DBL™ Bleomycin Sulfate For Injection

1. NAME OF THE MEDICINE

Bleomycin sulfate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains bleomycin sulfate as a lyophilised powder which is equivalent to 15,000 IU bleomycin activity. Each vial contains 55-70% of bleomycin A_2 and 25-32% of bleomycin B_2.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Bleomycin sulfate is an antineoplastic antibiotic which is a purified mixture of glycopeptides produced by a fermentation process employing the actinomycetes Streptoverticillium species. The bleomycin mixture contains predominantly the A_2 and B_2 peptides.

Bleomycin sulfate is a white or yellowish white or cream coloured amorphous hygroscopic powder. It is very soluble in water, slightly soluble in dehydrated alcohol, and practically insoluble in acetone and ether.

DBL Bleomycin Sulfate for Injection is a white to cream coloured lyophilised powder or plug. When reconstituted in Water for Injection, the pH of the solution is approximately 5.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bleomycin is indicated for palliation and treatment adjuvant to surgery and radiation therapy of the following neoplasms:

- Squamous cell carcinoma of the skin, head and neck and oesophagus (primary indication)
- Squamous cell carcinoma of the larynx, penis and uterine cervix
- Squamous cell carcinoma of the bronchus (response infrequent)
- Choriocarcinoma and embryonal cell carcinoma of the testis
- Advanced Hodgkin’s disease and other lymphomas
- Mycosis fungoides.

Note: Use of bleomycin after radiation therapy is less successful than use before radiation therapy.

Bleomycin is bone marrow sparing and may be used when other cytotoxic agents are contraindicated.

4.2 Dose and Method of Administration

Dosage

Initial treatment (intramuscular, intravenous or subcutaneous administration)

Total doses of over 300,000 IU should be given with great caution.

10,000 to 20,000 IU/m^2 of body surface area given weekly or twice weekly.

Alternatively, give 15,000 IU daily for 7 days followed by three weeks off-treatment and repeat twice so that a total dose of approximately 300,000 IU is administered.

Improvement of lymphomas and testicular tumours is prompt i.e. within two weeks while response by squamous cell cancers may take as long as three weeks.

A therapeutic response should be observed as the total dose approaches 150,000 IU, if this is not seen, consideration should be given to other therapy.

Note: When bleomycin is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses (see Sections 4.4 Special Warnings and Precautions for Use and 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Method of Administration

Bleomycin may be given by the intramuscular, intravenous, subcutaneous or intra-arterial routes.

Note: Because of the possibility of an anaphylactoid reaction, lymphoma patients should receive test doses of between 1-5 units, for the first two treatments. If no acute allergic reaction occurs within 4-6 hours, the balance of the dose may be given. Thereafter the regular dosage schedule may be followed, if no reaction occurs.

Directions for Reconstitution

For intramuscular or subcutaneous injection: dissolve the contents of the vial in 1-5 mL of Sterile Water for Injection or Sodium Chloride Intravenous Infusion 0.9%.

For intravenous or intra-arterial injection: dissolve the contents of the vial in 5-10 mL of diluent and administer slowly over a period of 10 minutes.

Suitable diluents are Water for Injections, Bacteriostatic Water for Injection and Sodium Chloride Intravenous Infusion 0.9%. Although Glucose Intravenous Infusion 5% has been used in the past, recent data suggests that it is not the diluent of choice, as over the concentration range of 300 to 15,000 IU/mL the content of Bleomycin A_2 + B_2 was consistently lower when Glucose Intravenous Infusion 5% was used.

Reconstituted solutions containing 150 to 15,000 IU/mL bleomycin prepared using the recommended diluents remain stable for periods of at least 24 hours when stored in the dark, at temperatures of 2-8°C or 25°C. Solutions of bleomycin sulfate in Sodium Chloride Intravenous 0.9% stored in the dark at 2-8°C for 10 days were chemically stable. However, in order to reduce the possibility of microbiological contamination, reconstituted injections should be used as soon as practicable after preparation. If storage of the reconstituted solution is necessary, store at 2-8° C for no more than 24 hours. Any unused portions must be discarded in compliance with acceptable procedures for the disposal of anticancer medicines.

