- ANTINEOPLASTIC ANTIBIOTIC -

BLEOCIN

<Bleomycin Hydrochloride for Injection>
– Abbreviation: BLM –

Powerful drug, Designated drug and Prescription-only drug*

* Caution: Use only pursuant to the prescription or directions of a physician, etc.

Storage
1. Store at room temperature (25 ℃ or below). 2. Keep out of reach of children.

	5 mg (potency) **15 mg (potency)**
International birth date	December 1968 (Japan)

Expiration date
2 years (The expiration date should be indicated on vial and the package).

Precaution For Handling
1. After reconstitutions, use as promptly as possible. 2. Avoid contact with the skin.

WARNING

Such serious pulmonary manifestation as interstitial pneumonia and pulmonary fibrosis, etc. may develop as a result of the administration of BLEOCIN, with occasional fatal outcome. Therefore, BLEOCIN must be administered only in those cases that are thought appropriate to receive BLEOCIN and a physician should keep the patient under observation during the administration of BLEOCIN and for a period (approximately 2 months) after the completion of administration. Particularly, administration of BLEOCIN to the elderly of age of 60 or over or patients with underlying diseases in the lung should only be performed after full consideration of "PRECAUTIONS".
Administration should be discontinued immediately on appearance of the initial symptoms of exertional dyspnea, fever, cough, crepitation (rale), abnormal chest X-ray findings and abnormalities of A-aDo_2, Pao_2 or DLco, etc., and appropriate measures should be taken.

CONTRAINDICATIONS (BLEOCIN is contraindicated in the following patients.)

(1) Patients with serious pulmonary function impairment or with chest X-ray findings suggesting diffuse fibrotic changes or any other remarkable changes. [Pulmonary function impairment or fibrotic lesions, etc. may deteriorate.]
(2) Patients with a history of hypersensitivity to this or a similar drug (peplomycin).
(3) Patients with serious renal function disorder. [Since excretion function is lowered, such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]
(4) Patients with serious heart disease. [Since cardiovascular function is lowered, such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]
(5) Patients with serious heart disease. [Since cardiovascular function is lowered, such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]
(5) Patients treated with radiation on the chest and around the chest [See 3. Drug Interactions in "PRECAUTIONS" section.]

DESCRIPTION

1. Composition

BLEOCIN contains the following ingredient per vial.

Ingredient	Active ingredient	Content per vial
	Bleomycin hydrochloride	5 mg (potency)
		15 mg (potency)

2. Product Description

BLEOCIN is white to yellowish white lyophilized product for injection.

Ingredient/content per vial	pH	Osmotic pressure ratio
5 mg (potency)	4.5-6.5	approx. 1
15 mg (potency)	4.5-6.5	approx. 1

pH: The pH value of a solution prepared by reconstituting the respective vial contents with distilled water for injection into a 5 mg (potency)/mL solution.
Osmotic pressure ratio: Ratio of the osmolarity between a solution of the respective vial contents in 5 mL of physiological sodium chloride and that of physiological sodium chloride solution.

INDICATIONS

Skin cancer, head and neck cancer (maxillary cancer, tongue cancer, lip cancer, pharyngeal cancer, laryngeal cancer, oral cavity cancer, etc.), lung cancer (especially, primary or metastatic squamous cell carcinoma), esophageal cancer, malignant lymphoma (reticulum cell sarcoma, lymphosarcoma, Hodgkin's disease, etc.), uterine cervical cancer, neuroglioma, and thyroid cancer.

DOSAGE AND ADMINISTRATION

1. Intravenous Injection

Dissolve 15-30 mg (potency) of Bleomycin hydrochloride in about 5-20 mL of a solvent suitable for intravenous injection such as physiological sodium chloride solution or dextrose solution, etc., and inject intravenously at a slow rate. In case of high fever, reduce the dose to 5 mg (potency) or less.

2. Intramuscular and Subcutaneous Injection

Dissolve 15-30 mg (potency) of Bleomycin hydrochloride in about 5 mL of a suitable solvent such as physiological sodium chloride solution, etc. and inject intramuscularly or subcutaneously.

In the case of subcutaneous injection into the area adjacent to the lesion(s), the concentration of Bleomycin hydrichloride is 1 mg (potency)/mL or less.

3. Intra-arterial Injection

Dissolve 5-15 mg (potency) of Bleomycin hydrochloride in a solvent suitable for injection such as physiological sodium chloride solution or dextrose solution, etc., and administer by one-shot intra-arterial injection or by continuous intra-arterial infusion.

