive of pleuropericarditis, during **CIPLA BLEOMYCIN** infusions. Although each patient must be individually evaluated, further courses of **CIPLA BLEOMYCIN** do not appear to be contraindicated. Pulmonary adverse events have been reported following the intrapleural administration of **CIPLA BLEOMYCIN**.

Gastrointestinal disorders:

Frequent: Nausea and vomiting, inflammation of the mucous

membranes, angular stomatitis.

Hepatobiliary disorders:

Less frequent: Hepatic toxicity, beginning as deterioration in liver function tests. Such toxicities may occur, however, at any time after initiation of therapy.

Skin and subcutaneous tissue disorders:

Frequent: Cutaneous side-effects including erythema, rash, pruritus, reddening and painful ulceration, particularly at pressure points, such as finger tips and elbows, striae, vesiculation, thickening, hyperpigmentation and tenderness of the skin, change in the nails and nail beds, alopecia, and contact dermatitis (see **"Special Precautions"**).

Renal and urinary disorders:

Less frequent: Renal toxicity, beginning as deterioration in renal function tests. Such toxicities may occur at any time after initiation of therapy.

General disorders and administrative site conditions:

Frequent: Fever and chills. Patients may frequently develop transient fevers, 3 to 5 hours after the intravenous injection of **CIPLA BLEOMYCIN**; however, fever can

generally be minimised by reducing the dosage.

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

Local reactions and thrombophlebitis at site of parental administration.

Pain at tumour site, muscle pain, phlebitis and other local reactions.

Special Precautions:

Pulmonary toxicity is potentially the most serious side-effect of **CIPLA BLEOMYCIN** (see **"WARNINGS"**). A unique pneumonitis, which can rapidly progress to pulmonary fibrosis and even death in some patients, occasionally develops as a result of therapy with **CIPLA BLEOMYCIN**. It is difficult to predict which patients will develop fibrosis. However, frequent chest X-rays and measurements of pulmonary function should be obtained during treatment with **CIPLA BLEOMYCIN**. Should a patient develop signs of pneumonitis, or if the X-rays show signs of infiltrates, **CIPLA BLEOMYCIN** should be discontinued immediately and the patient treated with corticosteroids and antibiotics, where appropriate.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to **CIPLA BLEOMYCIN** has been difficult. The earliest symptom associated with **CIPLA BLEOMYCIN** pulmonary toxicity is dyspnoea. The earliest sign is fine rales.

Radiographically, **CIPLA BLEOMYCIN**-induced pneumonitis produces non-specific patchy opacities. The most common changes in pulmonary function tests are a

decrease in total lung volume and a decrease in vital capacity. These changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to **CIPLA BLEOMYCIN** toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous oedema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling idiopathic interstitial fibrosis (the Hamman-Rich syndrome). These microscopic findings are non-specific. Similar changes are seen in e.g. radiation pneumonitis and *Pneumocystis jirovecii* pneumonitis.

To monitor the onset of pulmonary toxicity, X-rays of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, **CIPLA BLEOMYCIN** treatment should be discontinued until bleomycin toxicity can be ruled out as a cause. Studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{co}) during treatment with **CIPLA BLEOMYCIN** may be an indicator of subclinical pulmonary toxicity.

It is recommended that the DL_{co} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus **CIPLA BLEOMYCIN** should be discontinued when the DL_{co} falls below 30 to 35 percent of the pretreatment value.

Patients who have received **CIPLA BLEOMYCIN** are at greater risk of developing pulmonary toxicity when oxygen is administered during surgery (see

"INTERACTIONS"). While long exposure to very high oxygen concentrations is a known cause of lung damage after **CIPLA BLEOMYCIN** administration, lung damage can occur at lower concentrations than usually would be considered safe. Suggested preventive measures are:

1. Maintain inspired O_2 at concentrations approximately that of room air (25 percent) during surgery and the postoperative period.
2. Carefully monitor fluid replacement, focusing more on colloid administration than crystalloid administration.

Cutaneous side-effects are the most frequent side-effects, occurring in most treated patients (see **"Side-Effects"**). Cutaneous toxicity is a relatively late manifestation. It usually develops in the second and third week of treatment after 150 to 200 units of **CIPLA BLEOMYCIN** have been administered. Cutaneous toxicity appears to be related to cumulative dose. Cutaneous reactions include rash, erythema, pruritus, reddening and painful ulceration, particularly at pressure points, such as finger tips and elbows, striae, vesiculation, thickening, hyperpigmentation and tenderness of the skin. Change in the nails and nail beds, alopecia, and stomatitis are also frequently encountered. It was necessary to discontinue bleomycin, as contained in **CIPLA BLEOMYCIN**, therapy in some patients because of these toxicities. Local reactions and thrombophlebitis may occur at the site of parenteral administration. Contact dermatitis has also been observed following the application of **CIPLA BLEOMYCIN** to the skin of sensitive patients.

Cisplatin induced renal impairment may result in delayed clearance of **CIPLA BLEOMYCIN**, leading to increased bleomycin toxicity. The dosage of **CIPLA**

BLEOMYCIN should be reduced and caution is advised (see **"INTERACTIONS"**).

CIPLA BLEOMYCIN should be stopped in people with AIDS if cutaneous adverse effects are seen and rechallenge should be avoided.

Effect on ability to drive and operate machinery:

Patients may feel tired, weak or dizzy following treatment with **CIPLA BLEOMYCIN**. Patients should be advised to refrain from driving or operating machinery until they know how **CIPLA BLEOMYCIN** affects them.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Treatment is symptomatic and supportive.

IDENTIFICATION:

Lyophilised product:	A sterile, white to off-white lyophilised powder or cake supplied in clear glass single-dose vial of 5 mℓ capacity.
Reconstituted product:	Clear, colourless solution, free from visible particles.

PRESENTATION:

5 mℓ, clear, colourless, single-dose injection vial with a grey stopper and 20 mm aluminium tear-off seal, with red flip-off lid, containing 15 units of bleomycin in the form of a powder or cake, supplied in an outer carton made of white back board, type IV carton.

STORAGE INSTRUCTIONS:

Store the lyophilised product between 2 and 8 °C. Protect from light. Store vials in carton until required for use. **Bleomycin injection should be used immediately after reconstitution.**

The reconstituted product is for single use only. Discard any unused portion.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

45/26/0185

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

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