Dosage Adjustment

Intra-arterial administration

Intra-arterial infusion/perfusion is employed when increased drug concentrations at the cancer site are desired. The suggested dosage schedule is 30,000 to 60,000 IU once or twice a week until the total recommended dose of 300,000 IU is reached.

Repeat treatment

In patients for whom a course of bleomycin treatment provides an initial but incomplete response, a repeat course is suggested. Patients who show superficial improvement after one course e.g., in cases of squamous cell carcinoma, may benefit from a second course of treatment to prevent recurrence.

A repeat course may be commenced after a minimum of 3-4 weeks following completion of the first course, providing no sign of pulmonary toxicity have been observed (see Section 4.3 Contraindications). A total dose of 150,000 IU for repeat treatment is recommended.

In Impaired Renal Function

As bleomycin is mostly excreted unchanged and as there is a high correlation between renal bleomycin clearance and creatinine clearance, impairment of function may require reduction in dosage and careful monitoring for toxicity. Dosage reductions of 40-75% have been recommended for patients with creatinine clearance values of ≤40 mL/min.

In Impaired Liver Function

Use adult dose with caution.

Paediatric Dose

No data available.

Geriatric Dose

Adult dose should be used with caution, particularly in patients over 70 years (see Section 4.8 Adverse Effects (Undesirable Effects)).

4.3 Contraindications

Bleomycin is contraindicated in patients with known allergy or idiosyncrasy to the drug. Bleomycin is also contraindicated in patients with acute pulmonary infection or greatly reduced lung function.

A repeat course of therapy is contraindicated in any patient who has shown any signs of pneumonitis or decreased pulmonary function (see Section 4.4 Special Warnings and Precautions for Use).

4.4 Special Warnings and Precautions for Use

It is recommended that Bleomycin 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. Patients receiving bleomycin must be observed carefully and frequently during and after therapy.

After injection, bleomycin is readily absorbed and distributed in the body, particularly in the skin, lungs and any susceptible tumour tissue, leading to possible skin and pulmonary toxicity, as well as antitumour activity.

If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related.

Pulmonary Toxicity

No single predictive monitoring test for bleomycin-induced pulmonary toxicity has been identified. Frequent physical examinations should be undertaken. Cough, basal rales and pleuritic chest pain are frequent first signs of toxicity. Dyspnoea is usually the first symptom. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related. Pulmonary function tests (especially total lung volume (TLV) and forced vital capacity (FVC)) may be of value in detecting early lung changes, although these are not always predictive of subsequent toxicity. It has been suggested that bleomycin should be discontinued if FVC decreases rapidly. Baseline and subsequent monthly evaluation of carbon monoxide diffusion capacity (DL_{CO}) are also recommended, and bleomycin should be discontinued when the DL_{CO} is less than 30-35% of the pretreatment value.

The most commonly recommended method of monitoring the onset of pulmonary toxicity is weekly chest x-rays, which should be continued up to 4 weeks after completion of treatment. However, high resolution computer tomography is a more sensitive method of detection.

Other proposed methods of monitoring pulmonary toxicity include ^{99m}-Technetium scans and measurement of ESR, which has been found to increase prior to the development of symptomatic toxicity. However, the usefulness of these methods as predictors of development of toxicity have not been proven in clinical practice.

A method suggested to lower the incidence of pulmonary toxicity is the continuous intravenous administration of bleomycin.

- Anaesthesia

  Because of bleomycin's effects on lung tissue, patients who have received the drug are at increased risk of developing pulmonary toxicity when oxygen is administered during surgery. Long exposure to very high concentrations of oxygen is a known cause of lung damage, but after administration of bleomycin, lung damage can occur at oxygen concentrations lower than those usually considered safe. Therefore to minimize the risk in patients undergoing surgery who have received bleomycin the following is recommended:

  (i) FI O_2 concentration should be maintained at approximately that of room air (25%) during surgery and the post-operative period.

