For the use only of a Registered Medical Practitioner/ Oncologist or a Hospital or a Laboratory

Bleomycin Injection IP 15 Units

BLEOSTED 15 ब्लेओस्टेड

Rx Only

COMPOSITION

BLEOSTED 15

Bleomycin Injection IP 15 Units	
Each Sterile lyophilized vial contains	
Bleomycin Sulphate IP equivalent to	
Bleomycin Activity	15 Units
Mannitol IP	50 mg
Sodium Hydroxide IP	q.s.
Hydrochloric acid IP	q.s.

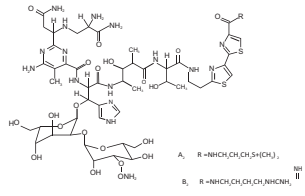
DESCRIPTION

Bleomycin Injection IP 15 Units is a white to off white colored lyophilized cake or discontinuous powder or aggregates of free flowing powder in 5mL vials.

Bleomycin Injection is a mixture of cytotoxic glycopeptides antibiotics isolated from a strain of streptomyces verticillus. It is freely soluble in water.

Its chemical name is N′-[3-(dimethylsul-phonio)propyl]bleomycin-amide (bleomycin A_2) and N′-[4-(guaniodobutyl)]bleomycin-amide (bleomycin B_2). (Main component: Bleomycin A_2, in which R is $[CH_3]_2S+CH_2CH_2CH_2$-)

The molecular formula of bleomycin A_2 is $C_{55}H_{84}N_{17}O_{21}S_3$ and a calculated molecular weight of 1414. The molecular formula of bleomycin B2 is $C_{55}H_{84}N_{20}O_{21}S_2$ and a calculated molecular weight of 1425. The structural formula of bleomycins A_2 and B_2 are shown below.



CLINICAL PHARMACOLOGY

Mechanism of Action

The exact mechanism of action of Bleomycin is unknown. Available data indicates that Bleomycin acts by 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. Bleomycin has been shown to cause cell cycle arrest in G2 and in mitosis.

Pharmacokinetics

Absorption: Bleomycin is rapidly absorbed following either intramuscular (IM) or subcutaneous (SC) administration reaching peak plasma concentrations in 30 to 60 minutes. Systemic bioavailability of bleomycin is 100% and 70% following IM and SC administrations, respectively, compared to intravenous bolus administration. Following IM doses of 1 to 10 units/m^2, both peak plasma concentration and AUC increased in proportion with the increase of dose. Following IV bolus administration of 30 units of bleomycin 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 two 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^2 in patients following a 15 units/m^2 IV 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.

Excretion: The primary route of elimination is via the kidneys. About 65% of the administered IV dose is excreted in urine within 24 hours. Total body clearance and renal clearance averaged 51 mL/min/m^2 and 23 mL/min/m^2, 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 IV administration.

INDICATIONS

Bleomycin Injection IP 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 Bleomycin 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.

CONTRAINDICATION

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

WARNINGS

Pulmonary Toxicity

Patients receiving Bleomycin Injection must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of pulmonary function. Pulmonary toxicities occur in 10% of treated patients. In some patients the nonspecific pneumonitis induced by Bleomycin Injection progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. 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 Bleomycin Injection. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses.

Renal and Hepatic Toxicity

Renal or hepatic toxicity, beginning as 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: Bleomycin can cause fetal harm when administered to a pregnant woman. There have been no studies in pregnant women. If Bleomycin 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 Bleomycin Injection.

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 Bleomycin may be required in these patients than those with normal renal function.

Dimensions: 90 x 260 mm

Pantone Colours: 1

Pantone Black C

Carcinogenesis, Mutagenesis and Impairment of Fertility
The carcinogenic potential of Bleomycin 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^2 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.

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 Bleomycin therapy.

Pediatric Use
Safety and effectiveness of Bleomycin in pediatric patients have not been established.

Geriatric Use
Pulmonary toxicity is more common in patients older than 70 years than in younger patients. Greater sensitivity of some older individuals has been reported. Bleomycin is 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.

DRUG INTERACTIONS
Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. Gemcitabine: May enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. Trastuzumab may enhance the neutropenic effect of Immunosuppressants. Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines.

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^2 as the cumulative dose of cisplatin exceeded 300 mg/m^2. 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.

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.

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

Hodgkin's Disease- 0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of Bleomycin appears to be dose-related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When Bleomycin for Injection 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.

Intramuscular or Subcutaneous
The Bleomycin injection 15 units vial should be reconstituted with 1 to 5 mL of Sterile Water for Injections, IP, Sodium Chloride Injection, 0.9%, IP, or Sterile Bacteriostatic Water for Injections, IP.

Intravenous
The contents of the 15 units vial should be dissolved in 5 mL of Sodium Chloride Injection, 0.9%, IP, and administered slowly over a period of 10 minutes.

Handling and Disposal
To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing Bleomycin Injection. All standard procedures applicable for proper handling of anticancer agents should be considered.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

OVERDOSE:
There is no antidote for overdoses of Bleomycin Injection .

STORAGE
Store the vials in the original carton between 2°C and 8°C (36°F to 46°F). Protect from light.

SHELF LIFE
24 Months

HOW SUPPLIED
BLEOSTED® IS
Bleomycin Injection IP 15 Units
Each sterile single dose lyophilized vial, individually packed in a carton.

Marketed by:

HALSTED PHARMA PRIVATE LIMITED,
Ground floor, Plot No.25-HIG, Survey No.912P, 913P, 941P, 944P, 945 to 962 and 964P, Phase XV, KPHB Colony, Kukatpally, Medchal - Malkajgiri District, Telangana State, India.
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Manufactured by:
HALSTED PHARMA PRIVATE LIMITED,
At: Village Gaunspura, Bhattain Road, Hambran, District Ludhiana-141008.