

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### ***APPLICATION NUMBER:***

**050443Orig1s036**

***Trade Name:*** BLENOXANE

***Generic or Proper Name:*** bleomycin sulfate for injection, USP

***Sponsor:*** Bristol-Myers Squibb

***Approval Date:*** May 10, 2010

***Indication:*** 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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 050443Orig1s036

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**050443Orig1s036**

**APPROVAL LETTER**



NDA 50443/S036

**SUPPLEMENT APPROVAL**

Bristol-Myers Squibb  
Attention: Beatrice Anduze-Faris, M.D.  
Group Director, Mature Products  
Global Regulatory Sciences  
P.O. Box 4000 (Mailstop D12-02)  
Princeton, NJ 08543-4000

Dear Dr. Beatrice Anduze-Faris:

Please refer to your Supplemental New Drug Application (sNDA) dated January 05, 2007, received January 10, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Blenoxane (Blenoxane sulfate) sterile lyophilized bleomycin sulfate (15Unit/vial and 30Unit/vial).

We also refer to your submission on March 26, 2010, in response to our proposed changes.

This "Changes Being Effected" supplemental new drug application provides for revisions to Administration Precautions section, Stability section, REFERENCES section, and editorial revisions.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B-05  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301)796-2219.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE(S):  
Content of Labeling (Package Insert)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50443	SUPPL-36	BRISTOL MYERS SQUIBB CO PHARMACEUTICA L RESEARCH INSTITUTE	BLENOXANE

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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AMNA IBRAHIM  
05/10/2010  
For Dr Robert Justice

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**050443Orig1s036**

**LABELING**

Rx only

# **BLENOXANE<sup>®</sup>**

**(bleomycin sulfate for injection, 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<sup>®</sup> (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**

### **Mechanism of Action**

Although the exact mechanism of action of BLENOXANE 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, BLENOXANE 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/m<sup>2</sup>, both peak plasma concentration and AUC increased in proportion with the increase of dose.

Following intravenous bolus administration of 30 units of BLENOXANE 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/m<sup>2</sup> in patients following a 15 units/m<sup>2</sup> intravenous bolus dose. Protein binding of bleomycin has not been studied.

### **Metabolism**

Bleomycin is inactivated by a cytosolic cysteine proteinase enzyme, bleomycin hydrolase. 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 of bleomycin 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/m<sup>2</sup> and 23 mL/min/m<sup>2</sup>, respectively.

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 in the urine after intravenous administration.

## **Special Populations**

### **Age, Gender, and Race**

The effects of age, gender, and race on the pharmacokinetics of BLENOXANE have not been evaluated.

### **Pediatric**

Children of less than 3 years of age have higher total body clearance than in adults, 71 mL/min/m<sup>2</sup> versus 51 mL/min/m<sup>2</sup>, respectively, following intravenous bolus administration. Children of more than 8 years of age have comparable clearance as in adults.

In children with normal renal function, plasma concentrations of bleomycin decline biexponentially as in adults. 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 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 BLENOXANE has not been evaluated.

## **Drug Interactions**

### **Drugs that Can 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 concomitant cisplatin with bleomycin, total body clearance of bleomycin decreased from 39 to 18 mL/min/m<sup>2</sup> as the cumulative dose of cisplatin exceeded 300 mg/m<sup>2</sup>. Terminal half-life of bleomycin also increased from 4.4 to 6.0 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 BLENOXANE 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 BLENOXANE therapy, no chest irradiation, and no recent change in systemic therapy. Overall survival did not differ between the BLENOXANE (n=44) and tetracycline treatment (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 (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 BLENOXANE. 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

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/m<sup>2</sup> basis) on days 6 to 15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. BLENOXANE 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/m<sup>2</sup> basis) given on gestation days 6 to 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

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 BLENOXANE 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 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 0.35 mg/kg weekly (3.82 units/m<sup>2</sup> 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 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.

## **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 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 BLENOXANE 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 (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 ( $DL_{CO}$ ) 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<sub>2</sub> 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 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.

### **Idiosyncratic Reactions**

In approximately 1% of the lymphoma patients treated with BLENOXANE, 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 **WARNINGS**). 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 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 BLENOXANE 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 BLENOXANE have been administered and appears to be related to the cumulative dose.

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

## **Other**

Vascular toxicities coincident with the use of BLENOXANE 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 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 have been reported. Anorexia and weight loss 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.

## **DOSAGE AND ADMINISTRATION**

**Because of the possibility of an anaphylactoid 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 dose schedule is recommended:

**Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma**—0.25 to 0.50 units/kg (10 to 20 units/m<sup>2</sup>) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

**Hodgkin's disease**—0.25 to 0.50 units/kg (10 to 20 units/m<sup>2</sup>) 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 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:

<b>Patient CrCL (mL/min)</b>	<b>BLENOXANE Dose (%)</b>
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 patient's measured serum creatinine (Scr) values using the Cockcroft and Gault formula:

$$\text{Males} \quad \text{CrCL} = [\text{weight} \times (140 - \text{Age})] / (72 \times \text{Scr})$$

$$\text{Females} \quad \text{CrCL} = 0.85 \times [\text{weight} \times (140 - \text{Age})] / (72 \times \text{Scr})$$

Where CrCL in mL/min/1.73m<sup>2</sup>, weight in kg, age in years, and Scr in mg/dL.

