1. Name of the medicinal product

Bleocip

2. Qualitative and quantitative composition

Each vial contains:

Bleomycin sulphate USP equivalent to

Bleomycin …. 15 units

As a sterile freeze-dried powder for reconstitution.

Excipient with known effects: Sodium

3. Pharmaceutical form

Intravenous / Intramuscular / Subcutaneous Injection

4. Clinical particulars

4.1 Therapeutic indications

a. Squamous cell carcinoma affecting the mouth, nasopharynx and paranasal sinuses, larynx, oesophagus, external genitalia, cervix or skin. Well differentiated tumours usually respond better than anaplastic ones.
b. Hodgkin's disease and other malignant lymphomas, including mycosis fungoides.
c. Testicular teratoma
d. Malignant effusions of serous cavities.
e. Secondary indications in which bleomycin has been shown to be of some value (alone or in combination with other drugs) include metastatic malignant melanoma, carcinoma of the thyroid, lung and bladder.

4.2 Posology and method of administration

Adults

Routes of administration

Bleomycin is usually administered intramuscularly but may be given intravenously (bolus or drip), intra-arterially, intrapleurally or intraperitoneally as a solution in physiological saline.

Local injection directly into the tumour may occasionally be indicated.

Recommended dose and dosage schedules

Squamous cell carcinoma and testicular teratoma:

Used alone the normal dosage is 15 x 10^3 IU (1 vial) three times a week or 30 x 10^3 IU (2 vials) twice a week, either intramuscularly or intravenously. Treatment may continue on consecutive weeks, or more usually at intervals of 3-4 weeks, up to a total cumulative dose of

500 x 10^3 IU although young men with testicular tumours have frequently tolerated twice this amount. Continuous intravenous infusion at a rate of 15 x 10^3 IU (1 vial) per 24 hours for up to 10 days, or 30 x 10^3 IU (2 vials) per 24 hours for up to 5 days may produce a therapeutic effect more rapidly. The development of stomatitis is the most useful guide to the determination of individual tolerance of maximum therapeutic response. The dose may need to be adjusted when bleomycin is used in combination chemotherapy. Use in elderly or children – see below.

Malignant lymphomas:

Used alone the recommended dosage regime is 15 x 10^3 IU (1 vial) once or twice a week, intramuscularly, to a total dose of 225 x 10^3 IU (15 vials). Dosage should be reduced in the elderly. The dose may need to be adjusted when bleomycin is used in combination chemotherapy. Use in elderly or children – see below.

Malignant effusions:

After drainage of the affected serous cavity 60 x 10^3 IU (4 vials) bleomycin dissolved in 100 ml physiological saline is introduced via the drainage needle or cannula. After instillation, the drainage needle or cannula may be withdrawn. Administration may be repeated if necessary subject to a total cumulative dose of 500 x 103 IU (about 33 vials). Use in the elderly or children – see below.

Combination therapy:

Bleomycin is commonly used in conjunction with radiotherapy, particularly in treatment of cancer of the head and neck region. Such a combination may enhance mucosal reactions if full doses of both forms of treatment are used and bleomycin dosage may require reduction, e.g. to 5 x 103 IU at the time of each radiotherapy fraction five days a week. Bleomycin is frequently used as one of the drugs in multiple chemotherapy regimes (e.g. squamous cell carcinoma, testicular teratoma, lymphoma). The mucosal toxicity of bleomycin should be borne in mind in the selection and dosage of drugs with similar toxic potential used in such combinations.

Elderly Patients:

The total dose of bleomycin used in the treatment of squamous cell carcinoma, testicular teratoma or malignant effusions should be reduced as indicated below:

Age in years	**Total Dose (IU)**	**Dose per week (IU)**
80 and over	100 x 10^3	15 x 10^3
70 – 79	150 – 200 x 10^3	30 x 10^3
60 – 69	200 – 300 x 10^3	30 – 60 x 10^3

Paediatric population

Administration of bleomycin to paediatrics should take place only under exceptional circumstances and in special centres. The dosage should be based on that recommended for adults and adjusted to body surface area or body weight.

