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Bleomycin for Injection, USP

Lyophilized powder bleomycin sulfate equivalent to 15 units bleomycin/vial

Antineoplastic, Antibiotic

Bleomycin for Injection, USP 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 comprised 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% 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%.

INDICATIONS AND CLINICAL USE

Bleomycin for Injection, USP should be considered an adjuvant 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 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 is also indicated in squamous cell carcinomas of the penis, cervix, and vulva.

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

Lymphomas

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

Testicular Carcinoma

Bleomycin for Injection 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 sulfate has been shown to be useful in the treatment of malignant pleural effusion and in the prevention of recurrence.

Other Malignancies

Bleomycin sulfate has been shown to produce responses in some renal carcinomas and soft tissue sarcomas.

CONTRAINDICATIONS

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

WARNINGS

Bleomycin for Injection, USP 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 comprised 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**.)

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.

An association between decreased renal function and enhanced bleomycin-related toxicities has been reported. 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 sulfate (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, fibrous 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 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 (DL_{CO}) during treatment with bleomycin may be an indicator to 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 the drug should be discontinued when the DL_{CO} 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 O₂ at concentrations approximately that of room air (25%) during surgery and the postoperative 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 weeks of treatment after 150 - 200 units of bleomycin have been administered and, in general, is related to total cumulative dose.

Idiosyncratic Reactions

In approximately one 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.

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.

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.

DOSAGE AND ADMINISTRATION

The following dosage schedule is recommended:

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

0.25 - 0.50 unit/kg (10 - 20 units/m²) given intravenously or intramuscularly weekly or twice weekly.

Hodgkin's Disease

0.25 - 0.50 unit/kg (10 - 20 units/m²) 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 sulfate 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 re-evaluated.

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

Note: When bleomycin sulfate 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 \leq 40 mL/min.

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

Reconstitution

Intramuscular or Subcutaneous Injection: Dissolve the contents of Bleomycin for Injection, USP 15 units/vial in 1 to 5 mL of Sterile Water for Injection, USP, or 0.9% Sodium Chloride Injection, USP. The final concentration of the reconstituted solution is 3 units/mL to 15 units/mL.

Intravenous or Intra-arterial Injection: Dissolve the contents of Bleomycin for Injection, USP 15 units/vial in 5 to 10 mL of 0.9% Sodium Chloride Injection, USP and administer slowly over a period of ten minutes. The final concentration of the reconstituted solution is 1.5 units/mL to 3 units/mL.

Intrapleural Infusion: Dissolve 60 units of Bleomycin for Injection, USP in 50 - 100 mL of 0.9% Sodium Chloride Injection, USP, resulting in 0.6 - 1.2 units/mL concentration, 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 anesthetics 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 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 should be segregated and incinerated at 1,000°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 should have bi-annual blood examinations.

PHARMACEUTICAL INFORMATION

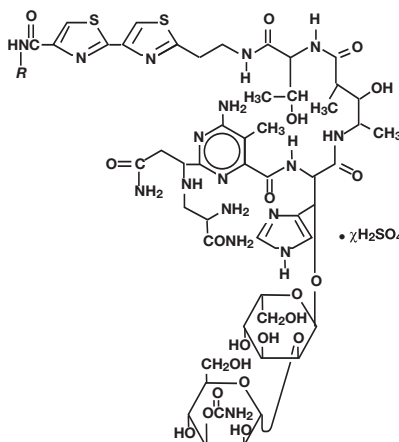
Drug Substance

Proper Name: Bleomycin Sulfate

Chemical Name: N'-[3-(dimethylsulfonio)-propyl] bleomycinamide

Molecular Formula: C₅₅H₈₄N₁₇O₂₁S₃

Structural Formula:



Bleomycin A₂:

R=[-(CH₂)₃-S⁺-(CH₃)₂]

Bleomycin B₂:

R=[-(CH₂)₄-NH-C(=NH)-NH₂]

Main Component: Bleomycin A₂, in which R=[(CH₃)₂S⁺CH₂CH₂CH₂-]

Molecular Weight: Bleomycin Sulfate: Approximately 1400
Bleomycin A₂: 1414
Bleomycin B₂: 1424

Description: Bleomycin sulfate is a white lyophilized powder. It is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus* which vary only in the terminal amine portion of the molecule. Over 60% of the bleomycin mixture is represented by bleomycin A₂, a complex glycopeptide. It is highly soluble in water. It has a pH of 4.5 - 6.0.

Composition

Each vial contains sterile bleomycin sulfate equivalent to bleomycin 15 units.

Note: A unit of bleomycin is equal to the formerly used milligram activity.

STABILITY AND STORAGE RECOMMENDATIONS

Bleomycin for Injection, USP dry powder should be stored between 2 and 8°C. Protect from light. Single-dose vial. Discard unused portion.

Stability of Reconstituted Solutions

Reconstituted Bleomycin for Injection, USP solution may be stored in refrigerator above freezing point for up to 48 hours.

Diluted Bleomycin for Injection is stable at 25°C for 24 hours in 0.9% Sodium Chloride Injection, USP in PVC bags.

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

AVAILABILITY OF DOSAGE FORMS

C103610 Bleomycin for Injection, USP is supplied in vials containing sterile bleomycin sulfate equivalent to bleomycin 15 units. Individually packaged.

Note: Vial stoppers do not contain natural rubber latex.

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