

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

64084

DRAFT FINAL PRINTED LABELING



Sterile Bleomycin Sulfate, USP

WARNING

It is recommended that sterile bleomycin sulfate 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. 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.

DESCRIPTION

Sterile Bleomycin Sulfate, 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.

Sterile bleomycin sulfate is a sterile lyophilizate containing bleomycin sulfate equivalent to 15 or 30 units of bleomycin. If needed, sulfuric acid is added to adjust pH to 4.5 to 6.0. It may be administered intravenously, intramuscularly or subcutaneously.

CLINICAL PHARMACOLOGY

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

In mice, high concentrations of bleomycin are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of bleomycin in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of bleomycin found in bone marrow may be related to high levels of bleomycin degradative enzymes found in that tissue.

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. In humans, 60% to 70% of an administered dose is recovered in the urine as active bleomycin.

INDICATIONS AND USAGE

Sterile bleomycin sulfate 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, gingiva, epiglottis, skin, larynx), penis, cervix, and vulva. The response to bleomycin is poorer in patients with head and neck cancer previously irradiated.

Lymphomas

Hodgkin's, reticulum cell sarcoma, lymphosarcoma.

Testicular Carcinoma

Embryonal cell, choriocarcinoma, and teratocarcinoma.

CONTRAINDICATIONS

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

WARNINGS

Patients receiving bleomycin sulfate 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 bleomycin progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended.

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

Renal or 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.

Usage in Pregnancy

Safe use of bleomycin sulfate in pregnant women has not been established.

ADVERSE REACTIONS

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.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult. The earliest symptom associated with bleomycin 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; 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. 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 (DL_{CO}) during treatment with bleomycin sulfate may be an indicator of 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.

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. Suggestive preventive measures are:

- (1) Maintain FI O₂ 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 rarely reported during bleomycin infusions. Although each patient must be individually evaluated, further courses of bleomycin do not appear to be contraindicated.

Idiosyncratic Reactions

In approximately 1% of the lymphoma patients treated with bleomycin sulfate 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 sulfate therapy in 2% of treated patients because of these toxicities.

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

Other

Vascular toxicities coincident with the use of bleomycin sulfate in combination with other antineoplastic agents have been reported rarely. 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 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.

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, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma - 0.25 to 0.50 units/kg (10 to 20 units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease—0.25 to 0.50 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 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 sulfate 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.

Administration

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

Intramuscular or Subcutaneous

Dissolve the contents of a sterile bleomycin sulfate 15 unit vial with 1 to 5 mL, 30 unit vial with 2 to 10 mL of Sterile Water for Injection, Sodium Chloride Injection or Bacteriostatic Water for Injection.

Intravenous

Dissolve the contents of the 15 unit vial with 5 mL, 30 unit vial with 10 mL or more of Sodium Chloride Injection 0.9% and administer slowly over a period of 10 minutes.

Stability

The sterile powder is stable under refrigeration (2° to 8°C) and should not be used after the expiration date is reached.

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

Procedure for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.^{1,7} There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Sterile Bleomycin Sulfate, USP

NDC 0013-1616-78 Each vial (green cap) contains sterile bleomycin sulfate equivalent to 15 units of bleomycin.

NDC 0013-1636-86 Each vial (pink cap) contains sterile bleomycin sulfate equivalent to 30 units of bleomycin.

Store under refrigeration 2° to 8°C (36° to 46°F).

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics, JAMA 1985 March 15.
3. National Study Commission on Cytotoxic Exposure-Recommendation for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia. 1983; 1:426-428.
5. Jones RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA — A Cancer Journal for Clinicians. 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990; 47:1033-1049.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm. 1986; 43:1193-1204.

PHARMACIA INC.
COLUMBUS, OHIO 43216

P106000295

February 28, 1995

NDC 0013-1616-78

Sterile Bleomycin Sulfate, USP

EQUIVALENT TO 15 UNITS BLEOMYCIN

For intravenous, intramuscular or subcutaneous use.
Store dry powder under refrigeration (2° to 8°C) (36° to 46°F).
CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for full prescribing information.
Contains bleomycin units of 15 units of bleomycin. If needed, sulfuric acid is added to adjust pH to 4.5 to 6.0.

