

## **Package leaflet: Information for the patient**

### **Bleomycin 15000 IU Powder for solution for injection/ infusion** bleomycin

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or hospital pharmacist or nurse.
- If you get any side effects, talk to your doctor or hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Bleomycin is and what it is used for
2. What you need to know before you are given Bleomycin
3. How to use Bleomycin
4. Possible side effects
5. How to store Bleomycin
6. Contents of the pack and other information

#### **1. What Bleomycin is and what it is used for**

This medicine contains the active ingredient bleomycin sulphate. Bleomycin is one of a group of medicines called cytostatic medicines. These medicines are anti-cancer medicines sometimes referred to as chemotherapy. They attack cancer cells and prevent them from dividing.

Bleomycin is used to treat:

- Certain types of cancer (squamous cell carcinomas) in the head and neck, cervix and external genitalia;
- Certain types of lymph node cancer (e.g. Hodgkin's disease and Non-Hodgkin's lymphoma of intermediate and high malignancy);
- Testicular cancer;
- Fluid accumulation in the lungs (as a result of cancer).

Bleomycin can be used alone, or in combination with other cancer medications, and/or in combination with radiotherapy.

#### **2. What you need to know before you are given Bleomycin**

##### **Bleomycin will not be given:**

- if you are allergic to bleomycin sulphate or to any similar anti-cancer medicine;
- if you have Ataxia telangiectasia (very rare inherited disease that leads to difficulties in coordinating your movements and the risk of infections).
- if you have an acute lung infection or severe lung impairment;
- if you have a history of lung damage (possibly) caused by bleomycin;
- during breast-feeding (see also "Pregnancy and lactation" section).

##### **Warnings and precautions**

Talk to your doctor or pharmacist or nurse before you are given Bleomycin if:

- you are over 60 years of age;
- your kidneys or liver no longer function properly;
- you have or have had a lung disease;

- you had lung irradiation prior to bleomycin treatment, or if you are having radiation therapy during bleomycin treatment;
- you have chickenpox
- you are being administered oxygen. Tell your doctor that you are using bleomycin

You must also tell your doctor if you have an operation planned as it may be necessary to adjust your treatment with bleomycin.

The patient groups specified above are more sensitive to bleomycin's harmful effects on the lungs. The doctor will probably examine you more often and/or take X-rays of your lungs. If you are treated with bleomycin, a regular lung function test should be performed, to monitor the possible adverse effects of bleomycin on the lungs.

If you have a cough and/or are short of breath, this can be a sign of the adverse effects of bleomycin on the lungs. In this case you should inform a doctor immediately.

Like other cytotoxic active substances, bleomycin can trigger tumour lysis syndrome in patients with rapidly growing tumours. Appropriate supportive treatment and pharmacological measures might prevent or alleviate such complications.

### **Other medicines and Bleomycin**

Tell your doctor or pharmacist if you are taking or using, have recently taken or used, or might take or use any other medicines.

An interaction is taken to refer to when (medicinal) products used together may influence each other's efficacy and/or side effects. An interaction may occur when bleomycin is used together with:

- Carmustine, mitomycin, cyclophosphamide, gemcitabine (medicines used for certain types of cancer) and methotrexate (a medicine used for certain types of cancer, rheumatism and severe skin diseases): there is an increased risk of harmful effects on the lungs;
- Cisplatin (an anti-cancer medicine) and other medicines that cause kidney damage: there is an increased risk of side effects from bleomycin (potentiation of pulmonary toxicity);
- Vinca alkaloids (a group of medicinal products used for certain types of cancer, e.g. vincristine, vinblastine): circulatory disturbances may occur in the extremities (fingers, toes, tip of the nose). In very severe cases the extremities can die (necrosis);
- Acetyldigoxin (a medicine for cardiac disorders): there is a risk that the effect of acetyldigoxin will be reduced;
- Phenytoin (a medicine for epilepsy): there is a risk that the effect of phenytoin will be reduced;
- Clozapine (a medicine for schizophrenia): it may cause more severe reduction in number of white blood cells which makes infections more likely.
- Radiotherapy: the risk of side effects on the lungs and/or mucous membranes is increased;
- Oxygen: you are at greater risk of pulmonary toxicity if you are given oxygen during anaesthesia;
- Gentamicin, amikacin and ticarcillin (medicines that inhibit the growth of bacteria): the efficacy of these substances may be reduced;
- Ciclosporine and tacrolimus (medicines that reduce efficacy of immune system): risk of excessive generation of lymphocytes.
- Granulocyte colony-stimulating factor: lung damage may be aggravated;
- Live vaccines: there is a risk of serious or life-threatening infections caused by the vaccine. Vaccinations with live vaccines should therefore not be administered to patients receiving bleomycin.