Reduced kidney function

With serum creatinine values of 2-4 mg%, it is recommended to half the above dosages. With serum creatinine above 4 mg%, a further reduction in dose is indicated.

Preparation of solution

For intramuscular injections the required dose is dissolved in up to 5 ml of suitable solvents such as physiological saline. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent.

For intravenous injections the dose required is dissolved in 5-200 ml of physiological saline and injected slowly or added to the reservoir of a running intravenous infusion. For intra-arterial administration a slow infusion in physiological saline is used. For intra-cavity injection 60 x 10^3 IU is dissolved in 100ml of normal saline.

For local injections bleomycin is dissolved in physiological saline to make a 1-3 x 10^3 IU/ml solution.

4.3 Contraindications

Bleomycin is contra-indicated in patients with acute pulmonary infection or chest X-ray findings suggesting diffuse fibrotic changes or greatly reduced lung function.

Patients with a past history of hypersensitivity or idiosyncratic reaction to an analogue of bleomycin.

4.4 Special warnings and precautions for use

Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients, patients with reduced kidney function, pre-existing lung disease, previous or concurrent radiotherapy to the chest and in patients who need administration of oxygen. It is significantly enhanced by thoracic radiation and by hyperoxia used during surgical anaesthesia.

The earliest symptom associated with pulmonary toxicity of bleomycin is dyspnoea. Fine rales are the earliest sign. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Patients should be treated with broad spectrum antibiotics and corticosteroids.

Patients undergoing treatment with bleomycin should have chest X-rays weekly. These should continue to be taken for up to 4 weeks after completion of the course and patients should be kept under clinical review for approximately 2 months. If breathlessness or lung infiltrates appear, not obviously attributable to tumour or to co-existent lung disease, administration of the drug must be stopped immediately and patients should be treated with a corticosteroid and a broad spectrum antibiotic. High oxygen concentrations should be used with caution in these cases.

Lung function tests which use 100% oxygen should not be used in patients who have been treated with bleomycin. Lung function tests using less than 21% oxygen are recommended as an alternative.

When bleomycin has been administered pre-operatively, reduced oxygen concentrations should be used during operation and post operatively.

Patients should be carefully monitored under the following conditions and bleomycin dosage should be reduced or prolong the dose interval based on clinical observation of the patient: These clinical conditions include the following:

- Patients treated previously or concurrently with radiation to the chest may develop more frequent or severe toxicity.
- Use with caution in patients with significant renal impairment as clearance may be reduced and toxicity increased (see Section 4.2).
- Use with caution in patients with severe heart disease or hepatic dysfunction as toxicity may be increased.
- Use with caution in patients with varicella as fatal systematic dysfunctions may occur.

Because bleomycin treatment may give rise to shock, if any abnormalities appear, withdraw bleomycin immediately, and take appropriate measures. (Because shock is likely to develop in patients with malignant lymphomas at the 1st – 2nd administration, you may start this drug treatment with lower dose and after establishing that no acute reactions to the drug occur, increase the dose to the usual level).

With long-term administration of bleomycin, peplomycin or other analogues of bleomycin, toxicity is thought to be additive, thus administration must be performed with care.

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

In adults or adolescents capable of reproduction, effects on the sexual glands should be considered.

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.

Intramuscular administration

Avoid repeated injections at the same site and innervated sites, particularly if administering to paediatrics. 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.

Excipient

Bleocip contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of interaction

When bleomycin is used as one of the drugs in multiple chemotherapy regimes the toxicity of bleomycin should be borne in mind in the selection and dosage of drugs with similar toxic potential. The addition of other cytotoxic drugs can necessitate changes and dose alterations. Increased pulmonary toxicity has been noted when bleomycin is given with cisplatin.

Previous or concurrent radiotherapy to the chest and/or administration of anti-tumour agents (e.g. cisplatin) are important factors in increasing the incidence and severity of lung toxicity such as interstitial pneumonia or pulmonary fibrosis.

Previous or concurrent radiotherapy to the head or neck is a factor increasing stomatitis and angular stomatitis may deteriorate. It may cause inflammation of pharyngolaryngeal mucosa infrequently resulting in hoarseness.

