PRODUCT MONOGRAPH

[Pr] BLEOMYCIN FOR INJECTION USP

Lyophilized Powder
15 units of bleomycin/vial (supplied as bleomycin sulfate)

Sterile

Antineoplastic, Antibiotic

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[Pr] Bleomycin for Injection USP

Lyophilized Powder
15 units of bleomycin/vial (supplied as bleomycin sulfate)

Sterile

Antineoplastic, Antibiotic

BLEOMYCIN FOR INJECTION (BLEOMYCIN SULFATE) SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A QUALIFIED PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS. ADEQUATE DIAGNOSTIC AND TREATMENT FACILITIES SHOULD BE AVAILABLE TO ALLOW APPROPRIATE MANAGEMENT OF THERAPY AND POSSIBLE COMPLICATIONS.

PATIENTS RECEIVING BLEOMYCIN FOR INJECTION MUST BE OBSERVED CAREFULLY AND FREQUENTLY DURING AND THERAPY. IT SHOULD BE USED WITH EXTREME CAUTION IN PATIENTS WITH SIGNIFICANT IMPAIRMENT OF RENAL FUNCTION OR COMPROMISED PULMONARY FUNCTION.

ACTIONS AND CLINICAL PHARMACOLOGY

Although the exact mechanism of action of bleomycin is unknown, available evidence indicates that the main mode of action is inhibition of DNA synthesis with some evidence of inhibition of RNA and protein synthesis.

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 a creatinine clearance of >35 mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of <35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases.

When administered intrapleurally 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% (see PRECAUTIONS).

INDICATIONS AND CLINICAL USE

Bleomycin for Injection USP should be considered palliative treatment to surgery and radiation therapy. It has been shown to be useful in the management of the following neoplasms:
Squamous Cell Carcinoma - Bleomycin for Injection USP is indicated in squamous cell carcinomas of the head and neck including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingiva and epiglottis; skin; larynx and paralarynx.

Bleomycin for Injection USP is also indicated in squamous cell carcinomas of the penis, cervix, and vulva.

The response to Bleomycin for Injection USP is poorer in patients with head and neck cancer who have received previous irradiation.

Lymphomas - Bleomycin for Injection USP is indicated in Hodgkin's disease and non-Hodgkin's lymphoma.

Testicular Carcinoma - Bleomycin for Injection USP is indicated in embryonal cell carcinoma, choriocarcinoma, and teratocarcinoma. Studies to date have revealed that the use of vinblastine sulfate with bleomycin sulfate increases the response rate of testicular tumours.

Malignant Pleural Effusion - When administered by intrapleural injection, Bleomycin for Injection USP has been shown to be useful in the treatment of malignant pleural effusion and in the prevention of recurrence.

CONTRAINDICATIONS

Bleomycin for Injection USP is contraindicated in patients who have demonstrated hypersensitivity to the drug.

WARNINGS

BLEOMYCIN FOR INJECTION SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A QUALIFIED PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS. ADEQUATE DIAGNOSTIC AND TREATMENT FACILITIES SHOULD BE AVAILABLE TO ALLOW APPROPRIATE MANAGEMENT OF THERAPY AND POSSIBLE COMPLICATIONS.

PATIENTS RECEIVING BLEOMYCIN FOR INJECTION MUST BE OBSERVED CAREFULLY AND FREQUENTLY DURING AND AFTER THERAPY. IT SHOULD BE USED WITH EXTREME CAUTION IN PATIENTS WITH SIGNIFICANT IMPAIRMENT OF RENAL FUNCTION OR COMPROMISED PULMONARY FUNCTION.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1% of treated patients, nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis, and death. 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 in the development of pulmonary toxicity. Frequent monitoring is essential. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of patients with lymphoma who were treated with bleomycin. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses. (See ADVERSE REACTIONS).

Renal and hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Pregnancy: Bleomycin may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with bleomycin. If bleomycin is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard.

Lactation: It is not known if bleomycin 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 from bleomycin, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The benefits and risks of nursing against discontinuing the drug must be weighed carefully.

PRECAUTIONS

Bleomycin for Injection USP should be used as indicated; the physician must carefully weigh the therapeutic benefit versus risk of toxicity.

