Bleomycin

DESCRIPTION:
Bleomycin for Injection, USP is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of Streptomyces verticillus. It is freely soluble in water.

Bleomycin for Injection, USP is provided as a sterile lyophilized powder for reconstitution containing 15 units per vial and 30 units per vial, which are intended for intramuscular, intravenous, subcutaneous, or intrapleural administration.

Its chemical name is N'-[3-(dimethylsulphone)propyl][bleomycin-amine base (bleomycin A2) and N'-[4-(guanodobuty)]bleomycin-amine (bleomycin B2).

(Main component: Bleomycin A2, in which R is [CH3]3Si(CH3)2CH2)

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.

CLINICAL PHARMACOLOGY:
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. When administered into the pleural cavity in the treatment of malignant pleural effusion, bleomycin acts as a sclerosing agent.

Pharmacokinetics
Absorption
Bleomycin is rapidly absorbed following either intramuscular, subcutaneous, intraperitoneal, or intrapleural administration reaching peak plasma concentrations in 30 to 60 minutes. Systemic bioavailability of bleomycin is 100% and 70% following intramuscular and subcutaneous administrations, respectively, and 45% following both intraperitoneal and intrapleural administrations, compared to intravenous and bolus administration.

Following intramuscular doses of 1 to 10 units/mL, both peak plasma concentration and AUC increased in proportion with the increase of dose.

Following intravenous 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 2 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/m² in patients following a 15 units/m² intravenous bolus dose. Protein binding of bleomycin has not been studied.

Metabolism
Bleomycin is inactivated by a cytosolic cysteine protease that hydrolyses the amide bond.

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 intravenous dose is excreted in urine within 24 hours. In patients with normal renal function, plasma concentrations decline biexponentially with a mean terminal half-life of 2 hours following intravenous bolus administration. Total body clearance and renal clearance averaged 51 mL/min/m² and 29 mL/min/m², respectively.

Follow ing intrapleural administration to patients with normal renal function, a lower percentage of drug (40%) is recovered in the urine, as compared to that found in the urine after intravenous administration.

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 of bleomycin as compared to that found in the urine after intravenous administration.

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 (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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

Drug Interactions
Drugs that 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 concurrent cisplatin with bleomycin, total body clearance of bleomycin decreased from 39 to 18 mL/min/m² as the cumulative dose of cisplatin increased 300 mg/m². 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.

Clinical Studies
Malignant Pleural Effusion
The safety and efficacy of bleomycin 60 units and tetracycline (1 g) as treatment for malignant pleural effusion were evaluated in a multicenter, randomized trial. Patients were required to have cytologically positive pleural effusion, good performance status (0, 1, 2), lung re-expansion following tube thoracostomy with drainage rates of 100 mL/24 hours or less, no prior intrapleural therapy, no prior systemic bleomycin therapy, no chest irradiation, and no recent change in systemic therapy. Overall survival did not differ between the bleomycin (n=44) and tetracycline (n=41) treatment groups. Of patients evaluated within 30 days of instillation, the recurrence rate was 36% (10/28) with bleomycin and 67% (13/19) with tetracycline (p=0.023). Toxicity was similar between groups.

INDICATIONS AND USAGE:
Bleomycin for Injection, USP should be considered a palliative treatment. It has been...
Bleomycin is widely distributed throughout the body 2 hours after drug administration. The area of 30 units of bleomycin to one patient with peritoneal and intrapleural administrations, muscular and subcutaneous administrations,

**Mechanism of Action**

**CLINICAL PHARMACOLOGY:**

The primary route of elimination is via the kidneys. About 65% of the administered dose is excreted by the kidney, and the risk of pulmonary complications in patients treated with bleomycin is increased in patients with impaired renal function. The enzyme bleomycin hydrolase is widely distributed in normal tissue, including 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, pulmonary toxicities may occur at lower concentrations that are usually considered safe. Suggested preventive measures are:

1. Maintain FIO2 at concentrations approximating that of room air (25%) during surgery and the postoperative period.
2. Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

**WARNINGS:**

Patients receiving bleomycin 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.

**Contraindications:**

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

**Usage in Pregnancy**

**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 bleomycin with doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m² basis) on days 1 to 5 of gestation produced malformations, shortened innominate artery and hydroureters. Bleomycin is abortifacient but not teratogenic in rabbits receiving 20 mg/kg/day on days 6 to 17 of gestation. Bleomycin is not a mutagen, and no mutagenic effects have been observed in bacteria or mammalian cells. Bleomycin is not known to cause chromosome breakage or gene mutation in vitro. There is no evidence of carcinogenic activity in animals treated with bleomycin.

Bleomycin is classified as a pregnancy category D drug because there is positive evidence of risk to the fetus. Bleomycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with bleomycin.

**PRECAUTIONS:**

**General**

Patients with creatinine clearance values of less than 1 mL/min should be treated with caution and their renal function should be carefully monitored during the administration of bleomycin. In patients with doses of bleomycin required to be in patients those than with normal renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of bleomycin in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of hyperplasia after intraperitoneal lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at 0.35 mg/kg weekly (3.82 units/m² weekly or about 30% at the recommended human dose), necropsy findings included deposition of lung fibrosis as well as various renal tumors. Bleomycin has been shown to be mutagenic both in vitro and in vivo, and it is unknown whether the effect of bleomycin on fertility have not been studied.

