

NDA 50-443/S-028
Bristol-Myers Squibb Pharmaceutical Research Institute
P.O. Box 4000
Princeton, NJ 08543-4000

AUG 25 1999

Attention: Joseph Linkewich, Pharm. D.
Director, U.S. Regulatory Liaison

Dear Dr. Linkewich:

Please refer to your supplemental new drug application dated July 15, 1998, received July 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Blenoxane (bleomycin sulfate for injection, USP).

We also refer to your amendment of August 3, 1999.

We note that this supplement was submitted as a "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c) and supersedes your April 18, 1996 final printed labeling submitted to approved supplements S024 and S025.

This supplemental new drug application provides for the addition of malaise to the ADVERSE REACTIONS section and minor editorial revisions. Your submission stated December 1, 1998 as the implementation date for the changes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted July 15, 1998). Accordingly, the supplemental application is approved effective on the date of this letter. Please submit final printed container/carton labels as soon as possible. These may be submitted as "final printed labeling for approved supplement S028."

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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If you have any questions, contact Dotti Pease, Senior Project Manager, at (301) 594-2473.

Sincerely,

Robert L. Justice, M.D.
Acting Division Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

RX only

BLENOXANE®
(bleomycin sulfate for injection, USP):
Formerly known as: sterile bleomycin
sulfate. USP

WARNING

It is recommended that BLENOXANE 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 BLENOXANE. 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 BLENOXANE.

DESCRIPTION

BLENOXANE® (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.

CLINICAL PHARMACOLOGY

Although the exact mechanism of action of BLENOXANE 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 BLENOXANE 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 BLENOXANE in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of BLENOXANE found in bone marrow may be related to high levels of BLENOXANE degradative enzymes found in that tissue.

In patients with normal renal function, 60% to 70% of an administered dose is recovered in the urine as active bleomycin. 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. It was reported that patients with moderately severe renal failure excreted less than 20% of the dose in the urine. This result would suggest that severe renal impairment could lead to accumulation of the drug in blood.

Information on the dose proportionality of bleomycin is not available.

When administered intrapleurally for the treatment of malignant pleural effusion, BLENOXANE acts as a sclerosing agent.

Following intrapleural administration to a limited number of patients (n=4), the resultant bleomycin plasma concentrations suggest a systemic absorption of approximately 45%.

The safety and efficacy of BLENOXANE 60U and tetracycline (1 gm) 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 hr. or less, no prior intrapleural therapy, no prior systemic BLENOXANE therapy, no chest irradiation and no recent change in systemic therapy. Overall survival did not differ between the BLENOXANE 60U (n=44) and tetracycline (n=41) groups. Of patients evaluated within 30 days of instillation, the recurrence rate was 36% (10/28) with BLENOXANE and 67% (18/27) with tetracycline (p=0.023). Toxicity was similar between groups.

INDICATIONS AND USAGE

BLENOXANE 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, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to BLENOXANE is poorer in patients with previously irradiated head and neck cancer.

Lymphomas

Hodgkin's Disease, non-Hodgkin's lymphoma.

Testicular Carcinoma

Embryonal cell, choriocarcinoma, and teratocarcinoma.

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

Malignant Pleural Effusion

BLENOXANE is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

CONTRAINDICATIONS

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

WARNINGS

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

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 BLENOXANE. Since these reactions 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

Pregnancy Category D:

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

There have been no studies in pregnant women. If BLENOXANE 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 BLENOXANE.

PRECAUTIONS

General

Bleomycin clearance may be reduced in patients with impaired renal function. No guidelines have been established for dose adjustments, but bleomycin should be used with extreme caution in patients with significant renal impairment.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

The carcinogenic potential of BLENOXANE in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at 0.35mg/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** section)

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 BLENOXANE therapy.

Pediatric Use

Safety and effectiveness of BLENOXANE in pediatric patients have 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.

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 BLENOXANE (bleomycin sulfate for injection, USP) has been extremely difficult. The earliest symptom associated with BLENOXANE pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, BLENOXANE-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 BLENOXANE 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 BLENOXANE 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. Suggested preventive measures are:

1. Maintain FIO_2 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 BLENOXANE infusions. Although each patient must be individually evaluated, further courses of BLENOXANE do not appear to be contraindicated.

Pulmonary adverse events which may be related to the intrapleural administration of BLENOXANE have been reported only rarely.

Idiosyncratic Reactions

In approximately 1 % of the lymphoma patients treated with BLENOXANE (bleomycin sulfate for injection, USP), 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 BLENOXANE 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 BLENOXANE have been administered and appears to be related to the cumulative dose.

Intrapleural administration of BLENOXANE has occasionally been associated with local pain. Hypotension possibly requiring symptomatic treatment has been reported infrequently. Death has been very rarely reported in association with BLENOXANE pleurodesis in these very seriously ill patients.

Other

Vascular toxicities coincident with the use of BLENOXANE 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 BLENOXANE in combination with vinblastine with or without cisplatin or, in a few cases, with BLENOXANE as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, BLENOXANE, 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.

Malaise was also reported as part of postmarketing surveillance.

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, non-Hodgkin's lymphoma, 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/in²) 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 BLENOXANE 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 BLENOXANE (bleomycin sulfate 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.

ADMINISTRATION

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

Intramuscular or Subcutaneous

The BLENOXANE 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 BLENOXANE 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

60 units of BLENOXANE is dissolved in 50—100 mL sodium chloride injection 0.9% 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 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 instillation of BLENOXANE. 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, BLENOXANE instillation may be appropriate when drainage is between 100—300 mL under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after BLENOXANE 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.

HOW SUPPLIED

BLENOXANE® (bleomycin sulfate for injection, USP) is available as follows:

NDC 0015-3010-20, 15 units per vial as bleomycin sulfate for injection, USP

NDC 0015-3063-01, 30 units per vial as bleomycin sulfate for injection, USP

Stability

The sterile powder is stable under refrigeration 2°C (36°F) to 8°C (46°F) and should not be used after the expiration date is reached.

BLENOXANE should not be reconstituted or diluted with D5W or other dextrose containing diluents. When reconstituted in D₅W and analyzed by HPLC, BLENOXANE demonstrates a loss of A₂ and B₂ potency that does not occur when BLENOXANE is reconstituted in 0.9% sodium chloride.

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

Procedures 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.

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; 253(11):1 590-1592.
3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commis-

sion 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. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK PRACTICE GUIDELINES). Am J Health-Syst Pharm 1996; 53:1669-1685.

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