Bleomycin should be administered preferably to patients who are hospitalized and who can be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function due to disease other than malignancy, and in patients over 70 years of age because of the apparent increased danger of pulmonary toxicity.

To monitor the onset of pulmonary toxicity, X-rays of the chest should be taken every 1-2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug related. Pneumonitis due to bleomycin should be treated with corticosteroids in an effort to prevent progression to pulmonary fibrosis. Infectious pneumonitis should receive appropriate antibiotic therapy.

Injection site reactions may occur during the administration of bleomycin (see ADVERSE REACTIONS). Therefore, it is recommended to closely monitor the injection site during drug administration.

Following intrapleural administration, resultant bleomycin plasma concentrations suggest a systemic absorption of approximately 45%. Thus, in the determination of cumulative exposure to bleomycin, systemic exposure following intrapleural administration of bleomycin for injection needs to be taken into account.

Since bleomycin is eliminated predominantly through renal excretion, the administration of nephrotoxic drugs with Blenoxane may reduce its renal clearance, potentially leading to bleomycin-related toxicity (see ACTIONS AND CLINICAL PHARMACOLOGY, WARNINGS, DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS)

An association between decreased renal function and enhanced bleomycin-related toxicities has been reported. Pharmacokinetic/pharmacodynamic relationships suggest that enhancement of toxicity is a 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 $\leq$ 40 mL/min.

ADVERSE REACTIONS

Pulmonary - Pulmonary toxicity is potentially the most serious side effect of Bleomycin for Injection (see WARNINGS).

The identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult. The reason for this is the lack of specificity of the clinical syndrome, the x-ray changes and even the tissue changes seen on examination of biopsy and autopsy specimens.

Bleomycin-induced pneumonitis apparently produces dyspnea and fine rales that are in no way different from those produced by infectious pneumonias, or the signs and symptoms produced by primary or metastatic lung disease in some patients.

On x-ray, bleomycin-induced pneumonitis produces patchy opacities, usually of the lower lung fields, that look the same as infectious bronchopneumonia or even lung metastases in some patients.

The microscopic tissue changes due to bleomycin toxicity are frequently present as 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 non specific and are similar to the changes produced in radiation

pneumonitis, pneumocystis pneumonitis, and at times reaction to long-standing malignant pulmonary disease.

Serial pulmonary function tests in 156 patients receiving bleomycin therapy revealed some demonstrable alteration in approximately 20%. The most common changes were a decrease in total lung volume and a decrease in vital capacity. However, no predictive correlation between these changes and the development of pulmonary fibrosis could be ascertained.
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, treatment should be discontinued until it can be determined if they are drug related. Studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DLco) during treatment with bleomycin may be an indicator to 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.

Patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered at 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 than usually would be considered safe. Suggestive preventive measures are:

1) maintain FI_{02} at concentrations approximately that of room air (25%) during surgery and the post-operative period.

2) carefully monitor fluid replacement, focusing more on colloid administration than crystalloid administration.

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

Pulmonary adverse events have been reported rarely following the intrapleural administration of bleomycin.

Skin and Mucous Membranes - Cutaneous effects are the most frequent side effects occurring in approximately 50% of treated patients. Cutaneous reactions include stomatitis, alopecia, hyperpigmentation, thickening, ulceration, erythema, hyperkeratosis, nail changes, rash, vesiculation, tenderness, pruritus, hyperesthesia, peeling, striae and bleeding. In 2.0% of treated patients it was necessary to discontinue bleomycin therapy because of these toxicities. Cutaneous toxicity is a relatively late manifestation developing usually in the 2nd and 3rd week of treatment after 150-200 units of bleomycin had been administered and, in general, was related to total cumulative dose. Scleroderma like skin changes have also been reported as part of postmarketing surveillance.

Idiosyncratic Reactions - In approximately 1 percent of patients with lymphoma who were treated with bleomycin, an idiosyncratic reaction, similar clinically to anaphylaxis, has been reported. The reaction may be immediate or delayed for several hours and occurs usually after

the first or second dose. It consists of hypotension, fever, chills, mental confusion and wheezing. Treatment is symptomatic, including volume expanders, pressor agents, antihistamines, and corticosteroids.

Other - Fever, chills and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of bleomycin. Pain at the tumor site, phlebitis, and other local reactions were reported infrequently. Malaise has also been reported as part of postmarketing surveillance.