### **Pregnancy, breast-feeding and fertility**

#### Pregnancy

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Animal studies have shown that this medicine can harm the embryo.

The use of bleomycin should be avoided during pregnancy, especially during the first 3 months.

If bleomycin treatment is vital during the first three months of pregnancy, a medical consultation on aborting the pregnancy is essential.

Both men and women must take measures to prevent a pregnancy during use of bleomycin, and for 6 months after the end of the treatment. If pregnancy occurs during treatment with bleomycin, genetic counselling is recommended.

Men who wish to father children in the future should seek advice on storing sperm before starting treatment with bleomycin because there is possibility of becoming irreversibly infertile by the treatment.

#### Breast feeding

It is not known whether bleomycin or the metabolically degraded materials are secreted in your milk, but since there is a possibility that bleomycin is harmful to your child, you must not breast-feed during treatment with bleomycin.

#### Fertility

Bleomycin therapy may cause irreversible infertility.

#### **Driving and using machines**

This medicinal product may affect your reactions and your ability to drive.

Possible side effects of chemotherapy with bleomycin may occur, such as nausea and vomiting. If you are affected by these side effects, you should not drive and/or operate machines that require you to be alert.

#### **Bleomycin Powder for solution for injection/infusion contains sodium**

This medicines contains less than 1 mmol sodium (23 mg) per dose, i.e essentially “sodium free”

### **3. How to use Bleomycin**

The doctor will calculate the required quantity for you, based on the dosage details specified later.

#### The usual dose:

The (total) dose depends on the indication, your age, renal function, and combination with other anticancer medicines. Your doctor will set the dose of bleomycin, the duration of the treatment, and the number of treatments. These can vary for each patient.

There is a risk of serious hypersensitivity reaction especially in lymphoma patients which may occur directly or sometime after administration. Therefore, your doctor will give you a test dose and will observe for 4 hours before starting bleomycin therapy for the first time.

#### Method of administration

Your doctor will administer bleomycin into a vein or artery, under the skin, into a muscle, directly into the tumour, or into the space surrounding the lungs (intrepleural), either by injection or using an infusion.

#### Use in children and adolescents

There is insufficient experience with regard to the administration of bleomycin in children and adolescents. Until more information is available, bleomycin should only be administered in children and adolescents in exceptional circumstances and at special facilities.

#### **If you have been given more Bleomycin than you should**

Symptoms that can occur if you have received too much Bleomycin include: low blood pressure, fever, increased heart rate and shock. If you notice any of the above symptoms, please tell your doctor, who will arrange for the appropriate treatment. Use of the medicinal product must be discontinued immediately.

Information for the doctor:

Information about treating an overdose can be found at the end of this leaflet.

#### **If you have not received Bleomycin when you should**

If you have missed an injection, please talk with your treating doctor, to clarify if and how to make up for the missed dose.

### **If you stop taking Bleomycin**

If you suddenly stop taking Bleomycin without consulting a doctor, the original symptoms may recur.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Bleomycin can cause immediate and delayed side effects. Fever on the day of injection is the earliest reaction. Loss of appetite, loss of hair, chills, fatigue, inflammation of the lungs (interstitial pneumonia) – shortness of breath or cough, inflammation of the mucous lining of the mouth and nausea may also occur. Pain at the injection site and in the tumour area has also been observed on occasion. Other sporadic side effects include a fall in blood pressure and local thrombophlebitis (inflammation of a vein) after administration into a vein.

Skin and mucosal lesions are the most common side effects and are observed in up to 50 % of the patients treated. They comprise redness; rash; itching; formation of ulcers, stretch marks and blisters; heavy pigmentation; and tenderness and swelling of the fingertips.

### **Serious side effects:**

If you develop any of the following side effects, tell your doctor immediately:

- Coughing
- Breathlessness
- Cracking or popping sound when breathing

You may need to have your treatment stopped.

