

DBL[®] BLEOMYCIN SULFATE FOR INJECTION

Name of medicine

Bleomycin sulfate

Presentation

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. Each vial contains bleomycin sulfate as a lyophilised powder, which is equivalent to 15,000 IU (15 units USP) bleomycin activity. Each vial contains 55-70% of bleomycin A₂ and 25-32% of bleomycin B₂.

Uses

Actions

Bleomycin sulphate 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.

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.

When administered intrapleurally for the treatment of malignant pleural effusion, bleomycin acts as a sclerosing agent. Following intrapleural administration the resultant bleomycin plasma concentrations suggest a systemic absorption rate of approximately 45%.

Pharmacokinetics

In mice, high concentrations of bleomycin are found in the skin, lungs, kidneys, peritoneum and lymphatics. Tumour cells of the skin and lungs have been found to have high concentrations of bleomycin in contrast to the low concentrations found in haematopoietic 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 > 35mL 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. Protein binding of bleomycin is less than 1%.

An association between decreased renal function and enhanced bleomycin-related toxicities has been reported. Pharmacokinetic/pharmacodynamic relationships suggest that enhancement of toxicity is a consequence of reduced renal clearance of bleomycin resulting in prolonged elimination half-life and increased area-under-the-plasma-concentration-vs.-time-curve compared to patients with normal renal function. Dosage reductions of 40-75% have been recommended for patients with creatinine clearance values ≤ 40 mL/min.

Indications

DBL[®] Bleomycin Sulfate for Injection 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 sulfate is poorer in patients with head and neck cancer previously irradiated.

Lymphomas: Hodgkin's disease and non-Hodgkin's lymphoma.

Testicular Carcinoma: Embryonal cell, choriocarcinoma, and teratocarcinoma.

DBL[®] Bleomycin Sulfate for Injection is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusion. Single dose instillation is generally sufficient.

Dosage and administration

Dosage

Because of the possibility of anaphylactoid reaction, lymphoma patients should be treated with 2 000 international units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedules are recommended:

Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma: 250 to 500 international units/kg (10,000 to 20, 000 international units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease: 250 to 500 international units/kg (10,000 to 20,000 international units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Pulmonary toxicity of bleomycin sulfate appears to be dose-related with a striking increase when the total dose is over 400,000 international units. Total doses over 400,000 international 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.

Improvements of Hodgkin's disease and testicular tumours is prompt and noted within two weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as three weeks before any improvement is noted.

Administration:

DBL[®] Bleomycin Sulfate for Injection may be given by the intramuscular, intravenous, subcutaneous or intrapleural routes.

Intramuscular or Subcutaneous: Dissolve the contents of a DBL[®] Bleomycin Sulfate for Injection vial in 1 to 5mL of Sterile Water for Injection, Sodium Chloride for Injection, or Bacteriostatic Water for Injection.

Intravenous: Dissolve the contents of the vial in 5mL or more of a solution suitable for injection, e.g. physiologic saline, and administer slowly over a period of ten minutes.

Malignant Pleural Effusion - 60,000 international units administered as a single dose bolus intrapleural injection.

For intrapleural administration dissolve 60,000 international units in 50-100 mL sodium chloride injection 0.9%, and administer through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The thoracostomy tube is then clamped. The patient should be moved from the supine to the left and right lateral position several times during the next four hours. The clamp is then removed and suction re-established.

The intrapleural injection of topical anaesthetics or systemic narcotic analgesia is generally not required.

As bleomycin is mostly excreted unchanged and as there is a high correlation between renal bleomycin clearance and creatinine clearance, modification of dose has been suggested for impairment of renal function. Dosage reductions of 40-75% have been recommended for patients with creatinine clearance values of ≤ 40 mL/min.

Contraindications

DBL[®] Bleomycin Sulfate for Injection is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

Warnings and precautions

Patients receiving Bleomycin Sulfate for Injection 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 sulfate progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent x-rays are recommended. Pulmonary toxicity may occur up to 1 month after Bleomycin Sulfate for Injection is discontinued.

Idiosyncratic reactions similar to anaphylaxis have been reported in 6% of lymphoma patients treated with bleomycin sulfate, and in approximately 1% of other patients. 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.

Gonadal suppression may occur and may be irreversible.

Pregnancy and Lactation

Use of bleomycin sulfate in pregnant women is not recommended as bleomycin sulfate has been shown to be teratogenic in mice.