  (ii) Fluid replacement should be carefully monitored, with emphasis on administration of colloid rather than crystalloid.

- Pneumonitis

  Pneumonitis due to bleomycin has been treated with corticosteroids in a effort to prevent progression to pulmonary fibrosis. Infectious pneumonitis should receive appropriate antibiotic therapy.

- Lung cancer

  Bleomycin should be used with extreme caution in patients with lung cancer as these patients show an increased incidence of pulmonary toxicity.

- Compromised pulmonary function due to disease other than malignancy

  Bleomycin should be used with extreme caution in patients with compromised pulmonary function as pulmonary toxicity may be particularly dangerous in these patients (see Section 4.3 Contraindications).

- Previous cytotoxic or radiation therapy (especially chest irradiation); smokers

  Bleomycin should be used with caution in patients who have had previous cytotoxic drug therapy or radiation therapy (especially chest irradiation), and in patients who smoke, since the risk of pulmonary toxicity may be increased in these patients.

- Cisplatin

  Cisplatin-induced renal function impairment may result in delayed clearance and bleomycin toxicity even at low doses. An increased incidence of bleomycin-induced pulmonary toxicity has been observed when these two agents are administered as part of an antineoplastic treatment regimen. Dosage reduction may be required (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

- Granulocyte colony stimulating factor (G-CSF)

  It has been suggested that concomitant administration of G-CSF and bleomycin may increase the risk of bleomycin-induced pulmonary toxicity, especially at higher doses,

although this has not been confirmed in clinical trials. If G-CSF is added to bleomycin-containing treatment regimens, patients should be closely observed for signs of pulmonary toxicity (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

- Combination therapy

  Pulmonary toxicity may be observed at lower doses of bleomycin when bleomycin is administered as part of a multi-drug treatment regimen. Patients should be closely monitored for signs of pulmonary toxicity (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

- Cumulative dose

  Pulmonary toxicity is more common in patients receiving a total dose of more than 400,000 IU.

Idiosyncratic Reactions

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of patients treated with Bleomycin (5% of lymphoma patients). Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

- Lymphoma patients

  All lymphoma patients should receive test doses of bleomycin before initiating full-dose therapy. (see Section 4.8 Adverse Effects (Undesirable Effects)).

Renal or Hepatic Toxicity

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.

Use in Renal Impairment

Bleomycin should be used with extreme caution in patients with severely impaired renal function (see Section 4.2 Dosage and Method of Administration - Dosage Adjustment).

Use in the Elderly

Patients over 70 years of age should be closely observed for signs of pulmonary toxicity due to bleomycin therapy (see Section 4.8 Adverse Effects (Undesirable Effects)).

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Pharmacodynamic interactions

- Anaesthetics, general, and oxygen

  Use in patients previously treated with bleomycin may result in rapid pulmonary deterioration, since bleomycin causes sensitisation of lung tissue to oxygen.

- Radiation therapy

  Radiation therapy, especially to the chest area, either prior to, during, or after bleomycin therapy may result in increased bleomycin toxicity. Dosage adjustment may be necessary.

- Antineoplastic agents

  Concurrent use may result in increased bleomycin toxicity, or in occurrence of pulmonary toxicity at lower doses of bleomycin (see Section 4.4 Special Warnings and Precautions for Use).

- Combination therapy

  Pulmonary toxicity may be observed at lower doses of bleomycin when bleomycin is administered as part of a multi-drug treatment regimen. Patients should be closely monitored for signs of pulmonary toxicity (see Section 4.4 Special Warnings and Precautions for Use).

- Granulocyte colony stimulating factor (G-CSF)

  It has been suggested that concomitant administration of G-CSF and bleomycin may increase the risk of bleomycin-induced pulmonary toxicity, especially at higher doses, although this has not been confirmed in clinical trials. If G-CSF is added to bleomycin-containing treatment regimens, patients should be closely observed for signs of pulmonary toxicity (see Section 4.4 Special Warnings and Precautions for Use).