Side effects can include the following:

### **Very common** (may affect more than 1 in 10 patients)

- interstitial pneumonitis (inflammatory changes in the lungs)
- pulmonary fibrosis (disease of the lung tissue caused by increased formation of connective tissue between the alveoli)
- laboured breathing
- loss of appetite
- weight loss
- nausea and vomiting
- mucositis (inflammation of the mucous membranes)
- stomatitis (inflammation of the mucous lining of the mouth)
- inflammatory redness of the skin
- itching
- striae (stretch marks)
- blistering
- hyperpigmentation (increased pigment formation)
- tenderness and swelling of the fingertips
- hyperkeratosis (excessive thickening of the skin)
- hair loss

### **Common** (may affect up to 1 in 10 people)

- Severe hypersensitivity reactions. These reactions may occur immediately, or after a delayed period of a few hours after the first or second dose. Tell your doctor straight away if you get any sudden

wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body). idiosyncratic reaction (various types of hypersensitivity reaction)

- headache
- acute respiratory insufficiency (acute respiratory distress syndrome - ARDS)
- respiratory failure
- pulmonary embolism
- rash, urticaria, erythema
- induration (hardening of the skin)
- swellings (due to fluid retention in the tissues)
- inflammatory skin reaction
- pyrexia, chills and malaise

**Uncommon** (may affect up to 1 in 100 people)

- myelosuppression (damage to the bone marrow)
- leukopaenia (reduction in white blood cell count)
- neutropaenia (reduction in neutrophil granulocytes in the blood)
- thrombocytopenia (reduction in platelets)
- haemorrhage (bleeding)
- dizziness
- confusion
- low blood pressure
- angular cheilitis (infection of the corners of the mouth) and diarrhoea
- deformation and discolouration of the nails, bulla formation at pressure points
- muscle and joint pain
- oliguria (decreased urine output)
- pain during urination
- polyuria (increased urine volume)
- urinary retention
- pain in the tumour area
- phlebitis (inflammation of a vein)
- hypertrophy (thickening) of the vein wall and venous access constriction (with i.v. administration)
- induration (hardening of the tissue following administration into a muscle or with local administration)

**Rare** (may affect up to 1 in 1000 people)

- Neutropaenic fever (fever caused by a decrease in white blood cells)
- heart attack, pericarditis (inflammation of the fibrous sac surrounding the heart) and chest pain
- cerebral infection, thrombotic microangiopathy (disease of the capillaries and arterioles), haemolytic uraemic syndrome (severe disease affecting the blood and kidneys)
- cerebral arteritis (inflammation of the small and medium-sized arteries in the brain)
- Raynaud's phenomenon (a vascular disorder), arterial thrombosis, deep vein thrombosis
- hepatic impairment
- scleroderma (hardening of the connective tissue)

**Vary rare** (may affect up to 1 in 10,000 people)

- Tumour lysis syndrome (condition following rapid breakdown of tumours)

**Not Known** (frequency cannot be estimated from the available data)

- Overwhelming infection (sepsis),
- severe reduction in blood cells (pancytopenia),
- reduction in red blood cells (anaemia),

**Reporting of side effects**

If you get any side effects talk to your doctor or hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website:

[www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for **MHRA Yellow Card** in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Bleomycin**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

For single use only. Discard any residues.

The reconstituted/diluted product should be used immediately.

Do not use Bleomycin if you notice any visible signs of deterioration in the product or the vial, e.g. discolouration of the powder or damage to the vial and the seal.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What bleomycin contains**

- The active substance is bleomycin (as bleomycin sulphate).  
Each vial contains 15,000 International Units (I.U.) of bleomycin (as bleomycin sulphate).
- The other ingredients are sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

### **What Bleomycin looks like and contents of the pack**

White to light yellowish freeze dried substance in type I clear glass vial closed with a bromobutyl rubber stopper and sealed with a flip-off aluminium seal.

Pack of 1 vial, 10 and 100 vials.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

#### **Marketing Authorisation Holder**

Accord Healthcare Limited  
Sage House, 319, Pinner Road, Harrow  
Middlesex HA1 4HF  
United Kingdom

#### **Manufacturer**

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**The following information is intended for medical professionals only:**

**Posology and method of administration**

Bleomycin is administered parenterally as an intramuscular injection, intravenous injection/infusion, intra-arterial injection/infusion, subcutaneous injection, intratumoural injection, or intrapleural instillation.