### **Administration**

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

## **Administration Precautions**

Caution should be exercised when handling BLENOXANE for injection. Procedures for proper handling and disposal of anticancer drugs should be utilized. Several guidelines on this subject have been published.<sup>1-4</sup> To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing BLENOXANE for injection. If BLENOXANE 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 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**

Sixty units of BLENOXANE 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 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 to 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<sup>®</sup> (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 D<sub>5</sub>W or other dextrose containing diluents. When reconstituted in D<sub>5</sub>W and analyzed by HPLC, BLENOXANE demonstrates a loss of A<sub>2</sub> and B<sub>2</sub> potency that does not occur when BLENOXANE is reconstituted in Sodium Chloride for Injection, 0.9%, USP.

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

## **REFERENCES**

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling occupational exposure to hazardous drugs. OSHA, 1999. [http://www.osha.gov/dts/osta/otm/otm\\_vi/otm\\_vi\\_2.html](http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html)

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. 2006;63:1172-1193.
4. Polovich M, White JM, Kelleher LO, eds. 2005. Chemotherapy and biotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh, PA: Oncology Nursing Society.

Manufactured by:

Nippon Kayaku Co., Ltd.

Tokyo, Japan

Distributed by:

Bristol-Myers Squibb Company

Princeton, NJ 08543 USA

Rev April 2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**050443Orig1s036**

**OTHER REVIEW(S)**

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

## **Division of Drug Oncology Products**

**Application Number:** NDA 50443/S036

**Name of Drug:** Bleomoxane (Bleomoxane sulfate) Sterile lyophilized bleomycin sulfate (15Unit/vial and 30Unit/vial) for intravenous, intramuscular, subcutaneous, or intrapleural injection.

**Applicant:** Bristol-Myers Squibb  
Princeton, NJ

## **Material Reviewed:**

**Submission Date(s):** January 05, 2007

**Receipt Date(s):** January 10, 2007

**Submission Date of Structure Product Labeling (SPL):** January 05, 2008

## **Background and Summary**

NDA 50443 is approved for Head and Neck Squamous Cell Carcinoma, Hodgkin's Disease, non-Hodgkin's Lymphoma, Testicular Carcinoma, and Malignant Pleural Effusion. S-036 provides for revisions to the Safe Handling information: adds Safe Handling Precautions in Section Dosage & Administration subtitle Administration, Section References, as well as Signature change to remove Bristol-Myers Squibb Oncology logo. The clinical, pharmacology/toxicology and editorial revisions identified in this RPM labeling review were concurred with Ke Liu, M.D., and Amir Shahlaee, M.D. (Clinical Team) and Leigh Verbois Ph.D. and Doo Young Lee Ham, Ph.D. (Pharmacology Toxicology Review Team). It was agreed that this RPM labeling review would suffice.

This CBE-0 supplemental application was submitted to CDER's electronic document room.

The purpose of CBE S036 is to incorporate Safe Handling changes. The labeling submitted CBE S036 dated "[REDACTED]<sup>(b)(4)</sup>" was compared to the approved Label dated "Revised August 2005" from the annual report (submitted August 25, 2005). The applicant also communicated via email that Bleomycin sulfate is no longer manufactured. I requested that this information be placed in the 2008 Annual Report. The applicant did, the annual report states: "manufacturing of Bleomycin Sulfate for Injection ceased as of February 2006. The marketing of the product was discontinued at the end of 2007, and there is no finished product currently in BMS inventory. If and when, production resumes at our approved manufacturer (Nippon Kayaku, Japan), appropriate data will be supplied."

Deletions are shown as ~~strikeouts~~ and additions are shown as double underlines. The following revisions were noted.

**Package Insert**



(b) (4)

## **Conclusions**

Recommendations made from the Pharmacology Toxicology Review Team are changes which improve the labeling given that Blenoxane is teratogenic, carcinogenic, and mutagenic. The revised labeling was forwarded to Bristol Myers Squibb. Further revisions were made by, submitted March 26, 2010 (identified as "Revised April 2010") were agreed by FDA. Supplement 036 is approved, and an approval letter will be sent out.

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Lisa Skarupa, RN, MSN  
Regulatory Project Manager

Supervisory Comment/Concurrence:

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Frank Cross,  
Chief, Project Management Staff

Drafted: L. Skarupa/ 9/15/2008

Revised/Initialed: LS 10/19/2008; March 26, 2010; April 22, 2010; April 26, 2010

Finalized: xxxx

Filename: Blenoxane N50443 S\_036 RPM Labeling Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50443	SUPPL-36	BRISTOL MYERS SQUIBB CO PHARMACEUTICA L RESEARCH INSTITUTE	BLENOXANE

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/s/

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