Because of bleomycin's sensitisation of lung tissue, patients who have received bleomycin pre-operatively are at greater risk of developing pulmonary toxicity when oxygen is administered at surgery and a reduction in inspired oxygen concentration during operation and post-operatively is recommended (See Section 4.4).

In patients treated for testicular cancer with a combination of bleomycin and vinca alkaloids a syndrome has been reported corresponding to Raynaud's disease, ischaemia which can lead to necrosis of peripheral parts of the body (fingers, toes, nose tip).

The following clinical incompatibilities have been noted:-Cytotoxics possibly reduce the absorption of phenytoin. Concomitant use of bleomycin with clozapine should be avoided due to an increased risk of agranulocytosis.

4.6 Fertility, pregnancy and lactation

Pregnancy

The administration of this drug to pregnant patients, or women suspected of being pregnant, is not recommended. The use of bleomycin should be avoided whenever possible during pregnancy, particularly during the first trimester.

Lactation

Bleomycin should not be given to mothers who are breast feeding.

Fertility

Bleomycin can cause congenital malformations. Conception during and six months after treatment is not advisable. Women should not become pregnant during and six months after treatment.

4.7 Effects on ability to drive and use machines

This depends on the patient's condition and should be considered in co-operation with the doctor.

4.8 Undesirable effects

The most frequently observed adverse reactions in 1613 patients receiving bleomycin were pulmonary manifestations such 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 nail changes (11.2%).

System Organ Class	**Very Common** ≥1/10	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100
Neoplasms, Benign, Malignant			Pain at the site of tumour

and Unspecified (including Cysts and Polyps)			
Blood and lymphatic system disorders			Leukopenia
Metabolism and Nutrition disorders	Anorexia		
Nervous system disorders		Headache	Dizziness
Vascular disorders		Haemorrhage	Shock; vein wall hypertrophy; venous stenosis
Respiratory, thoracic and mediastinal disorders	Interstitial pneumonia; pulmonary fibrosis		
Gastrointestinal disorders	Weight decrease; nausea; vomiting; stomatitis	Angular stomatitis	Diarrhoea
Hepatobilliary disorders			Hepatocellular injury
Skin and subcutaneous tissue	Alopecia; skin hypertrophy; pigmentation; deformation and discolouration of the nail; scratch dermatitis	Rash; urticaria; erythroderma	
Musculoskeletal and connective tissue disorders	Scleroderma		
Renal and Urinary disorders			Oliguria; dysuria; pollakiuria; urinary retention; polyuria; feeling of residual urine
General disorders and administration site conditions	Fever; rigors; malaise		Injection site induration;

Like most cytotoxic agents bleomycin can give rise to both immediate and to delayed toxic effects. The most immediate effect is fever on the day of injection. Anorexia, tiredness or nausea also may occur. Pain at the injection site or in the region of the tumour has occasionally been reported, and other rare adverse effects are hypotension and local thrombophlebitis after intravenous administration.

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.

The majority of patients who receive a full course of bleomycin develop lesions of the skin or oral mucosa. Induration, hyperkeratotis, reddening, tenderness and swelling of the tips of the fingers, ridging of the nails, bulla formation over pressure points such as elbows, loss of hair and stomatitis are rarely serious and usually disappear soon after completion of the course.

The most serious delayed effect is interstitial pneumonia, which may develop during, or occasionally after, a course of treatment. This condition may sometimes develop into fatal pulmonary fibrosis, although such an occurrence is rare at recommended doses. Previous or concurrent radiotherapy to the chest is an important factor in increasing the incidence and severity of lung toxicity.

A few cases of acute fulminant reactions with hyperpyrexia and cardiorespiratory collapse have been observed after intravenous injections of doses higher than those recommended. Hypotension, hyperpyrexia and drug-related deaths have been reported rarely following intra-cavitary instillation of bleomycin.

During post-marketing surveillance the following events have been reported: sepsis, pancytopenia, thrombocytopenia, anaemia, neutropenia, chest pain, myocardial infarction, Raynaud's syndrome, embolism, thrombosis, digital ischaemia and cerebral infarction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via local reporting system.