**Posology:**

Adults

- 1) Squamous cell carcinoma  
Intramuscular or intravenous injection of  $10\text{-}15 \times 10^3$  IU/m<sup>2</sup> body surface area (BSA), once or twice a week at intervals of 3-4 weeks up to a total cumulative dose  $400 \times 10^3$  IU. Intravenous infusion of  $10\text{-}15 \times 10^3$  IU/m<sup>2</sup>/day for 6-24 hours on 4 to 7 consecutive days, at intervals of 3-4 weeks.
- 2) Hodgkin's disease and non-Hodgkin's lymphoma  
When used alone, intramuscular or intravenous injection of  $5\text{-}15 \times 10^3$  IU/m<sup>2</sup> BSA, once or twice a week, up to a cumulative dose of  $225 \times 10^3$  IU. Because of the possibility of anaphylactoid reactions, lymphoma patients should be treated with lower doses (for instance  $2 \times 10^3$  IU) for the first two applications. If there are no acute reactions after 4 hours of observation the normal dose schedule can be followed.
- 3) Testicular tumours  
Intramuscular or intravenous injection of  $10\text{-}15 \times 10^3$  IU/m<sup>2</sup> BSA once or twice a week, at intervals of 3-4 weeks up to a total cumulative dose of  $400 \times 10^3$  IU.  
The intravenous infusion of the dose of  $10\text{-}15 \times 10^3$  IU/m<sup>2</sup> BSA/day is performed for 6-24 hours on 5-6 consecutive days, at intervals of 3-4 weeks.
- 4) Malignant pleural effusions  
 $60 \times 10^3$  IU in 100 mL physiological saline solution intrapleurally, as a single dose, which can be repeated after 2-4 weeks, depending on the response.  
Since approximately 45 % of bleomycin is absorbed, this should be taken into account for the total cumulative dose (body surface area, kidney function and lung function).

The development of stomatitis is the most useful guide to the determination of individual tolerance with respect to the maximum dose. A total cumulative dose of  $400 \times 10^3$  IU (corresponding to  $225 \times 10^3$  IU/m<sup>2</sup> BSA) should not be exceeded in patients under 60, because of the increased risk of pulmonary toxicity in all indications. In lymphoma patients, the total dose should not be more than  $225 \times 10^3$  IU.

In cases of Hodgkin's disease and testicular tumours, improvement occurs rapidly and can be observed within two weeks. If no improvement is observed by then, an improvement is unlikely. Squamous cell carcinomas respond more slowly. In some cases it can take up to three weeks before an improvement is noted.

Elderly patients (from the age of 60)

The total dose of bleomycin in elderly patients should be reduced according to the following table:

Age in years	Total dose	Dose per week
80 and over	$100 \times 10^3$ IU	$15 \times 10^3$ IU
70-79	$150\text{-}200 \times 10^3$ IU	$30 \times 10^3$ IU
60-69	$200\text{-}300 \times 10^3$ IU	$30\text{-}60 \times 10^3$ IU
Under 60	$400 \times 10^3$ IU	$30\text{-}60 \times 10^3$ IU

Children and adolescents

There is insufficient experience with regard to the administration of bleomycin in paediatric patients. Until more information is available, bleomycin should only be administered in children in exceptional circumstances and at special facilities. If administration is indicated as part of a combination regimen the dosage is usually calculated based on the body surface area and adjusted to meet the individual requirements of each patient. Current specialized protocols and guidelines should be consulted for the appropriate treatment regimen.

#### Renal insufficiency

In case of renal failure, especially if creatinine clearance <35 ml / min, elimination of bleomycin is delayed. There are no specific guidelines for dose adjustment in these patients, but it is recommended that patients with moderate renal impairment (GFR 10-50 ml / min) should receive 75% of the usual dose administered at the usual dosing intervals and patients severe renal failure (GFR below 10 ml / minute) should receive 50 % of the usual dose, given at the normal dosing interval. No dose adjustment is required dosing in patients with a GFR greater than 50 ml / minute.

#### Combination therapy

The dose might require adjustment when bleomycin is used in combination therapy.

