For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Bleomycin Sulphate for Injection BP

Bleocip

WARNING

It is recommended that Bleomycin for Injection be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary fibrosis is the most severe toxicity associated with Bleomycin for Injection.

The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with Bleomycin for Injection.

COMPOSITION

Each vial contains:

Bleomycin Sulphate Ph.Eur.
equivalent to Bleomycin.....15,000 IU
As a sterile, freeze dried powder
for reconstitution.

DOSAGE FORM

IV/ IM / Subcutaneous injection

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Although the exact mechanism of action of bleomycin is unknown, available evidence indicates that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis. Bleomycin is known to cause single, and to a lesser extent, double stranded breaks in DNA. In *in vitro* and *in vivo* experiments, bleomycin has been shown to cause cell cycle arrest in G2 and in mitosis.

Pharmacokinetics

Absorption: Bleomycin is rapidly absorbed following either intramuscular (IM) or subcutaneous (SC), administration reaching peak plasma concentrations in 30 to 60 minutes. Systemic bioavailability of bleomycin is 100% and 70% following IM and SC administrations, respectively, compared to intravenous bolus administration. Following IM doses of 1 to 10 units/m^2, both peak plasma concentration and AUC increased in proportion with the increase of dose.

Following IV bolus administration of 30 units of bleomycin to one patient with a primary germ cell tumor of the brain, a peak CSF level was 40% of the simultaneously obtained plasma level and was attained in two hours after drug administration. The area under the bleomycin CSF concentration x time curve was 25% of the area of the bleomycin plasma concentration x time curve.

Distribution

Bleomycin is widely distributed throughout the body with a mean volume of distribution of 17.5 L/m^2 in patients following a 15 units/m^2 IV bolus dose. Protein binding of bleomycin has not been studied.

Metabolism

Bleomycin is inactivated by a cytosolic cysteine proteinase enzyme, bleomycin hydrolase. The enzyme is widely distributed in normal tissues with the exception of the skin and lungs, both targets of bleomycin toxicity, Systemic elimination of the drug by enzymatic degradation is probably only important in patients with severely compromised renal function.

Excretion

The primary route of elimination is via the kidneys. About 65% of the administered IV dose is excreted in urine within 24 hours. In patients with normal renal function, plasma concentrations of bleomycin decline biexponentially with a mean terminal half-life of 2 hours following IV bolus administration. Total body clearance and renal clearance averaged 51 mL/min/m^2 and 23 mL/min/m^2, respectively.

Special Populations

Age, Gender, and Race

The effects of age, gender, and race on the pharmacokinetics of bleomycin have not been evaluated.

Pediatric

Children of less than 3 years of age have higher total body clearance than in adults, 71 mL/min/m^2 versus 51 mL/min/m^2, respectively, following IV bolus administration. Children of more than 8 years of age have comparable clearance as in adults.

In children with normal renal function, plasma concentrations of bleomycin decline biexponentially as in adults. The volume of distribution and terminal half-life of bleomycin in children appears comparable to that in adults.

Renal Insufficiency

Renal insufficiency markedly alters bleomycin elimination. The terminal elimination half-life increases exponentially as the creatinine clearance decreases. Dosing reductions were proposed for patients with creatinine clearance values of <50 mL/min.

Hepatic Insufficiency

The effect of hepatic insufficiency on the pharmacokinetics of bleomycin has not been evaluated.

Drug Interactions

Drugs That Can Affect Renal Clearance

Because bleomycin is eliminated predominantly through renal excretion, the administration of nephrotoxic drugs with bleomycin may affect its renal clearance. Specifically, in one report of 2 children receiving concomitant cisplatin with bleomycin, total body clearance of bleomycin decreased from 39 to 18 mL/min/m^2 as the cumulative dose of cisplatin exceeded 300 mg/m^2. Terminal half-life of bleomycin also increased from 4.4 to 6 hours. Fatal bleomycin pulmonary toxicity has been reported in a patient with unrecognized cisplatin-induced oliguric renal failure.

INDICATIONS

Bleomycin for Injection should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma

Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to bleomycin is poorer in patients with previously irradiated head and neck cancer.

Lymphomas

Hodgkin's Disease, non-Hodgkin's lymphoma.

Testicular Carcinoma

Embryonal cell, choriocarcinoma, and teratocarcinoma.

DOSAGE AND ADMINISTRATION

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

The following dose schedule is recommended:

Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma - 0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease - 0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily, or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of 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.

Note: When Bleomycin for Injection is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's Disease and testicular tumors is prompt and noted within 2 weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as 3 weeks before any improvement is noted.

Use in Patients with Renal Insufficiency

The following dosing reductions are proposed for patients with creatinine clearance (CrCL) values of less than 50 mL/min:

Patient CrCL (mL/min)	Bleomycin for Injection, Dose (%)
50 and above	100
40 to 50	70
30 to 40	60
20 to 30	55
10 to 20	45
5 to 10	40

CrCL can be estimated from the individual patient's measured serum creatinine (Scr) values using Cockcroft and Gault formula:

Males CrCL = [weight x (140 - Age)]/(72 x Scr)

Females CrCL = 0.85 x [weight x (140 - Age)]/(72 x Scr)

Where CrCL in mL/min/1.73m^2, weight in kg, age in years, and Scr in mg/dL.