It is not known if bleomycin sulfate 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 from bleomycin sulfate, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machines

Bleomycin Sulfate may be likely to produce minor or moderate adverse effects that may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

Other

The carcinogenic potential of bleomycin sulfate in humans is unknown. Given its mechanism of action, it should be considered to be a possible carcinogen in man. Bleomycin has been shown to be mutagenic in both *in vitro* and *in vivo* test systems. Bleomycin is teratogenic in rats and mice given the drug during organogenesis. The effects of bleomycin sulfate on fertility have not been established.

Adverse effects

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 400,000 international units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Pulmonary complications are more likely in smokers, following general anaesthesia or radiotherapy. Mortality may be as high as 10% in patients who have received pulmonary irradiation.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to bleomycin sulfate has been extremely difficult. The earliest symptom associated with bleomycin sulfate pulmonary toxicity is dyspnoea. The earliest sign is fine rales.

Radiographically, bleomycin sulfate-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 sulfate toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous oedema, 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, e.g. similar changes are seen in radiation pneumonitis, pneumocystic pneumonitis,

To monitor the onset of pulmonary toxicity, x-rays 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 pre-treatment value.

Because of bleomycin's sensitisation of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in any clinical situation. 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 than usually would be considered safe. Suggested preventive measures are: (1) Maintain $FI O_2$ at concentrations approximating that of room air (25%) during surgery and the post-operative period. (2) Carefully monitor fluid replacement, focusing more on colloid administration than crystalloid administration.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during bleomycin sulfate infusions. Although each patient must be individually evaluated, further courses of bleomycin sulfate do not appear to be contraindicated.

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

Idiosyncratic Reactions: In approximately 6% of the lymphoma patients treated with bleomycin sulfate and in approximately 1% of other patients, an idiosyncratic reaction, similar clinically to anaphylaxis, 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.

Skin 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, pruritis, 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. It usually develops in the 2nd and 3rd week of treatment after 150,000 to 200,000 international units of bleomycin sulfate have been administered and appears to be related to the cumulative dose.

Other: Fever, chills, and vomiting are frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumour site, phlebitis, and other local reactions have been reported infrequently.

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 cerebrovascular arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with bleomycin sulfate in combination with vinblastine with or without cisplatin or, in few cases, with bleomycin sulfate 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 sulfate, vinblastine, hypomagnesaemia, or a combination of any of these factors.

Intrapleural administration of bleomycin sulfate 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 bleomycin sulfate pleurodesis in these very seriously ill patients.

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 **PRECAUTIONS**).
- 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 **PRECAUTIONS**).
- 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 **PRECAUTIONS**).

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 **PRECAUTIONS**).
- 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.

Overdosage

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.

Pharmaceutical precautions

Directions for reconstitution

For intramuscular or subcutaneous injection: dissolve the contents of the vial in 1-5mL 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 5-10mL 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 (0.3 - 15units USP) /mL the content of Bleomycin A₂ + B₂ was consistently lower when Glucose Intravenous Infusion 5% was used.

Reconstituted solutions containing 150 to 15,000 IU (0.15 - 15units USP)/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 drugs.

Special Precautions for Storage

Store below 25°C. Protect from light.

Medicine classification

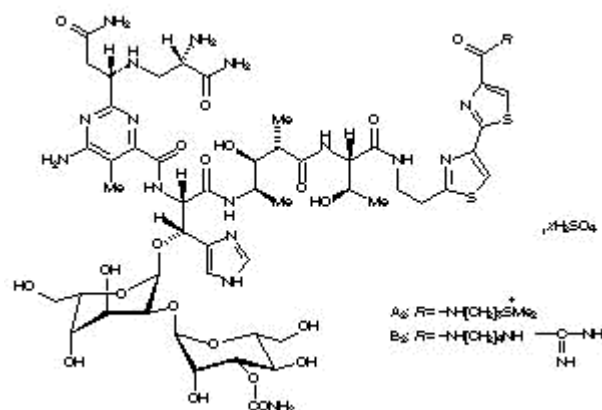
Prescription Medicine.

Package quantities

DBL[®] Bleomycin Sulfate for Injection is available in vials containing 15,000 IU (15 units USP) of bleomycin.

Further information

Bleomycin sulfate is an antineoplastic antibiotic which is a purified mixture of glycopeptides produced by a fermentation process employing the actinomycetes *Streptovercillium* species. The bleomycin mixture contains predominantly the A₂ and B₂ peptides. The CAS number of bleomycin sulfate is 9041-93-4. The structure of bleomycin sulfate is shown below:



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.

Name and address

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