**Pregnancy**

**Pregnancy “Category D”** (See WARNINGS).

**Nursing Mothers**

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 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 (see BOXED WARNING, WARNINGS, and ADVERSE REACTIONS, Pulmonary). Other reported clinical experience has not identified other differences in response or toxicity between elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**ADVERSE REACTIONS:**

**Pulmonary**

A severe idiosyncratic reaction (similar to anaphylaxis) consisting of hypotension, mental confusion, fever, chills, and wheezing has been observed in approximately 5% of lymphoma patients treated with bleomycin. Since these reactions usually occur after the second dose, careful monitoring is essential after these doses (see ADVERSE REACTIONS, Idiosyncratic Reaction, Pulmonary).

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

**Idiosyncratic Reactions**

**Adverse reactions have been reported in approximately 1% of treated patients.** They consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hydropernictosis, 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 been reported.**

Skin toxicity is a relatively late manifestation usually developing in the third to fifth week of therapy. Fever, chills, and vomiting have been reported in approximately 1% of patients treated with bleomycin, and in the third week of treatment after 150 to 200 units of bleomycin have been administered and appear to be related to the drug. Intrapleural administration of bleomycin has been associated with local pain. Hypotenstion possibly requiring pressor agents and angioedema have also been reported. Death has been reported in association with bleomycin pleurisy in seriously ill patients.

**Other**

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported. There are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy, hemolytic uremic syndrome, and cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of a syndrome occurring in patients treated with bleomycin in combination with vinblastine without cisplatin or other drugs. Bleomycin has been proposed as a single agent. It is currently unknown if the cause of the syndrome in these cases is the combination of vascular compromise, bleomycin, vinblastine, and hypomagnesemia, or a combination of any of these factors.

**Prevention:**

After treatment with bleomycin, patients 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 schedule is recommended:

**Squamous cell carcinoma, non-Hodgkin’s lymphoma, testicular carcinoma** – 0.25 to 0.5 units/kg (10 to 20 units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

**Hodgkin’s Disease** – 0.25 to 0.5 units/kg (10 to 20 units/m²) 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 for Injection, USP 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, USP 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.

**Malignant Pleural Effusion** – 60 units administered as a single dose bolus intrapleural injection (see ADMINISTRATION, Intrapleural).

**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:

<table>
<thead>
<tr>
<th>Patient CrCl (mL/min)</th>
<th>Bleomycin for Injection, USP Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 and above</td>
<td>100</td>
</tr>
<tr>
<td>40 to 50</td>
<td>70</td>
</tr>
<tr>
<td>30 to 40</td>
<td>60</td>
</tr>
<tr>
<td>20 to 30</td>
<td>55</td>
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<tr>
<td>10 to 20</td>
<td>45</td>
</tr>
<tr>
<td>5 to 10</td>
<td>40</td>
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</tbody>
</table>

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

- Males: $\text{CrCl} = \left( \frac{\text{weight} \times (140 - \text{Age})}{72 \times \text{Scr}} \right)$
- Females: $\text{CrCl} = \left( \frac{0.85 \times (\text{weight} \times (140 - \text{Age}))}{72 \times \text{Scr}} \right)$

Where CrCl is mL/min/1.73 m², weight in kg, age in years, and Scr in mg/dL.

**ADMINISTRATION:**

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

**Administration Precautions**

Caution should be exercised when handling Bleomycin for Injection. Procedures for proper handling and disposal of antineoplastic drugs should be utilized. Several guidelines on this subject have been published. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing Bleomycin for Injection. If Bleomycin for Injection contacts the skin, immediately wash the skin thoroughly with soap and water. If contact with mucous membranes occurs, the membranes should be flushed immediately and thoroughly with water. More information is available in the references listed below.

**Intramuscular or Subcutaneous**

The Bleomycin for Injection 15 units vial should be reconstituted with 1 to 5 mL of Sterile Water for Injection, USP, Sodium Chloride for Injection, 0.9%, USP, or Sterile Bacteriostatic Water for Injection, USP. 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 10 mL respectively, of Sodium Chloride for Injection, 0.9%, USP, and administered slowly over a period of 10 minutes.

**Intrapleural**

Sixty units of Bleomycin for Injection are dissolved in 50 to 100 mL Sodium Chloride for Injection, 0.9%, USP, and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The literature suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and re-establishment of negative intrapleural pressure prior to instillation of a sclerosing agent. Therefore, the amount of drainage from the chest tube should be as minimal as possible prior to instillation of Bleomycin for Injection. Although there is no conclusive evidence to support this contention, it is generally accepted that chest tube drainage should be less than 100 mL in a 24-hour period prior to sclerosis. However, Bleomycin for Injection instillation may be appropriate when drainage is between 100 to 300 mL under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after Bleomycin for Injection instillation. The patient is moved from the supine to the left and right lateral positions several times during the next four hours. The clamp is then removed and suction re-established. The amount of time the chest tube remains in place following sclerosis is dictated by the clinical situation.

The intrapleural injection of topical anesthetics or systemic narcotic analgesia is generally not required.

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

**HOW SUPPLIED:**

Bleomycin for Injection, USP is available as follows:

- **Product NDC No. No.**
  - 103610 63323-136-10 15 units per vial, individually packaged.
  - 103720 63323-137-20 30 units per vial, individually packaged.

**Stability**

The sterile powder is stable under refrigeration 2°C to 8°C (36°F to 46°F) and should not be used after the expiration date is reached. Bleomycin for Injection should not be reconstituted or diluted with D5W or other dextrose containing diluents. When reconstituted in D5W and analyzed by HPLC, Bleomycin for Injection demonstrates a loss of As and B potency that does not occur when Bleomycin for Injection is reconstituted in Sodium Chloride for Injection, 0.9%, USP.

Bleomycin for Injection is stable for 24 hours at room temperature in Sodium Chloride.

The container closure is not made with natural rubber latex.

**REFERENCES:**


FRESENIUS KABI
Lake Zurich, IL 60047
www.fresenius-kabi.us

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