Pharmacokinetic interactions

- Cisplatin

  Cisplatin-induced renal function impairment may result in delayed clearance and bleomycin toxicity even at low doses. An increased incidence of bleomycin-induced pulmonary toxicity has been observed when these two agents are administered as part of an antineoplastic treatment regimen. Dosage reduction may be required (see Section 4.4 Special Warnings and Precautions for Use).

- Digoxin

  Serum levels of Digoxin may be reduced and its actions may be decreased. It is thought that drug-induced alterations of the intestinal mucosa may be involved in the reduced GI absorption.

- Phenytoin

  Serum concentrations of phenytoin may be decreased due to decreased absorption or increased metabolism of Phenytoin.

4.6 Fertility, Pregnancy and Lactation

Effects on Fertility

The effects of bleomycin on fertility are not known.

Use in Pregnancy - Pregnancy Category D

Category D: *Bleomycin has caused, is suspected to have caused or may be expected to cause, an increase incidence of human fetal malformations or irreversible damage. It may also have adverse pharmacological effects.*

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

Use in Lactation

It is not known whether bleomycin is excreted in breast milk. Due to the potential for serious adverse effects in infants, it is recommended that breastfeeding is discontinued prior to administration of bleomycin sulfate to the mother.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Serious or Life-threatening Effects

Pulmonary Toxicity

The most serious toxicity of Bleomycin is a subacute or chronic pneumonitis that progresses to interstitial fibrosis and may be fatal. This occurs in approximately 10% of treated patients, about 1% of whom have died of pulmonary fibrosis. Pulmonary toxicity is both age and dose related, being more common in patients over 70 years of age and in those receiving over 400,000 IU total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Also, when used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

This toxicity is frequently seen in those with underlying lung disease such as emphysema and in those previously treated with pulmonary or mediastinal irradiation.

The identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult. The clinical symptoms and x-ray findings of bleomycin pulmonary toxicity are not easily distinguished from other syndromes commonly observed in cancer patients, including progressive metastatic tumour (especially lymphangitic tumour), infectious processes such as *Pneumocystis carinii* or cyto-megalovirus, or radiation injury.

The first symptoms to appear are dyspnoea, with cough, and low grade fever, commonly occurring 4-10 weeks after initiation of therapy, although the time of onset of pulmonary toxicity may vary from during therapy to up to six months after the cessation of therapy.

The microscopic tissue changes due to bleomycin toxicity are frequently present as 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 non-specific and are similar to the changes produced in radiation pneumonitis, pneumocystic pneumonitis, and at times reaction to long standing malignant pulmonary disease.

Pulmonary function tests have revealed some alteration in the pulmonary status such as decreased total lung volume and decreased vital capacity, but these tests have proved to be of limited value in predicting pulmonary fibrosis. It has been suggested that Bleomycin should be discontinued if forced vital capacity decreases rapidly.

Concurrent or prior lung irradiation will also predispose patients to increased pulmonary toxicity.

Pulmonary toxicity is seen more commonly in smokers.

Idiosyncratic Effects

Hypersensitivity reactions consisting of hypotension, fever, chills, mental confusion and wheezing have occurred in approximately 1% of patients receiving bleomycin.

This idiosyncratic reaction occurs mainly in lymphoma patients (5%), may be immediate or delayed for several hours, and usually occurs after the first or second dose. The reaction has resulted in death. Treatment of anaphylactoid reactions is supportive and symptomatic and may include volume expansion, vasopressor therapy, antihistamines, and corticosteroids.

Cardiovascular

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy

(haemolytic – uremic syndrome) or cerebrovascular arteritis. Acute chest pain syndrome, acute pericarditis, fulminant fatal hyperpyrexia and fulminant, fatal angioedema have been reported.