4. Frequency of Injection

As a general rule, BLEOCIN is injected twice a week. This dose may be increased to once a day (every day) or decreased to once a week, depending on the patients' condition.

5. Total Dose

Total dose of Bleomycin hydrochloride is determined by tageting a disappearance of tumor(s), but should not exceed 300 mg (potency)

<Precautions>

(1) There is significant individual variation in the appearance of adverse reactions, and since adverse reactions can appear even with relatively small doses, it is important to be fully cognizant of "PRECAUTIONS" concerning its use.
It is necessary to begin with a low dosage, in relation to the condition of the patient and the disease.

(2) The total dosage should not be over 300 mg (potency). Furthermore, in case of multi-route administration, it is necessary to consider the resulting additive dosage.

(3) In cases that have received peplomycin, as a general rule, the amount of that drug administered must be included in the computation of the overall dosage of Bleomycin.

PRECAUTIONS

1. Careful Administration (BLEOCIN should be administered with care in the following patients. The dosage should be reduced or the intervals between administrations of the drug should be prolonged, based on clinical observation of the patient.)

(1) Patients with a history of, or accompanied by pulmonary dysfunction.
[Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]

(2) The elderly of age of 60 or over
[Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]

(3) Patients with renal dysfunction.
[Adverse reactions may occur strongly.]

(4) Patients with heart disease.
[Adverse reactions may occur strongly.]

(5) Patients receiving, or having received radiotherapy over the chest.
[Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. may occur.]

(6) Patients with hepatic dysfunction.
[Adverse reactions may occur strongly.]

(7) Patients with varicella.
[Fatal systemic dysfunctions may occur.]

2. Important Precautions

(1) Interstitial pneumonia or pulmonary fibrosis

Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis may occur. It is important to keep the patient under sufficient observation [see 2) below] and be aware that the crepitation (rale) can be an early sign of these conditions. If any abnormality is noted, administration should be immediately discontinued, adrenal cortex hormones should be administered for the treatment of idiopathic pulmonary fibrosis and a suitable antibiotic for the prevention of secondary infection should be also given.

1) In patients with underlying disease in the lung or in the elderly of age of 60 or over, interstitial pneumonia or pulmonary fibrosis appears with a high rate of frequency even with administration of low doses less than 150 mg (potency), thus great care is required.

2) Patients receiving this drug should be maintained under sufficient observation of clinical symptoms as fever, cough, and exertional dypsnea and should also be followed up to detect any abnormality on chest X-ray film or the crepitation (rale). Also, where such examination techniques are available, alveolar-arterial oxygen tension difference ($A\text{-}aDo_2$), pulmonary arterial oxygen (Pao_2) and carbon monoxide diffusing capacity (DLco), etc. should be examined. These observations and examinations should periodically be taken not only during the administration of the drug, but also for a period of approximately 2 months after the completion of administration.

3) $A\text{-}aDo_2$ and Pao_2, etc. should be examined once a week if possible, and if there is an increase $A\text{-}aDo_2$ or decrease Pao_2 during 2 consecutive weeks, administration should be discontinued. If there is a worsening of either of these parameters greater than 10 Torr, careful observation of other clinical symptoms is necessary and if it is judged that these are adverse reactions related to the drug, administration should be immediately discontinued and administration of steroid be commenced. Also, the same steps should be taken if there is a decrease of more than 15% in DLco.
In cases with poor pulmonary function in which administration is unavoidable, the treatment must be followed with great care and if any further decrease in pulmonary function is recognized, administration should be discontinued immediately.

(2) With long-term administration, adverse reactions may appear strongly and become prolonged, thus administration must be performed with care.

(3) In cases that have received peplomycin or other forms of bleomycin, toxicity is thought to be additive, therefore the necessary caution to observe the adverse reactions should be taken.

(4) Attention should be paid to the appearance or exacerbation of infection and any bleeding tendency.

(5) In children or patients at an age capable of reproduction, particular effects on the sexual glands should be considered.

3. Drug Interactions

1) Contraindications for coadministration (BLEOCIN should not be coadministered with the following drugs, etc.)

Drugs, etc.	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Irradiation to the thorax and its peripheral	Signs and Symptoms: Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis may occur. Treatment: See 2. Important Precautions in"PRECAUTIONS" section.	Both irradiation and this drug may induce serious interstitial pneumonia and pulmonary fibrosis.

2) Precautions for coadministration (BLEOCIN should be administered with care when coadministered with the following drugs, etc.)