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome) or cerebrovascular arteritis.

There are also reports of Raynaud's phenomenon occurring in patients treated with bleomycin in combination with vinblastine with or without cisplatin or, in 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.

Bleomycin occasionally has been associated with local pain following intrapleural administration. Hypotension requiring symptomatic treatment has been reported infrequently. Very rarely death has been reported in association with bleomycin pleurodesis in very seriously ill patients.

Injection site local soft tissue toxicity has been reported following administration of bleomycin and may result in edema, pain and necrosis.

Toxicity to the renal, hepatic and central nervous systems are rare, but as with any potent drug, these symptoms should be monitored It is noteworthy that there has been no evidence of bone marrow or immunological depression. This is contrary to the currently available antineoplastic drugs.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

DOSAGE AND ADMINISTRATION

The following dosage schedule is recommended:

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

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

Malignant Pleural Effusion: 60 units administered as a single intrapleural injection (see RECONSTITUTION).

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

Pulmonary toxicity from 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.

Improvement or responses in testicular carcinoma and Hodgkin's lymphoma are usually prompt and noted within 2 weeks. When responses are not seen within this period of time, continued therapy with bleomycin should be reevaluated.

Responses in patients with squamous cell cancers are slow, requiring up to three weeks before onset of response is noted.

Note: When bleomycin is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses. Bleomycin-related toxicities also may be more frequent in patients with impaired renal function and dose modification has been suggested. Dosage reductions of 40-75 % have been recommended for patients with creatinine clearance values ≤ 40 mL/min.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

RECONSTITUTION

Intramuscular or Subcutaneous Injection - Dissolve the contents of a Bleomycin for Injection USP vial in 1 to 5 mL of Sterile Water for Injection, Sodium Chloride for Injection or Bacteriostatic Water for Injection.

Intravenous - Dissolve the contents of the vial in 5-20 mL of Sodium Chloride Injection 0.9 % and administer slowly over a period of ten minutes.

Intrapleural Infusion: Dissolve 60 units of Bleomycin for Injection USP in 50 - 100 mL of Sodium Chloride Injection 0.9%, and administer as a rapid push through a thoracostomy tube following drainage of excess pleural fluid and the confirmation of complete lung expansion. The thoracostomy tube is then clamped and the patient is moved from the supine to the left and right lateral positions during the next four hours. The clamp is then removed and suction re-established. The amount of time the thoracostomy tube remains in place following sclerosis is based on individual patient requirements.

In general, intrapleural injection of local anaesthetics or systemic narcotic analgesia is not required.

SPECIAL INSTRUCTIONS FOR HANDLING AND DISPOSAL

1. Preparation of Bleomycin for Injection USP should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel preparing Bleomycin for Injection USP should wear PVC gloves, safety glasses, disposable gowns and masks.

3. All needles, syringes, vials and other materials which have come in contact with Bleomycin for Injection USP should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

4. Personnel regularly involved in the preparation and handling of Bleomycin for Injection USP should have bi-annual blood examinations.

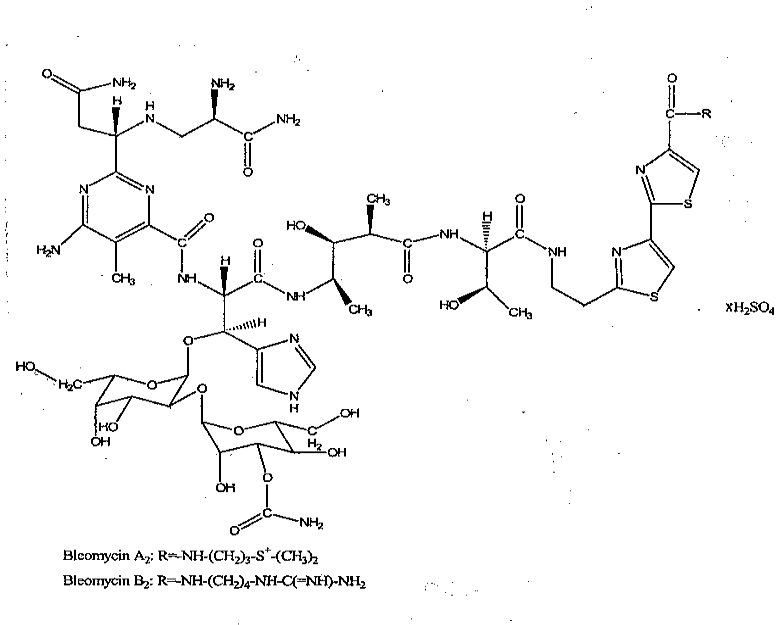
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Bleomycin Sulfate