Pharmacia
PHARMACIA INC.
COLUMBUS, OHIO 43216
NDC 0013-1616-78
15 UNITS BLEOMYCIN Sulfate, USP
1 VIAL

JUN 3 1996

APPROVED



1 VIAL
15 UNITS BLEOMYCIN
EQUIVALENT TO
Sterile Bleomycin Sulfate, USP
NDC 0013-1616-78



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Sterile Bleomycin Sulfate, USP	Sterile Bleomycin Sulfate, USP	Sterile Bleomycin Sulfate, USP	Sterile Bleomycin Sulfate, USP
<p>EQUIVALENT TO 15 UNITS BLEOMYCIN</p> <p>For intravenous, intramuscular or subcutaneous use.</p> <p>Each sterile vial contains a lyophilized bleomycin sulfate equivalent to 15 units of bleomycin. If needed, sulfuric acid is added to adjust pH to 4.5 to 6.0.</p> <p>CAUTION: Federal law prohibits dispensing without prescription.</p>	<p>STORE DRY POWDER UNDER REFRIGERATION (2° to 8°C) (36° to 46°F).</p> <p>15</p> <p>1 VIAL P106070395</p>	<p>EQUIVALENT TO 15 UNITS BLEOMYCIN</p> <p>For intravenous, intramuscular or subcutaneous use.</p> <p>Each sterile vial contains a lyophilized bleomycin sulfate equivalent to 15 units of bleomycin. If needed, sulfuric acid is added to adjust pH to 4.5 to 6.0.</p> <p>CAUTION: Federal law prohibits dispensing without prescription.</p>	<p>USUAL DOSAGE: See package insert for full prescribing information.</p> <p>15</p> <p>1 VIAL</p>
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NDC 0013-1636-86

Sterile Bleomycin Sulfate, USP

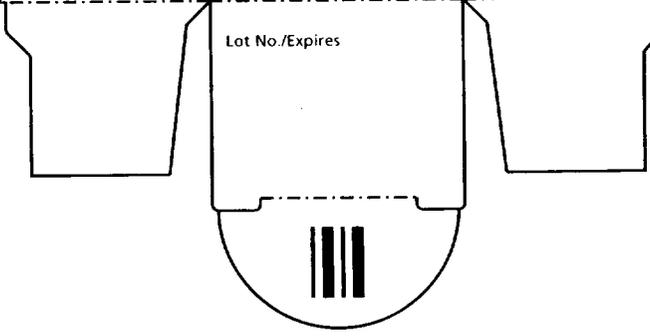
EQUIVALENT TO 30 UNITS BLEOMYCIN

For intravenous, intramuscular or subcutaneous use.
Store dry powder under refrigeration (2° to 8°C) (36° to 46°F).

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See package insert for full prescribing information.
Contains bleomycin sulfate

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1 VIAL
30 UNITS BLEOMYCIN
EQUIVALENT TO
Sterile Bleomycin
Sulfate, USP

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**Sterile Bleomycin
Sulfate, USP**

**Sterile Bleomycin
Sulfate, USP**

**Sterile Bleomycin
Sulfate, USP**

**Sterile Bleomycin
Sulfate, USP**

**EQUIVALENT TO
30 UNITS BLEOMYCIN**
For intravenous,
intramuscular or
subcutaneous use.

Each sterile vial contains a
lyophilizate of bleomycin
sulfate equivalent to 30
units of bleomycin. If
needed, sulfuric acid is
added to adjust pH to
4.5 to 6.0.

CAUTION: Federal law
prohibits dispensing without
prescription.

 Pharmacia

STORE DRY POWDER
UNDER REFRIGERA-
TION (2° to 8°C)
(36° to 46°F).

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1 VIAL

 Pharmacia

P106170395

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For intravenous,
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 Pharmacia

USUAL DOSAGE:
See package insert for
full prescribing
information.

30

1 VIAL

PHARMACIA INC.
COLUMBUS, OHIO 43216

Lot No./Expires