More Common Effects

Body as a whole: Fever, chills and headache frequently follow parenteral administration of bleomycin (20-50%). These reactions have been reported to occur most frequently with large single doses and occur within a few hours of administration lasting 4-12 hours. Usually, febrile reactions become less frequent with continued use of the drug but may occur sporadically and re occur later in the treatment course.

Gastrointestinal: Anorexia, nausea and vomiting (20-50%) (anorexia and weight loss may persist after discontinuing therapy), tiredness.

Mucocutaneous (50%): Hypoesthesia which may progress to hyperesthesia, urticaria, erythematous swelling, tenderness, pruritis, hyperpigmentation (particularly in those areas subject to friction or pressure and in skin folds, nail cuticles, scars, and I.M. injection sites), patchy hyperkeratosis, alopecia, ichthyosis, rash, striae, vesiculation, peeling, and bleeding, mucositis, stomatitis, ulcerations of the tongue and lips. This toxicity is usually evident within 1-3 weeks following initiation of therapy and appears to be reversible and dose related, usually after 150,000 to 200,000 IU of bleomycin has been administered and, in general, is related to total cumulative dose. In 0.2% of patients it was necessary to discontinue treatment because of this toxicity.

When bleomycin is administered intra-arterially, dermal lesions are most common in the region supplied by the artery used. The incidence of mucocutaneous adverse events is increased when bleomycin sulfate is given in combination with radiotherapy to head and neck.

Less Common Effects

Body as a whole: Idiosyncratic reactions occurring in 1% of patients (5% of lymphoma patients) (see Serious or Life-threatening Effects).

Cardiovascular: Diverse vascular toxicities (see Serious or Life-threatening Effects), hypotension (more common after intra-pleural administration), sudden onset of an acute chest pain syndrome, suggestive of pleuropericarditis (although each patient must be individually evaluated, further courses of bleomycin do not appear to be contraindicated), occular haemorrhage.

There are isolated reports of Raynaud's phenomenon occurring in patients treated with a combination of bleomycin and vinblastine with or without cisplatin, or, in a few cases, with bleomycin as a single agent. It is currently unknown if the cause of the Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, cisplatin-induced hypomagnesaemia or a combination of any or all of these.

Central nervous system: CNS toxicity is rare, but monitoring is advised. Disorientation and aggressive behaviour have been reported.

Haematologic: Thrombocytopenia, leukopenia, slight depression of haemoglobin levels. Bleomycin does not frequently produce serious bone marrow toxicity.

Hepatic: Liver toxicity beginning as deterioration in liver function tests has been reported infrequently.

Injection site: Pain at injection site, phlebitis, other local reactions.

Renal: Renal toxicity beginning as deterioration in renal function tests has been reported infrequently.

Haematuria and cystitis have been reported.

Respiratory: Pulmonary toxicity (10%) (see Serious or Life-threatening Effects)

4.9 Overdose

Symptoms

There has been no reported case of overdosage. The acute reaction would probably include hypotension, fever, rapid pulse and general symptoms of shock.

Treatment

There is no specific antidote for Bleomycin overdosage. Treatment should be symptomatic and supportive. In the event of respiratory complications treatment with a corticosteroid may be beneficial and the administration of a broad spectrum antibiotic is advisable. Bleomycin is probably not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Although the precise mechanism of action of bleomycin is not fully known, it is thought that the primary action is to produce single and double-strand breaks in DNA, leading to inhibition of cell division and growth, and inhibition of DNA synthesis in the cells.

Bleomycin is probably most effective against cells in the M and G_2 (premitotic) phase of the cell cycle. Bleomycin has not been shown to have an immunosuppressive effect *in vitro* and shows no significant inhibition of immune response in patients treated with the drug.

Bleomycin-inactivating enzyme has been detected in both normal and malignant cells and is particularly prominent in liver. The enzyme is not found in lung or skin, two normal tissues sensitive to bleomycin action.

Clinical Trials

No data available.