Drugs, etc.	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Other antitumor agents Irradiation	Signs and Symptoms: Such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis may occur. Treatment: See "2. Important Precautions in "PRECAUTIONS" section.	Both this drug and other antitumor agents may induce serious interstitial pneumonia and pulmonary fibrosis.
Irradiation for area of head and neck	Stomatitis and angular stomatitis may deteriorate. It may cause inflammation of pharyngolaryngeal mucosa infrequently, resulting in hoarseness.	Both irradiation and this drug may cause inflammation of pharyngolaryngeal mucosa.

4. Adverse Reactions

< Summary >[1]

The frequently observed adverse reactions to this drug in total 1,613 patients (374 patients at the approval and 1,239 investigated after initial marketing) were such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis (10.2%), sclerosis of skin, pigmentation (40.6%), fever and rigors (39.8%), alopecia (29.5%), anorexia and weight decrease (28.7%), general malaise (16.0%), nausea and vomiting (14.6%), stomatitis (13.3%), and change of nail (11.2%).

(1) Clinically significant adverse reactions

1) Interstitial pneumonia, pulmonary fibrosis (10%): Since serious interstitial pneumonia and pulmonary fibrosis may occur, it is necessary to make careful observations and if any change in A-aDo_2, Pao_2, or DLco or any abnormality of the chest roentgenogram, etc. is recognized [see (1)-3) in "Important Precautions" section], or if pulmonary manifestation such as cough, exertional dyspnea or crepitation (rale) develop, etc., administration should be immediately discontinued and administration of adrenal cortex hormones and treatment with a suitable antibiotic, etc. be commenced.

2) Shock (< 0.1%): Because BLEOCIN treatment may give rise to shock, if any abnormalities appear, withdraw BLEOCIN immediately, and take appropriate measures. (Because shock is likely to develop in patients with malignant lymphomas at the 1st - 2nd administration, start initial and 2nd dose of BLEOCIN treatment with 5 mg (potency) or less. After confirmation that no acute reactions to the drug occur, increase the dose to the usual level).

3) Hemorrhage (2%): Exercise care in hemorrhage which may in some cases result from a rapid necrosis of the cancer lesion due to this drug treatment.

(2) Other adverse reactions

	≥ 10%	10% >, ≥ 1%	< 1%
Hypersensitivity *1)		Rash, urticaria and erythroderma associated with fever	
Skin	Alopecia and hypertrophy of the skin, pigmentation, deformation and discoloration of the nail		
Gastrointestinal	Anorexia, nausea and vomiting, and stomatitis	Angular stomatitis	Diarrhea
Hepatic			Hepatic disturbances
Urinary			Oligurea, micturition pain, pollakiuria and feeling of residual urine
Hematologic			Leukopenia
Psychoneurologic		Headache	Dizziness
Injection sites			
Intravenous injection *2)			Hypertrophy of the venous wall and narrowing of the venous lumen
Intramuscular or local injection			Induration
Others	Fever *3) and malaise		Pain at the tumor site

*1) Withdraw this drug in such cases

*2) In such cases, change the application site or switch to intramuscular injection.

*3) Fever may develop with a lag time of 4-5 hours or more after the administration of this drug. Because a dose-response relation exists between the fever and dose at a given time, if the fever is severe, appropriate measures should be taken such as administering a reduced dose at shorter intervals, or antihistaminic and antipyretic agents before and/or after administration of this drug.

5. Use in the Elderly

Because interstitial pneumonia or pulmonary fibrosis is likely to occur in the elderly of age of 60 or over, this drug should be administered with care.

[The frequency of such serious pulmonary manifestation as interstitial pneumonia or pulmonary fibrosis, etc. has been increased by age, 5.9% in the under 50, 8.1% in the 50's, 10.9% in the 60's and 15.5% in the patients aged 70 or more.]

6. Use during Pregnancy, Delivery or Lactation

(1) The administration of this drug is not recommended to pregnant patients or women suspected of being pregnant. [This drug has been reported to cause fetal malformation in laboratory animals (mice and rats)]

(2) Administration to nursing mother should be avoided. If administration of this drug is absolutely necessary, instruct the patient to discontinue breast feeding.

[The safety of this drug in nursing mothers has not been established.]

7. Pediatric Use

Particular care is required concerning the appearance of adverse

reactions when administering this drug to children.
[The safety of this drug in children has not been established.]

8. Precautions concerning Use

(1) Intravenous administration: Vascular pain may occur, therefore, it is important to pay due attention to concentration of the injection and administration rate. Give intravenously as slowly as possible.

(2) Intramuscular administration: To avoid affecting tissue and nerves, etc., the following points must be considered.