The bleomycin dosage should be reduced in conjunction with radiotherapy since the risk of mucosal damage is increased. Dose adjustment may also be required when bleomycin is used in combination chemotherapy. Details regarding treatment regimens applied for certain indications can be found in the current literature.

#### **Method of administration and preparation of the solution for injection:**

N.B.: The entire contents of a vial (15000 IU) should be dissolved in the appropriate quantity of solvent for preparation of the solution. The quantity of units required for the treatment is then taken from this solution.

#### **Incompatibilities**

Bleomycin should not be mixed with solutions of essential amino acids, riboflavin, ascorbic acid, dexamethasone, aminophylline, benzylpenicillin, carbenicillin, cefalotine, cefazoline, diazepam, furosemide, glutathione, hydrogen peroxide, hydrocortisone Na succinate, methotrexate, mitomycin, nafcillin, penicillin G, substances containing sulphhydryl groups, terbutaline, or thiols. As bleomycin forms chelating agents with bi- and trivalent cations it should not be mixed with solutions that contain such ions (in particular copper).

#### Intramuscular injection

Dissolve the contents of a vial in 1-5 mL physiological saline solution. Since repeated i.m. injections at the same site can cause local discomfort, it is recommended to change the injection site regularly. In the event of excessive local discomfort, a local anaesthetic can be added to the injection solution, e.g. 1.5-2 mL lidocaine HCl 1%.

#### Intravenous injection

Dissolve the contents of a vial in 5-10 mL physiological saline solution and inject slowly over a period of 5-10 minutes. Fast bolus injections are to be avoided, because they lead to high intrapulmonary plasma concentrations, increasing the risk of lung damage.

#### Intravenous infusion

Dissolve the contents of a vial in 200-1,000 mL physiological saline solution.

#### Intra-arterial injection

Dissolve the contents of a vial of bleomycin in at least 5 mL physiological saline solution and inject over a period of 5-10 minutes.

#### Intra-arterial infusion

Dissolve bleomycin in 200-1,000 mL physiological saline solution. The infusion can be administered over a few hours to a number of days. Heparin can be added to prevent thrombosis at the injection site, especially if the infusion is administered over a longer period.

Injection or infusion into an artery supplying the tumour tends to exhibit higher efficacy than other systemic routes of administration. The toxic effects are the same as with intravenous injection or infusion.

#### Subcutaneous injection

Dissolve the contents of a vial in maximum 5 mL physiological saline solution. Absorption following subcutaneous injection is delayed and may resemble a slow i.v. infusion. This form of administration is rarely used. Care must be taken to avoid intradermal injection.

#### Intratumoural injection

Bleomycin is dissolved in physiological saline solution, producing a concentration of  $1-3 \times 10^3$  IU/mL; this solution is then injected into the tumour and the surrounding tissue.

#### Intrapleural instillation

Following drainage of the pleural cavity, bleomycin dissolved in 100 ml physiological saline solution and instilled via the puncture cannula or drainage catheter. The cannula or catheter is then removed. In order to ensure uniform distribution of the bleomycin in the serous cavity, position of patient should be changed every 5 minutes for a period of 20 minutes. Approximately 45% of Bleomycin will be absorbed; this has to be considered for total dose (body surface area, kidney function, lung function).

Perivascular administration of bleomycin does not usually require any specific measures. If in doubt (highly concentrated solution, sclerotic tissue, etc.) perfusion can be performed with a physiological saline solution.

The reconstituted/diluted product should be used immediately.

Single use only, the reconstituted solution is a clear pale yellow solution. Any unused solution should be discarded.

#### **Special precautions for disposal and other handling**

The general guidelines for safe handling of cytotoxic medicinal products must be adhered to. Appropriate precautions should be taken to avoid contact with the skin, mucous membranes and eyes. In the event of contamination, the parts affected should be washed thoroughly with water.

Urine produced for up to 72 hours after administration of bleomycin should be handled wearing protective clothing.

#### **Information on treating an overdose**

There is no specific antidote. It is virtually impossible to eliminate bleomycin from the body by dialysis.

The acute reaction following an overdose consists of hypotension, fever, tachycardia, and generalised shock. Treatment is exclusively symptomatic. In the event of respiratory complications, the patient should be treated with a corticosteroid and a broad-spectrum antibiotic. Usually the lung reaction to an overdose (fibrosis) is not reversible, unless diagnosed at an early stage.