BLEOZ

(BLEOMYCIN FOR INJECTION)

Composition:

Each vial contains:
Bleomycin Sulphate IP
Equivalent to Bleomycin 15units

DESCRIPTION

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

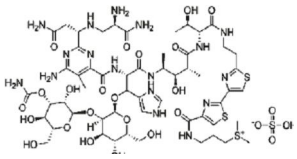
It is available as a lyophilized powder for intramuscular, intravenous or subcutaneous injection. Each vial contains sterile bleomycin sulfate equivalent to 15 units or 30 units of bleomycin. Sulfuric acid or Sodium hydroxide used, if necessary to adjust the pH.

Bleomycins are a group of related basic glycopeptides which differ in the terminal amine substituent of the common structural unit, bleomycin acid. The main components of Bleomycin for Injection are bleomycins A2 and B2. Chemically, bleomycin A2 is N1-[3-(dimethylsulfonio)propyl]-bleomycinamide and bleomycin B2 is N1-[4-(aminoiminomethyl)amino]butyl]-bleomycinamide.

The molecular formula of bleomycin A2 is C55H84N17O21S3 and a calculated molecular weight of 1414. The molecular formula of bleomycin B2 is C55H84N20O21S2 and a calculated molecular weight of 1425. The structural formula of bleomycins A2 and B2 are shown below.

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.

STRUCTURE



CLINICAL PHARMACOLOGY

Mechanism of Action

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

Bleomycin is known to cause single, and to 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 treatment of malignant pleural effusion, BLEOZ acts as a sclerosing agent.

Pharmacokinetics

Absorption

Bleomycin is rapidly absorbed following either intramuscular, subcutaneous, intraperitoneal, or intrapleural administered reaching peak plasma concentration 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/m^2, both peak plasma concentration and AUC increased in proportion with increase if dose.

Followings intramuscular bolus administration of 30 units of BLEOZ 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 17.5L/m^2 in Patients following a 15 units/m^2 intravenous bolus dose. Proteins binding of bleomycin has not been studied.

Metabolism

Bleomycin in inactived by a cysteine proteinase, bleomycin hydrolase.The enzyme is widely distributed in normal tissues with the exception of the skin and lungs, both targets of bleomycin toxicity. Systemic 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 with 24 hour. In patients with normal renal function plasma concentration of bleomycin decline biexponentially with a mean terminal half-life clearance averaged 51ml/min/m^2 and 23ml/min/m^2.

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

Age, Gender and Race

The effect of age, gender and race on the pharmacokinetics of **BLEOZ** have not been evaluated.

Pediatric

Children of the less than 3 years of age have higher total body clearance than in adult, 71 ml/min/m^2

Respectively, following intravenous bolus administration. Children of more than 8 year of age have comparable clearance as in adult.

In children with normal renal function plasma concentration of bleomycin decline biexponentially as in adult. 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 decrease. Dosing reduction were proposed for patients with creatinine clearance value of < 50ml/min (see PRECAUTIONS and DOSAGE AND ANDMINSTRATION).

Hepatic Insufficiency

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

Rag Interaction

Drugs that can Affect Renal Clearance

Because bleomycin is eliminated predominantly through renal excretion, the administration of nephrotoxic drugs with affect its renal clearance, specifically, in one report of 2 children receiving concomitant with bleomycin, total body clearance of bleomycin

decreased from 39 to 18 ml/min/m^2 as the cumulative dose cisplatin exceeded 300 mg/m^2. Terminal half- life of bleomycin also increased from 4.4 to 6.0 hours. Fatal bleomycin pulmonary has been reported in a patient with unrecognized cisplatin-induced oilguric renal failure.

Clinical Studies

Malignant Pleural Effusion

The Safety and efficacy of BLEOZ 60 unit and tetracycline (1g) as treatment for malignant pleural effusion were evaluated in multicenter, randomized trial. Patients were required to have cytological positive pleural effusion, good performance status (0, 1, 2), lung reexpansion following tube thoracotomy with drainage rates of 100 ml/24 hours or less, no prior intrapleural therapy, no prior systemic BLEOZ therapy, no recent change in systemic therapy. Overall survival did not differ between the BLEOZ (n=44) and tetracycline rate was 36% (10/28) with BLEOZ and 67% (18/27) with tetracycline (p=0.023).Toxicity was similar between groups.

INDICATIONS

BLEOZ 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, plate, lip, buccal mucosa, gingivae, skin, larynx), Penis, cervix, and vulva. The response to BLEOZ is poorer in patients with previously irradiated head neck cancer.

Lymphomas

Hodgkin's diseases, non-Hodgkin's lymphoma

Testicular Carcinoma

Embryonal cell, choriocarcinoma and teratocarcinoma.

BLEOZ has also been shown to be useful in the management of:

Malignant Pleural Effusion

BLEOZ is effective as ascierosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

DOSAGE AND ADMINSTRATION

Because of the possibility of an anaphylactiod reaction. Lymphoma 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 doses 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, 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 intramuscular should be given.