1) Since intramuscular administration may cause induration at the injection site. Avoid repeated injections at the same site. Take special care to neonates, prematures, infants and children.
2) Pay due attention to avoid injection at innervated sites.
3) If insertion of the injection needle evokes intense pain, or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.

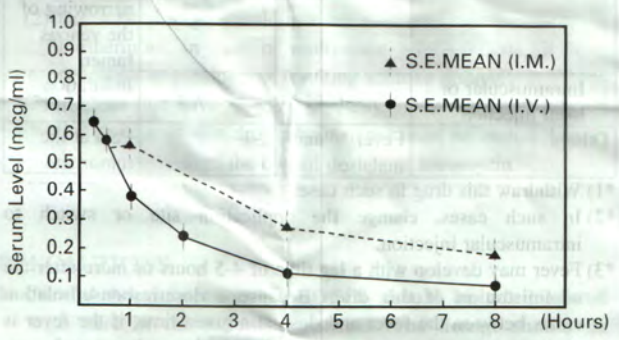
9. Other Precautions

According to the foreign reports, the occurrences of cardiac infarction, cerebral infarction, etc. are reported when this drug was administered with other antineoplastic agents.

PHARMACOKINETICS [2)]

< Blood concentration >

The figure below shows the serum concentrations of Bleomycin in groups of 4 cancer patients given 15 mg (potency) of bleomycin intravenously or intramuscularly by a crossover design.



CLINICAL STUDIES

The response rates for each disease are summarized below.

Disease	Response rate
Skin cancer	57.4% (58/101)
Head and neck cancer	55.6% (69/124)
Squamous cell lung carcinoma	50.0% (11/22)
Esophageal cancer	70.6% (36/51)
Malignant lymphoma	73.8% (31/42)
Uterine cervical cancer	57.1% (52/91)
Neuroglioma	41.0% (16/39)
Thyroid cancer	71.1% (32/45)

PHARMACOLOGY [3)-5)]

1. Antitumor activity

(1) In vitro: It has been demonstrated that bleomycin inhibits growth and DNA/protein synthesis in $HeLaS_3$ cells, Ehrlich cancer cells and Yoshida sarcoma cells, etc.

(2) In vivo: Disappearance of spontaneous lymphosarcoma in dogs are observed.

2. Mechanism of action

The main mechanism of action is the inhibition of DNA synthesis and the spilitting of DNA strand.

PHYSICOCHEMISTRY

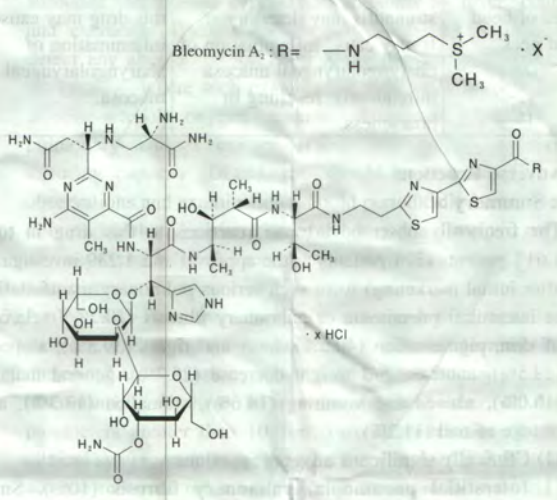
Nonproprietary name: Bleomycin hydrochloride (JAN)
Bleomycin (INN)

Abbreviation: BLM

Molecular formula: $C_{55}H_{84}ClN_{17}O_{21}S_3 \cdot HCl$ (BLM-A_2)

Molecular weight: 1487.49 (BLM-A_2)

Structural formula: The structure of its main component, Bleomycin A_2 (content ratio: 55-70%) is shown below.



Description: Bleomycin hydrochloride occurs as a white to yellowish white powder. It is freely soluble in water, slightly soluble in ethanol, and practically insoluble in ether.

PACKAGING

5 mg (potency): 1 vial
15 mg (potency): 1 vial

REFERENCES

1) IYAKUHIN FUKUSAYO JOHO (Information on Adverse Reactions to Drugs), **17**: (February, 1967)
2) Ikeda, S., et al.: GAN TO KAGAKU RYOHO (Jpn. J. Cancer Chemother.), **7**: 756 (1980)
3) Umezawa, H., et al.: J. Antibiotics, **20**: 277 (1967)
4) Umezawa, H., et al.: J. Antibiotics, **21**: 379 (1968)
5) Umezawa, H., et al.: J. Antibiotics, **20**: 15 (1967)

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