Administration

Bleomycin for Injection may be given by the intramuscular, intravenous or subcutaneous routes.

Intramuscular or Subcutaneous

The Bleomycin for Injection 15 units vial should be reconstituted and dissolved with 1 to 5 mL of Sterile Water for Injection, Sodium Chloride for Injection, 0.9% or Bacteriostatic Water for Injection. The Bleomycin for Injection 30 units vial should be reconstituted with 2 to 10 mL of the above diluents.

Intravenous

The contents of the 15 units or 30 units vial should be dissolved in 5 mL or more or 10 mL or more, respectively of Sodium Chloride for Injection, 0.9% and administered slowly over a period of 10 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CONTRAINDICATIONS

Bleomycin for Injection is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS AND PRECAUTIONS

General

Patients receiving bleomycin must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended.

A severe idiosyncratic reaction (similar to anaphylaxis) consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses.

Renal Impairment

It should be used with extreme caution in patients with significant impairment of renal function.

Patients with creatinine clearance values of less than 50 mL/min should be treated with caution and their renal function should be carefully monitored during the administration of bleomycin. Lower doses of bleomycin may be required in these patients than those with normal renal function.

Renal toxicity, beginning as deterioration in renal function tests, has been reported, infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Hepatic Impairment

Hepatic toxicity, beginning as deterioration in liver function tests, has been reported, infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Pregnancy

Category D

Bleomycin can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m^2 basis) on days 6-15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits, at IV doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m^2 basis) given on gestation days 6-18.

There have been no studies in pregnant women. If Bleomycin for Injection is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of child bearing potential should be advised to avoid becoming pregnant during therapy with Bleomycin for Injection.

Lactation

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued by women receiving bleomycin therapy.

Pediatric Use

Safety and effectiveness of Bleomycin for Injection in pediatric patients have not been established.

Geriatric Use

In clinical trials, pulmonary toxicity was more common in patients older than 70 years than in younger patients. Other reported clinical experience has not identified other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bleomycin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

UNDESIRABLE EFFECTS

Pulmonary

This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Some published reports have suggested that the risk of pulmonary toxicity may be increased when bleomycin is used in combination with G-CSF (filgrastim) or other cytokines. However, randomized clinical studies completed to date have not demonstrated an increased risk of pulmonary complications in patients treated with bleomycin and G-CSF.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to bleomycin sulfate has been extremely difficult. The earliest symptom associated with bleomycin sulfate pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, bleomycin-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to bleomycin toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, 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 the Hamman-Rich syndrome. These microscopic findings are nonspecific; e.g. similar changes are seen in radiation pneumonitis and pneumocystic pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DLCO) during treatment with Bleomycin for Injection, USP may be an indicator of subclinical pulmonary toxicity. It is recommended that the DLCO be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DLCO falls below 30% to 35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations that are usually considered safe. Suggested preventive measures are:

1. Maintain FI O_2 at concentrations approximating that of room air (25%) during surgery and the post operative period.
2. Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during Bleomycin for Injection infusions. Although each patient must be individually evaluated, further courses of Bleomycin for Injection do not appear to be contraindicated.

Idiosyncratic Reactions

In approximately 1% of the lymphoma patients treated with Bleomycin for Injection, 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 volume expansion, pressor agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes

These are the most frequent side effects, being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue bleomycin therapy in 2% of treated patients because of these toxicities.

Scleroderma-like skin changes have also been reported as part of postmarketing surveillance.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150 to 200 units of bleomycin have been administered and appears to be related to the cumulative dose.

Other

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogenous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with bleomycin in combination with vinblastine with or without cisplatin, or, in a few cases, with bleomycin as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Fever, chills and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

Malaise was also reported as part of postmarketing surveillance.

STORAGE :

Store under refrigeration
between 2-8°C (36-46°F)
Protect from light.

Presentation:

Bleocip 1 vial of 15 units.

Last updated Mar 2013

Cipla

21069623

PACKAGING DEVELOPMENT

Product Name: Bleocip Injection	**Material No.:** 21069623	**Version:** 01	**Item:** Leaflet	**Co-ordinator: Shilpa**	**Artist:** Shashikant	**Date:** 24/04/2018
Colours: BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA) ■ Black				**INK:** Oil based Ink from DIC OR MICRO		
Design: Folded	**Supersedes: HW90 H**			**Software:** Illustrator CC		
Fonts: ----	**Links:** NA					
Actual Size: 108 x 350 mm	**Size after folding: 108 x 21 mm**	**Pharmacode:4348_MINI**	**Grain Direction :** Parallel to length			**Screen : # __**
Material: 54 GSM Maplitho Paper			**Varnish: NA**	**Artwork Print Size:** ☐ actual ☐ scaled		
Path: F:\Jobs\OTC\Sandhya\Lebanon\Bleocip\21069623 Bleocip Leaflet Lebanon.ai						

- **Instructions / Remark: NA**
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately.
  NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER
- The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details .

Checked by	Artist	Cordinator	file loaded in Server	Section Head
Pharma Code	☐	☐		
2D Code	☐	☐		
QR Code	☐	☐		
Bar Code	☐	☐		
Artwork	☐	☐		
Spell check	☐	☐		