Chemical Name: Bleomycin A_2: N^1-[3(dimethylsulphonio)propyl]bleomycin-amide
Bleomycin B_2: N^1-4(guanidobuty)bleomycin

Chemical Structure:



Molecular Formula: Bleomycin A_2: $C_{55}H_{84}N_{17}O_{21}S_3$
Bleomycin B_2: $C_{55}H_{84}N_{20}O_{21}S_2$

Molecular Mass: Bleomycin A_2: 1414 g/mol
Bleomycin B_2: 1424 g/mol

Description: Bleomycin sulfate is a white to off-white amorphous powder. Highly soluble in water, methanol; slightly soluble in ethanol. Practically insoluble in acetone, ethyl acetate, butyl acetate and ether.

COMPOSITION

Bleomycin for Injection USP (bleomycin sulfate) is supplied in vials; each vial contains sterile lyophilized bleomycin sulfate equivalent to 15 units of bleomycin. Hydrochloride acid and/or sodium hydroxide may be used as pH adjusters.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

STABILITY AND STORAGE RECOMMENDATIONS:

Bleomycin for Injection USP dry powder should be stored between 2-8°C. Protect from light.

STABILITY OF RECONSTITUTED SOLUTIONS

Reconstituted Bleomycin for Injection USP solution may be stored in refrigerator above freezing point for up to 72 hours.

Diluted Bleomycin for Injection USP is stable at 25°C for 48 hours in 0.9% Sodium Chloride Injection.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

AVAILABILITY OF DOSAGE FORMS

Bleomycin for Injection USP is supplied as single use vials containing sterile bleomycin sulfate equivalent to bleomycin 15 units (as lyophilized bleomycin sulfate), 1 vial per box.

PHARMACOLOGY

Animal Pharmacology

Bleomycin sulphate is well absorbed upon intramuscular, intraperitoneal and subcutaneous administration.

After administration of bleomycin, high concentrations are found in the skin, lungs, kidneys, peritoneum, lymphatic system and tumors, and this distribution is considered to have some relation to its effectiveness in the squamous cell carcinoma of human patients and to its toxicity. Bleomycin sulphate is excreted mainly by the kidney, with 69% of a dose (in rabbits) being eliminated, as active bleomycin, within 8 hours. In pregnant mice, bleomycin sulphate is recovered in high concentration in the amniotic fluid and to a lesser extent in the foetus.

Human Pharmacology

Blood concentrations have been studied in a few patients after intravenous or intramuscular injections of 15 units bleomycin. Although intravenous administration gives, as expected, higher initial levels these are more sustained after intramuscular injection.

TOXICOLOGY

1. The acute toxicity has been thoroughly investigated in mice, rats and dogs.

Acute Toxicity (units/kg of Copper-Free Bleomycin)

Animal	Sex	I.V.	I.P.	S.C.
Mice	M	210	312	200
Mice	F	187	190	188
Rats	M		168	168
Rats	F		143	226
Dogs	M	< 100		

2. The subacute toxicity has been studied in groups of 20 Wistar rats for 30 days. Daily intraperitoneal doses of 0.3 units/kg and 0.9 units/kg were well tolerated; no significant changes were observed in the blood picture, histopathology, or in the biochemical tests. Above this level, toxic effects on lung and skin began to appear.

3. Various chronic studies utilizing rats, dogs and monkeys showed that the principal toxic effect of bleomycin is epithelial in nature, affecting the lungs, skin and kidneys. Hematopoietic toxicity, however, is only associated with high doses.

Carcinogenesis, Mutagenesis, Impairment of fertility: The carcinogenic potential of bleomycin in humans is unknown. Given its mechanism of action, it should be considered to be a possible carcinogen in man. Bleomycin has been shown to be mutagenic in both *in vitro* and *in vivo* test systems. Bleomycin is teratogenic in rats and mice given the drug during organogenesis. The effects of bleomycin on fertility have not been established.

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