Pulmonary toxicity of BLEOZ appear 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 BLEOZ is used in combination with other antineoplastic agent, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's disease and testicular turnover is prompt and noted within 20 weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancer 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 reduction are proposed for patients with creatinine clearance (CRCL) value of les than 50 ml/min

Patient CRCL (mL/min)	BLEOZ Dose (%)
50 and above	100
40-50	70
30-40	60
20-30	55
10-20	45
5-10	40

CrCL can be estimated from the individual patients measured serum creatinine (Scr) value using the Cockcroft and Gault formula:

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

Females CrCL = 0.85 x [weight × (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

BLEOZ may be given by the intramuscular, intravenous, subcutaneous, or intrapleural routes.

Administration Precautions

Caution should be exercised when handling **BLEOZ** for injection. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published. 1-4 To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing **BLEOZ** for injection. If **BLEOZ** for injection contacts 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 **BLEOZ** 15 units vial should be reconstituted with 1 to 5ml of Sterile Water for Injection, IP, Sodium Chloride for Injection, 0.9%, USP, or Sterile Bacteriostatic Water for Injection, USP. The **BLEOZ** 30 units vial should be reconstituted with 2 to 10ml 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 10minutes.

Intrapleural

Sixty units of **BLEOZ** are dissolved in 50 to 100ml Sodium Chloride for Injection, 0.9%, USP, and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung exapansion. The literature

suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and reestablishment 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 sclerosis. However, **BLEOZ** 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 **BLEOZ** 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 reestablished. 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.

WARNING:

It is recommended that BLEOZ be administration 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 ready available.

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

A sever idiosyncratic reaction of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1 % of lymphoma patients treated with BLEOZ.

BLEOZ (bleomycin sulfate for injection, USP) is a mixture of cytotoxic glycopeptide antibiotics isolated

From a strain of Streptomyces verticillus. It is freely soluble in water

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.

WARNINGS

Patients receiving **BLEOZ** 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%, the nonspecific pneumonitis induced by **BLEOZ** progresses to pulmonary fibrosis and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended (see ADVERSE REACTIONS: Pulmonary).

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 **BLEOZ.** Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses (see ADVERSE REACTIONS: Idiosyncratic Reactions).

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.

Usage in Pregnancy

Pregnancy Category D

BLEOZ 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/m2 basis) on days 6 to 15 of gestation caused sketal malformations, shortened innominate artery and hydroureter. **BLEOZ** is abortifacient but not teratogenic in rabbits at intravenous doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m2 basis) given on gestation days 6 to 18.

There have been no studies in pregnant women. If **BLEOZ** 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 childbearing potential should be advised to avoid becoming pregnant during therapy with

PRECAUTIONS

General

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 **BLEOZ** may be required in these patients than those with normal renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of **BLEOZ** in humans is unknown. A study in F344type male rats demonstrated an increased incidence of nodular hyperplasia after induce lung carcinogenesis by nitroamines, 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 dose-related injection site fibrosarcomas as well as various renal tumors. Bleomycin has been shown to be mutagenic both in vitro and in vivo. The effects of bleomycin on fertility have not been studied.

Pregnancy

Pregnancy Category D

See WARNINGS.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of **BLEOZ** in pediatric patients have not been established.

Geriatric Use

In clinical trials, pulmonary toxicity was more common in patients older than 70years than in younger patients (see BOXED WARNING, WARNINGS, and ADVERSE REACTION: Pulmonary). Other reported clinical experience has not identified other differences in responses between elderly and younger patients, but 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.

ADVERSE REACTIONS

Pulmonary

The most serious side effects are pulmonary adverse reactions, 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 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 **BLEOZ** has been extremely difficult. The earliest symptom associated with **BLEOZ** pulmonary toxicity is dyspnea. The earliest sign is fine rales. Radiographically, **BLEOZ** – 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 **BLEOZ** 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 of a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific; eg, 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 (see WARNINGS). 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 **BLEOZ** 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 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.

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

Drug Interactions

Idiosyncratic Reactions

In approximately 1% of the lymphoma patients treated with **BLEOZ** 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 (see WARNING). It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, presser agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes

These adverse reactions have been reported in approximately 50% of treated patients. They 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 **BLEOZ** 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 second and third week of treatment after 150 to 200 units of **BLEOZ** have been administered and appears to be related to the cumulative dose.

Intrapleural administration of **BLEOZ** has been associated with local pain. Hypotension possibly requiring symptomatic treatment has been reported. Death has been reported in association with **BLEOZ** pleurodesis in seriously ill patients.

Other

Vascular toxicities coincident with the use of **BLEOZ** in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous 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 **BLEOZ** in combination with vinblastine with or without cisplatin or, in a few cases, with **BLEOZ** 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** vinblasine, hypomagnesemia, or a combination of any of these factors. Fever, chills and vomiting have been reported and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions have been reported. Malaise has been reported.

OVERDOSE

No information provided.

CONTRAINDICATIONS

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

STORAGE: Store in cool place. Protect from light.

PRESENTATION: 15 units per vial as Bleomycin Sulphate injection, IP

Manufactured in India by:

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