4.9 Overdose

The acute reaction to an overdosage of bleomycin would probably include hypotension, fever, rapid pulse and general symptoms of shock.

Treatment is purely symptomatic. In the event of respiratory complications the patient should be treated with a corticosteroid and a broad-spectrum antibiotic. There is no specific antidote to bleomycin.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group- Other cytotoxic antibiotics

ATC code: LO1D C01

Bleomycin is a basic, water-soluble glycopeptide with cytotoxic activity. The mechanism of action of bleomycin is believed to involve single-strand scission of DNA, leading to inhibition of cell division, of growth and of DNA synthesis in tumour cells.

Apart from its antibacterial and antitumour properties, bleomycin is relatively free from biological activity. When injected intravenously it may have a histamine-like effect on blood pressure and may cause a rise in body temperature.

5.2 Pharmacokinetic properties

Bleomycin is administered parenterally. After intravenous (IV) administration of a bolus dose of 15 x 10^3 IU/m^2 body surface, peak concentrations of 1 to 10 IU are achieved in plasma. Following the intramuscular (IM) injection of 15 x 10^3 IU peak plasma concentrations of about 1 IU/ml have been reported. The peak plasma concentration is reached 30 minutes after an IM injection. Continuous infusion of bleomycin 30 x 10^3 IU daily, for 4 to 5 days, resulted in an average steady state plasma concentration of 100-300 milli IU/ml. After IV injections of bleomycin in a dose of 15 x 10^3 IU/m^2 body surface, the area under the serum concentration curve is, on average, 300 milli IU x min x ml^{-1}.

Bleomycin is only bound to plasma proteins to a slight extent. Bleomycin is rapidly distributed in body tissues, with the highest concentrations in skin, lungs, peritoneum and lymph. Low concentrations are seen in the bone marrow. Bleomycin could not be detected in cerebrospinal fluid after intravenous injection. Bleomycin appears to cross the placental barrier.

The mechanism for bio-transformation is not yet fully known. Inactivation takes place during enzymatic breakdown by bleomycin hydrolase, primarily in plasma, liver and other organs and, to a much lesser degree, in skin and lungs. When bleomycin was administered as an IV bolus injection in a dose of 15 x 10^3 IU/m^2 body surface, initial and terminal half-lives were 0.5 and 4 hours respectively. Given as a continuous intravenous infusion in a dose of 30 x 10^3 IU daily for 4 to 5 days bleomycin disappears from plasma with initial and terminal half-lives of about 1.3 hours and 9 hours, respectively. About two thirds of the administered drug is excreted unchanged in the urine, probably by glomerular filtration. Approximately 50% is recovered in the urine in the 24 hours following an IV or IM injection. The rate of excretion, therefore, is highly influenced by renal function; concentrations in plasma are greatly elevated if usual doses are given to patients with renal impairment with only up to 20% excreted in 24 hours. Observations indicate that it is difficult to eliminate bleomycin from the body by dialysis.

5.3 Preclinical safety data

Animal experiences have revealed that bleomycin, like most cytotoxics, may have teratogenic and carcinogenic potential.

Bleomycin has been reported to cause fibrosarcoma and renal carcinoma in a laboratory animal (rat) administered subcutaneously.

Bleomycin has been reported to cause foetal malformation in laboratory animals (mice and rats).

6. Pharmaceutical particulars

6.1 List of excipients

Sodium hydroxide pellets

Water for injection

6.2 Incompatibilities

Bleomycin solution should not be mixed with solutions of essential amino acids, riboflavine, ascorbic acid, dexamethasone, aminophylline or frusemide.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store under refrigeration between 2°C – 8°C (36-46° F).

6.5 Nature and contents of container

Carton containing one vial of 5 ml

6.6 Special precautions for disposal and other handling

Bleomycin should be handled with care. Precautions should be taken to avoid bleomycin coming into contact with skin, mucous membranes or eyes, but in the event of contamination the effected part should be washed with water.

7. Marketing authorisation holder

Cipla Ltd

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8. Marketing authorisation number(s) ---

NA

9. Date of first authorisation/renewal of the authorization ---

NA

10. Date of revision of the text

May, 2017