5.2 Pharmacokinetics Properties

Absorption

Bleomycin is well absorbed in animals upon parenteral administration. Intramuscular injection of 15 units in man resulted in a maximum serum concentration of 1 milliunit/mL thirty minutes after administration. Intravenous injection of 15 units in man resulted in a maximum serum concentration of 3.3 milliunits/mL.

Distribution

In mice, bleomycin diffusing from the blood produces high concentrations in the skin, lungs, kidneys, peritoneum, lymphatic system and susceptible tumour tissue if present. Bleomycin crosses the placenta, but does not cross the blood brain barrier. Equilibrium dialysis and gel permeation experiments suggest that less than 1.0% of the drug is protein-bound after incubation with normal human serum *in vitro*.

Metabolism

The majority of a bleomycin dose is not readily metabolised. The highest rate of metabolism occurs in the liver and gastrointestinal tract. A lower rate of metabolism also occurs in skin, lungs, kidneys, muscle and serum. The products of bleomycin metabolism are not known.

Excretion

Bleomycin is primarily excreted in the urine. After intravenous injection an average of 40% of the administered dose is recovered unchanged in the urine within 24 hours. After IM injection 20% is recovered in the urine after 6 hours. The plasma half-lives have varied from 15-60 minutes in patients with normal renal function following intravenous administration. The serum half-life is prolonged in patients with renal dysfunction. In one patient with severe renal dysfunction the biological half-life was 21 hours when the creatinine clearance was 10.7 mL/min, and 13 hours when the creatinine clearance was 15.2 mL/min. There were undetectable serum levels of bleomycin 72 hours after the intravenous dose.

5.3 Preclinical Safety Data

Genotoxicity

Bleomycin is mutagenic in both *in vitro* and *in vivo* test systems.

Carcinogenicity

It is not known whether bleomycin is carcinogenic in humans. However, an increased incidence of nodular hyperplasia was noted in F344/N male rats with lung cancer induced by nitrosamines, after bleomycin treatment. In another study where bleomycin was administered subcutaneously to rats at a dose of 0.35 mg/kg weekly (or about 30% the recommended human dose), necropsy findings included dose related injection site fibrosarcomas and various renal tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Water for injection

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

Refer to outer carton for expiration date.

6.4 Special Precautions for Storage

Store below 25°C. Protect from light.

6.5 Nature and Contents of Container

DBL Bleomycin Sulfate for Injection is available in vials containing 15,000 IU of bleomycin.

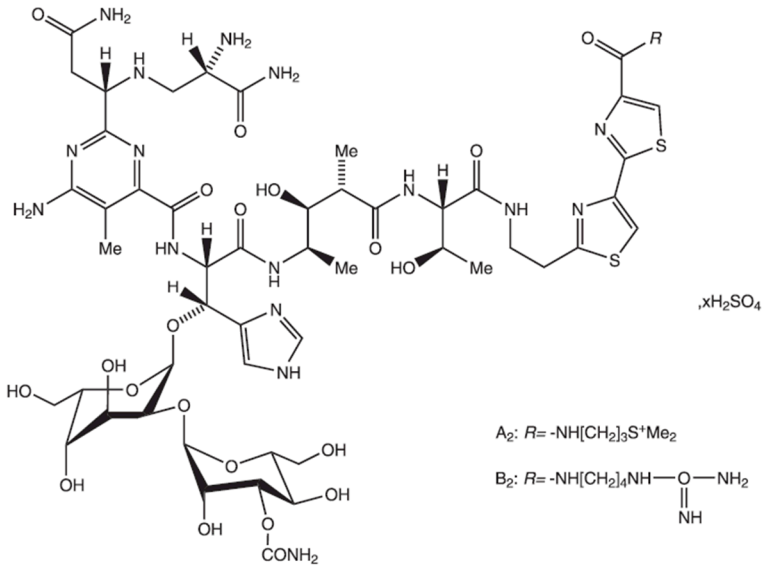
6.6 Special Precautions for Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical Structure

The structure of bleomycin sulfate is shown below:



CAS Number

9041-93-4.

7. NAME AND ADDRESS OF PRODUCT OWNER

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